An Adaptive System for Patient-Controlled Analgesia

Vol. 1

by

This thesis is submitted for the degree of Doctor of Philosophy

Department of Electrical and Electronic Engineering
The University of Melbourne
Australia
Declaration of Originality

This is to certify that the work presented in this thesis is original except where due reference is made in the text to all other material used. To the best of my knowledge, none of the work presented here has been previously published, presented or submitted for a higher degree.

Mr Zheng-Ming Xu produced a prototype adaptive PCA system of which the bolus and infusion algorithms in the normal adaptation range were incorporated in the system presented here.

This thesis less exclusions is less than 100 000 words in length.

Heiko Rudolph

November 1995
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Mr Zheng-Ming Xu produced a prototype adaptive PCA system. I am grateful for his help and advice particularly in the initial stages of this project.

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An Adaptive System for Patient-Controlled Analgesia
I would like to especially thank my parents Dr Fritz and Mrs Rosi Rudolph for their support and encouragement at all times and during the time of research in particular.
Dedication

Dedicated to:
My parents: Dr Fritz Rudolph and Mrs Rosi Rudolph,
my grandparents and
Rungarun Maneerote and Yi Liao
Abstract

Patient-Controlled Analgesia (PCA) has become accepted as an important means of self-regulated relief from post-surgical pain. In commonly used PCA systems, patients use a hand-held push-button to indicate the presence of pain and initiate a predetermined bolus of drug infusion. A disadvantage of this system is that no means is provided to accommodate variations in the intensity of pain or the sensitivity of the patient to the analgesic in use apart from the frequency of button pushing. A fixed rate background infusion is usually an option.

A new adaptive PCA system is proposed to provide improved PCA through the use a variable background infusion, the provision for an extended high range of analgesic dosages and a novel handset which allows patients to rate their pain. The total system is under the control of an expert algorithm and is proposed to overcome some of the shortcomings of current systems.

The specially designed handset allows patients to indicate a range of pain intensities and so vary the level of drug administration. Data derived from the handset signals provide a basis for the expert system to adapt the drug dosage to patient sensitivity as well as pain intensity. The variable background infusion is used to supplement analgesic requested by patients and is periodically adjusted by the expert algorithm. In addition an oximeter provides direct monitoring of the patient and this safety measure allows for a wider range of adaptation under expert system control.

Although clear superior pain relief from the adaptive system could not be statistically established for the small trial population, clinical trials on 20 patients at the Royal Melbourne Hospital have indicated that the system provides effective pain control and is well accepted by both patients and clinical staff.
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Thesis Overview

Chapter 1 introduces the concept of Patient-Controlled Analgesia (PCA) and lays the groundwork for the system described in this thesis.

Chapter 2 gives an outline of the factors which led to the development of conventional PCA as well as giving a broader perspective of the field of pain relief.

Chapter 3 reviews the literature in the field of PCA and examines the major issues currently being debated.

Chapter 4 outlines the theoretical foundations for the proposed new adaptive PCA system.

Chapter 5 describes the implementation of the actual PCA system based on the theoretical foundations of chapter 4.

Chapter 6 deals with the issue of safety in the adaptive PCA system described in this thesis. The system developed here has been trialled on patients at the Royal Melbourne Hospital.

Chapter 7 describes the clinical trials performed using the adaptive PCA system. Analysis and evaluation of data obtained from trials.

Chapter 8 critically evaluates the project, its hypotheses and the results obtained from clinical trials and makes some suggestions for future research.

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### Glossary of Abbreviations

<table>
<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AI</td>
<td>Artificial Intelligence</td>
</tr>
<tr>
<td>ASCII</td>
<td>American Standard Code for Information Interchange</td>
</tr>
<tr>
<td>CO2</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
</tr>
<tr>
<td>DC</td>
<td>Direct Current i.e. zero frequency</td>
</tr>
<tr>
<td>EEPROM</td>
<td>Electrically Erasable Programmable Read Only Memory</td>
</tr>
<tr>
<td>EMR</td>
<td>Electromagnetic Radiation</td>
</tr>
<tr>
<td>ETCO2</td>
<td>End-Tidal Carbon Dioxide (CO2)</td>
</tr>
<tr>
<td>FIFO</td>
<td>First-in First-out - a concept used in data queuing</td>
</tr>
<tr>
<td>FIR</td>
<td>A type of digital filter known as a Finite Impulse Response filter</td>
</tr>
<tr>
<td>HC11</td>
<td>The Motorola M68HC11 E2 microcontroller</td>
</tr>
<tr>
<td>IBM</td>
<td>International Business Machines - a registered trademark</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular - usually refers to a method of administering medication</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IO</td>
<td>Input Output</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LED</td>
<td>Light Emitting Diode</td>
</tr>
<tr>
<td>M68HC11 E2</td>
<td>A Motorola microcontroller featuring built-in ROM and RAM</td>
</tr>
<tr>
<td>MEAC</td>
<td>Minimum Effective Analgesic Concentration</td>
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<tr>
<td>PACO2</td>
<td>Alveolar carbon dioxide tension</td>
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<tr>
<td>PC</td>
<td>Personal Computer</td>
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<tr>
<td>PCA</td>
<td>Patient-Controlled Analgesia</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>PCB</td>
<td>Printed Circuit Board</td>
</tr>
<tr>
<td>prn</td>
<td>pro re nata</td>
</tr>
<tr>
<td>RAM</td>
<td>Random Access Memory</td>
</tr>
<tr>
<td>ROM</td>
<td>Read Only Memory</td>
</tr>
<tr>
<td>RR</td>
<td>Respiration Rate</td>
</tr>
<tr>
<td>SpO2</td>
<td>Arterial Oxyhaemoglobin Saturation</td>
</tr>
<tr>
<td>TSR</td>
<td>Terminate Stay Resident (a type of program)</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale (pain intensity measurement tool)</td>
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Chapter 1  Patient-Controlled Analgesia

"Despite modern surgery and anaesthesia, patients continue to associate surgery with severe pain; postoperative pain for which they will receive inadequate analgesia"

"The plethora of new parenteral agents which the pharmaceutical companies have introduced over the past 20 years is not a reminder that we have not found the right drug but a reminder that we have not found the optimal mode of administration of perfectly adequate analgesic drugs." [Stapleton, Austin & Mather 1978].

1.0 Introduction

Effective treatment of severe pain has been one of medicine’s great challenges. Despite the existence of potent analgesics, many patients continue to experience inadequate pain relief. This thesis addresses a way of improving post-operative pain relief by improving the method by which analgesics are administered. Patient-Controlled Analgesia (PCA) is such a method.

1.1 A General Description of PCA

In its simplest form, a PCA system consists of an electronically-controlled infusion pump connected to a programmable device. When patients experience pain they trigger the infusion pump by means of a button or handset extending from the pump, causing it to deliver a preset dose of analgesic referred to as a ‘bolus amount.’ Following the infusion of the bolus, the timing device precludes the further administration of analgesic for a minimum time period usually called the ‘lockout period’. The lockout period prevents a subsequent dose of analgesic being administered until the first dose has had time to take effect. Figure 1.1 below shows a simplified PCA system.
Modern PCA devices elaborate on the basic scheme outlined above by giving the patient and clinician greater control over the bolus amounts, lockout period, dosage limits and alarm conditions. Some devices also permit a low level background infusion to tide the patient over periods of sleep when no bolus requests are made.

The analgesic dosage levels at which patients experience pain relief vary greatly, as does the patients sensitivity to pain. Using PCA, patients are able to determine their own analgesic requirements.

The PCA devices discussed in this thesis are intended for post-operative patients unless stated otherwise. In a typical PCA application, patients judged as being suitable will receive pre-operative education in the use of PCA. Post-operatively, the patients again receive basic PCA education. Standard nursing care is carried out as for non-PCA patients.

1.2 Rationale for this PCA System

This project aims to explore the better methods of adapting intravenous PCA more closely to individual patient requirements by taking into account some of the psychological and physiological bases of pain relief as it relates to PCA. It is envisaged that the use of an expert knowledge base coupled to more sophisticated technology and improved user interfaces will form a vital step in providing improved pain relief. The system presented here will initially restrict itself to morphine as the

Figure 1.1 A general PCA system.
analgesic agent although equianalgesic doses of pethidine, fentanyl or alfentanil are possible as well.

1.2.1 Limitations and Areas of Possible Improvements of Conventional PCA Systems.

Conventional PCA is defined here as PCA using fixed bolus sizes and an optional fixed level background infusion as prescribed by the pain service in a hospital. Conventional PCA suffers from a number of shortcomings which are listed below in abbreviated form. Each of the points is more fully discussed and referenced in later chapters. The new system proposed in this thesis aims to address these shortcomings.

1) Difficulty in setting the appropriate bolus size given the large variations in analgesic amounts required for adequate analgesia between patients. The bolus size usually prescribed for the majority of patients does not vary very much. With conventional fixed bolus systems, the patient has only one degree of freedom, i.e. a bolus at a fixed level or no bolus. In current practice, this means that the only way in which a patient can access increasing amounts of analgesic for severe pain is through an increased number of bolus requests. However, as each request entails a minimum lockout period, higher dosages can be achieved only over some time. Furthermore, it is not possible to request less than the fixed bolus amount.

2) The above problem is further exacerbated when the widespread practice of underprescribing nurse administered pain relief is translated into conservative PCA prescriptions (general underprescription: [Marks & Sachar 1973, Donovan et al. 1979, Fulton 1993] ). Instances of this have been observed at the Royal Melbourne Hospital. The effectiveness of PCA was limited in such cases. How much PCA is generally affected by this tendency for underprescription is not clear at this stage but it is suspected that most PCA prescriptions do not vary very much from a standard range. General underprescription of acute pain medication is discussed in more detail in section 2.5.4.

3) The background infusion level is difficult to set accurately such that the patient derives some benefit without being at risk of excessive amounts of opioids. A possible reason for this difficulty may be the large interpatient variation in adequate analgesic levels. The level at which analgesia is experienced varies up to five- or
even ten-fold between patients and can also vary over time in an individual patient [Gourlay et al. 1988, Bennett 1985]. The optimal background infusion level can therefore be elusive and require time to find. In some patients, no background infusion at all may be indicated while in others the required infusion level may change over time. Opinion regarding the utility of a background infusion is divided, more details can be found in section 3.2.3. The background infusion in conventional PCA systems also presents an additional risk of human programming error.

4) There is evidence for an upper self-imposed demand limit amongst patients [Keer-Szanto 1979, McCoy et al. 1993, Mather et al. 1990]. This means that in the presence of continuing pain, patients will not make more than a certain number of requests even though more may be possible. The exact number varies with individuals. Although not much research has been done on the practical ramifications of this phenomenon, it may be that coupled with conservative PCA prescriptions, this could be an as yet largely unrecognized problem with conventional PCA.

5) Immediately following surgery, patients occasionally may require higher than usual amounts of analgesic. It is a widely held belief that early adequate post-operative pain relief, at whatever dosage level the patient requires it, seems to ensure greater continuing comfort and enhanced recovery with fewer complications [Libreri 1995, Bennett 1985, Panfilli et al. 1988, Lange et al. 1988, Wasylak et al. 1990, Ouchi et al. 1991, Finlay et al. 1984, APMGP 1992]. Some particularly pain sensitive patients also require especially high amounts of analgesic for some time during the post-operative period. These requirements for higher doses of analgesia are not necessarily accommodated using conventional PCA with standard PCA prescription, especially when one considers points 2 and 4 above. The importance of the immediate post-operative period is discussed at length in section 4.2.

6) It has been found that most PCA mishaps, such as those in many areas of technology, occur at the human-machine interface level [Callan1990, Institution of Engineers Australia March 1993, Radcliffe 1991]. Thus it is felt that there is room for improvement in the user interfaces of current PCA technology. To be safe in practice, a PCA system needs to be easy to use, both for the clinical staff and the patients [Runciman et al. 1993].

*An Adaptive System for Patient-Controlled Analgesia*
7) Although not necessarily a shortcoming it should be noted that conventional PCA technology usually does not always use electronic monitoring devices to supervise patients. Monitoring the patient to ensure vital parameters are not exceeded is not an integral part of current PCA therapy but a desirable one[]. (Monitoring devices in anaesthesia are reviewed in depth by Webb et al. [Webb et al. 1993].)

Chapter 4 gives extensive details on the theoretical foundations of the new proposed PCA system.

1.3 Summary

The overriding aim of this PCA system is to provide better pain relief in areas where conventional PCA technology is not at its optimum.

It is proposed to explore some of the theoretical underpinnings of PCA and to propose a PCA system which incorporates new hypotheses and propositions regarding self-administered pain relief. It is thought that such a system will be more adaptive to individual patient’s need and will be able to provide improved analgesia.
Chapter 2  The Case for PCA

2.0 Introduction

This chapter gives an outline firstly of an aspect of the psychology and history of pain and secondly the factors which led to the development of PCA.

2.1 A Historical Survey of Pain Perception

The problem of pain has been a wellspring for much of mankind’s religious and medical thinking. Pain is one of the most powerful and insistent sensations and a force behind much of man’s behaviour in the physical world. It has also been a fertile ground for a plethora of religious interpretations and a focal point around which some of the philosophical thinking of a culture has crystallised. This section gives a very brief overview of the history of pain interpretation in the West, based on Jaros’ outline [Jaros 1991].

It is thought that ancient civilizations, such as the Egyptians and Assyro-Babylonians, ascribed pain caused by disease to intrusive forces such as spirits or magical fluids. One of the roles of the shaman or priest was to facilitate the release of the destructive elements in the afflicted’s body. This release could take the form of vomiting, sweating, blood letting or a variety of other means.

The concept of pain in western thought has evolved from roots in the ancient Greek, Roman and Hebrew civilizations. The Greeks believed that enduring great physical or psychological pain would enable one to achieve a greater measure of courage and nobility, while Plato thought the sensations of pleasure and pain distracted the soul from knowing what was real.

With the ascent of the Church in western Europe, Greek teachings were repudiated and found their way into Persia and influenced a variety of Arabic scholars and physicians. The Arab physician Avicenna (AD 980-1036) developed a theory of pain based on the four temperaments of heat, cold, dryness and moistness, an
imbalance of which gave rise to 15 different types of pain. It is interesting to note that the Chinese use the same four temperaments with the addition of wind as a fifth temperament [Kenyon 1983].

After the collapse of the Roman Empire, the church of the Middle Ages gained in power and from Judaism adopted the connection of sin with punishment and punishment with pain. The English word ‘pain’ is derived from the Latin word ‘poena’ meaning punishment. The otherworldly outlook of the Medieval Church placed little emphasis on worldly comforts and held that the suffering and pain of the human condition was a result of Original Sin and thus just punishment. Disease was seen as punishment which also cleansed in a purgative sense and to expend too much effort in the alleviation of suffering could even be seen as transgressing against God’s divine order.

With the Renaissance came a renewed interest in man, nature and the scientific method. The belief of Original Sin was gradually replaced by a belief in the original purity of human beings, who then became corrupted by the effects of disease, poverty and injustice. Manipulating the natural order to minimise these negative influences was seen as a legitimate way to improve the physical and spiritual condition of mankind. This was a time of intense study of the human body through dissection and experimentation. However the acceptance of analgesia met with considerable resistance on moral grounds as recently as the late nineteenth century and in the Catholic Church required formal approval from Pope Pius XII.

At present, western civilization has almost completely secularized pain. Through the use of over-the-counter analgesics, biofeedback and patient-controlled analgesia, the locus of control has shifted more from external deities to the individual. Thus, PCA can be seen as part of a progression towards greater self-responsibility of the individual. This is a theme found not only in the area of pain relief, but in the changing western health profession in which the onus for health is gradually being placed more on the individual.

The origin and nature of pain, whilst researched and studied extensively by modern science is still a mystery. As more is known about the mechanisms of pain it becomes apparent that pain is not a function of one particular body system and cannot be removed from human experience. While research has opened a more comprehensive view of the mechanisms of pain, that view has not become simpler but rather more complex. As the individual struggles to assume increased responsibility for his or her health and pain, this complexity may indeed lead to either the external deities becoming resurrected in a contemporary form or replaced by the individual divinity of each person. In terms of psychology, the shift from external deities to

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individual responsibility can be viewed as a movement of the locus of control from a powerful outside centre to the individual self.

A more detailed and physiologically based account of the history and development of neural blockade is given by Fink [Fink 1988]. The evolution of pain concepts and the use of neural blockade is further discussed by Bonica [Bonica 1988].

While it is recognized that the physiology of pain is fundamental to analgesic therapies this adaptive PCA system builds on an already established modality and will focus on the psychological aspects of PCA and any implications relating to adaptive PCA. The physiology of pain has been extensively reviewed by Cousins and Bridenbaugh (eds.) [Cousins and Bridenbaugh 1988]. A good introduction to the physiology of pain and anaesthetic action is given by Strichartz in Cousins and Bridenbaugh’s book [Strichartz 1988].

2.2 A Working Definition of Pain

The physiological nature of pain is still poorly understood at present. As far as PCA is concerned, the working definition used here is: “pain is whatever the experiencing person says it is, existing whenever the experiencing person says it does” [Roop 1991]. A definition of pain adopted in 1986 by the Subcommittee on Taxonomy of the International Association for the Study of Pain (IASP) is “Pain is an unpleasant experience associated with actual or potential tissue damage, or described in terms of such damage” [Drasner et al. 1992, Merskey 1979]. It can be seen that by definition pain is subjective and cannot be measured directly as such.

Pain is simultaneously a physiological and a psychological experience. The physiological effects of pain are quite well known and include increased oxygen consumption, decreased lung volume, immobility and a variety of hormonal and metabolic responses.

Pain itself also tends to vary over time and this would ideally require a constant adjustment of the analgesic level. In oncology pain and in post-operative pain, the phenomenon of breakthrough pain has been observed. Breakthrough pain is a period of severe pain over and above the chronic temporal components and can be difficult to control [Citron et al. 1985].

Nocioceptive pain has responded better to opioid analgesic treatment than neuropathic pain which has been thought to respond only minimally. Recent research
using PCA has however shown some success in treating neuropathic pain using morphine [Jadad et al. 1992].

2.3 The Psychology of Pain

The psychological impact of pain is just as real as the physiological component and consists of emotional and socio-cultural factors and the patient’s general psychological disposition. The integration of psychologic principles with pharmacologic treatment has been discussed by Chapman [Chapman 1992]. A general overview of the psychological aspects of pain can be found in Melzack [Melzack 1988].

It is generally accepted that a positive relationship exists between anxiety and experienced pain [Christoph 1991; Lange 1988, Gill 1992, Melzack 1988]. Fear of pain can in turn heighten anxiety. Possible lack of control over severe pain can significantly increase patients’ anxiety levels. Christoph points out that “Unmanaged pain contributes to the development of critical care psychosis and personality disorders” [Christoph 1991]. This view is also echoed by Drasner [Drasner et al. 1992]. It should be borne in mind that the pain under discussion here is of perceived levels of pain that cannot be readily controlled by orally or rectally administered analgesics. PCA has often been credited with reducing anxiety by giving patients control over their environment and reducing the time to administer pain relief [Lange 1988, Drasner et al. 1992]. The reduction of anxiety stemming from a sense of control over pain should not be underestimated. This aspect of pain control is further discussed below.

2.4 The Concept of ‘Locus of Control’ as a Predictor of Analgesic Requirements

The subjective value of PCA for the patient can perhaps be better appreciated if one looks at the control aspect of patient-controlled analgesia. In psychology the term ‘locus of control’ has emerged to describe a person’s perception of control or influence over life circumstances. Egan describes the concept of ‘locus of control’ as follows [Egan 1990a].

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An essential part of adult life consists of control over the activities of daily life, such as when and where to eat, choice of recreational activities, which friends to see and when to go to bed and get up, to name just a few. Teenagers wrest control from their parents in an effort to attain adult status. Prisoners are deprived of freedom of movement and choices in life, which amounts to a loss of control. Control can be thought of as the ability to determine outcomes from one’s responses. Hospitalization and surgery generally involves the loss of control over even the most basic functions, taken for granted as an adult. That loss of control includes loss of mobility, privacy, and control over basic bodily functions of eating and elimination, all in an unfamiliar environment. If one considers the evidence in the literature that loss of control is intrinsically anxiety provoking and couples this with the fact that surgery is often a physically and psychologically traumatic experience, it can be appreciated that the psychological aspects of hospitalization are indeed very important. In addition it should be borne in mind that the perception of pain itself is modulated by anxiety and that anxiety in turn is generally thought to heighten perceived pain. Thus the issue of pain and control over pain can be seen as a focal point in the hospitalization experience of the patient.

Research in the area of control has yielded some of the following results in experimental settings [Egan 1990a]:

1) If people believe that they have control over an unpleasant stimulus such as an electric shock, they endure more powerful shocks and for a longer time. As a corollary, if people perceive that they have no control to stop an unpleasant event, they tend to perceive it as more aversive. Perceived lack of control tends to increase anxiety which in turn leads to increased pain perception.

2) Control does not have to be real nor exercised to be effective. Knowledge of control, even if not exercised, is often beneficial.

3) Given a small shock intensity, people prefer predictable shocks over unpredictable ones.

4) People generally choose to have control themselves unless they perceive another person as much better at averting an unpleasant stimulus.

Control theory has been applied in the Multi-dimensional Health Locus of Control (MHLC) inventory, where three areas of control are defined in terms of whether
people believe their health is a result of their own actions or not. These three areas are 1) internality, 2) powerful others and 3) chance externality. People classified as ‘internals’ believe their health is largely in their own hands, while ‘externals’ believe that their health is the result of powerful others, luck or fate. In a study by Johnson and colleagues, it was found that patients who were mainly ‘internals’ used less analgesic than externals [Johnson et al. 1989 (abstract: 1988), Magnani et al. 1989]. PCA was used in Johnson’s study, whereas in a study by Taenzer, conventional therapy was used and no correlation between locus of control and analgesic usage was found [Taenzer et al. 1986].

Apart from any predictive value regarding analgesia, the ultimate value of control theory may be in helping the medical profession to understand the psychological benefits of PCA. PCA addresses the issue of control and emotion by giving patients some measure of control over their pain in an environment in which otherwise even common place control over basic bodily functions has been removed [Chapman 1992].

2.5 The Case for PCA

PCA has gradually become a more popular pain management modality both with patients and clinical staff. The thrust behind the development of PCA has been an increasing awareness from as early as 1952 of the inadequacy of the conventional methods of administering pain relief [Papper 1952, Tamsen, 1986; Lubenow 1991, Marks & Sachar 1973].

A major turning point was reached with a publication by Marks and Sachar in 1973, which placed the percentage of patients experiencing inadequate analgesia as high as 73% [Marks & Sachar 1973, Ferrante et al. 1990]. A steady stream of articles have echoed these findings since then, variously quoting figures for insufficient analgesia of at least 50 % [Ferrante et al. 1990].

One of the major reasons for inadequate analgesia is the method of analgesic administration, in particular the practice of pro re nata (p.r.n.) and scheduled intramuscular (IM) injections at three or four hourly intervals. This practice results in a peak and trough effect as illustrated in figure 2.1 below. The patient experiences very large swings in blood concentration over the four hourly bolus intervals, with attendant large changes in analgesia. The range in which analgesia is experienced is
relatively small, and as the plasma concentration varies the patient receives satisfactory analgesia only for a relatively short time.

Figure 2.1 The peak and trough effects of conventional IM analgesia (solid line) compared to PCA (dashed line). (From: Ferrante M. F., Orav E. J., Rocco A. G., Gallo J., "A statistical model for pain in patient-controlled analgesia and conventional opioid regimens", Anesth. Analg., Vol 67 pp457-461, 1988). Note: This figure does not take into account the effects of acute tolerance where patients will require larger doses at shorter intervals with increasing side effects.

In a study using pethidine (meperidine) it was found that the analgesic drug concentration only exceeds the Minimum Effective Analgesic Concentration (MEAC is the minimum analgesic blood concentration point at which a patient moves from some pain to effective analgesia [Austin et al 1998a] ) for approximately 35% of the dosing interval, while peak concentrations varied up to five-fold and the time to reach this peak varied between 4 to 108 minutes between patients [Austin et al. 1980a, Rigg et al. 1978, Lubenow et al. 1991]. Austin also showed in 1980 that the pethidine blood concentrations of patients with four hourly intramuscular injections varied by up to half of the maximum levels [Austin et al. 1980].

The advantages of PCA are perhaps best understood by describing the difficulties encountered in pain relief and how they are dealt with in conventional intramuscular regimens. The problems in pain relief are discussed below and can best be subdivided...
into four groups: pharmacology, method of administration, the nature of pain itself, and patient variation.

2.5.1 Opioids Used for Pain Management and Their Unwanted Effects

Pharmacologically, the ideal analgesic would have quick onset of action, no unwanted effects, no ceiling effects and no tolerance. No drug meets all these requirements, but morphine and pethidine (meperidine) present the best compromise and are the most frequently used [Lubenow 1991].

In practice the unwanted effects of opioid analgesics are varied. The extent and the type of unwanted effects which appear at various concentrations depend on each individual patient. A balance between analgesic effects and unwanted effects must be found for each individual. PCA is uniquely suited for this task, as it allows each patient to find his or her own balance between some of the unpleasant unwanted effects and analgesia. The following is a list of common systemic effects of opioid agonists used in PCA [Mather et al. 1990, Eige 1992].

Central nervous system effects usually consist of diminished responsiveness to nociceptive stimuli, mood elevation and sedation. In addition, further effects may include mental clouding, dizziness, dysphoria and hallucinations.

Respiratory system effects are primarily reduced ventilatory response to CO2 (and to hypoxia) with the potential for respiratory depression. Unfortunately, potency of analgesia parallels the respiratory depressant action, so that as a patient receives more analgesic the risk of respiratory depression also increases. Respiratory depression is the most serious of the acute unwanted effects of opioids.

Effects on the gastrointestinal system especially ileus include nausea and vomiting as well as uncoordinated gut activity, often resulting in constipation.

Circulatory system effects are minimal at standard post-operative doses. Morphine and pethidine can sometimes cause hypotension.

Other effects of morphine include generalized itching, disrupted sleep and nightmares [Fulton et al. 1993].

It should be noted that the proposed PCA system features safety monitoring devices to monitor respiration rate, arterial oxygen saturation (SpO2) and end-tidal carbon dioxide concentration (ETCO2), primarily with the aim of detecting respiratory
depression due to oversedation from analgesics. Respiratory depression resulting in apnoea is the most serious of the unwanted effects, although less severe effects are also of concern and may be the reason for discontinuation of PCA therapy.

The ratio of efficacy to toxicity is referred to as the therapeutic index and is traditionally defined in the literature as the ratio of the amount producing the adverse effect in 50 percent of the test population to the amount producing the desired effect in 50 percent of the test population. A high therapeutic index indicates a drug in which the unwanted effects are minor and the desired effects dominate. For PCA, a drug with a high therapeutic index would be particularly important because of the large differences, in between patients in amounts required for efficacy. However, the commonly used drugs in acute pain relief have a small therapeutic index relative to the range of effective dosages required by patients. This is one of the reasons which makes a generalised approach to acute pain relief difficult, particularly as there are no suitably objective parameters of a patient’s analgesic requirements. This last point will be discussed at length below.

### 2.5.2 The Relationship Between Plasma Concentration of Opioids and Analgesia

The relationship between plasma concentration of opioids and analgesia is highly nonlinear. There is a point in many patients where a minimal increase in analgesic will take the patient from quite severe pain to near total analgesia. Despite increasing analgesic plasma concentrations, pain can be quite severe up to a ‘maximum concentration with severe pain’ called the MCP point. Then with a minimal increase of opioid, the patient can be taken to almost complete analgesia at a level called the minimum effective analgesic concentration (MEAC) [Ferrante 1990]. The concept of MEAC is not universally accepted, and a detailed outline of the debate surrounding the MEAC is given in section 3.2.1.

Plasma levels and pain experienced do not generally have a close correlation across patients but do have better correlation within individual patients [Austin et al. 1980, Tamsen 1986, Hill et al. 1993]. Since there is such great interpatient variability in plasma levels at which analgesia is experienced, and the emphasis in PCA is on effective pain relief, the approach here has been to consider pharmacodynamics first. It is thought that the use of pharmacokinetics is primarily to understand drug
mechanisms rather than to provide dosing goals, except in the absence of pharmacodynamics.

2.5.3 Patient Variation

The method of administering opioid analgesics intramuscularly (IM) suffers from a number of problems which are largely exacerbated by interpatient variation. These are as follows:

1) Erratic interpatient variability in blood absorption time of the injected analgesic. Peak absorption times between 10 to 100 minutes have been found by a number of researchers [Berkowitz et al. 1975, Stanski et al. 1978, Austin et al. 1980, et al. 1982].

2) The peak plasma concentrations of analgesics vary between patients for equal doses injected. In one study, using pethidine, the peak plasma concentration varied up to five-fold and the time to reach this peak varied seven-fold [Austin et al. 1980].

3) The MEAC mentioned in section 2.5.2 above, varies up to five- or even eight-fold between patients, while the effective safe concentration range of opioid analgesics is relatively narrow [Austin et al. 1980, Tamsen 1986, Hill et al. 1993]. This is one of the major difficulties in providing pain relief for a large number of individuals using a standard protocol. A ten-fold interpatient variation of analgesic blood serum concentrations has been reported by Bennet, and a five-fold variation by Gourlay [Bennet et al. 1985, Gourlay 1988].

PCA studies have found that patients usually titrate their analgesic blood concentrations to a near constant level, which only varies by approximately 30% [Gourlay et al 1988]. It has been found that for successful analgesia the blood levels should remain relatively constant. Thus, we have the situation of widely differing MEAC levels between patients, but a near constant MEAC for each individual patient [Shade 1992, Drasner et al. 1992].

The age of the patient is a further source of variation in sensitivity to opioids. Older patients were found to be more sensitive than younger patients [Ferrante 1990,
Bellville et al. 1971]. However, this is not universally accepted. According to Mather, the sensitivity of older patients should not be exaggerated, and older patients should not be considered ‘supersensitive’ to ventilatory depression [Mather et al. 1990].

2.5.4 An Evaluation of Traditional Methods of Analgesic Administration

There has been a growing consensus regarding the inadequacy of deterministic intramuscular analgesics because a significant proportion of patients still experience insufficient analgesia despite advances in analgesic pharmacology [Papper 1985]. In fact, it has become apparent that the actual methods of drug administration are equally important in determining successful analgesia as the analgesics themselves [Ferrante 1985]. Given the limitations of current analgesic drugs, the method of delivery must be optimized to extract maximum benefit from the available drugs. PCA represents one such method.

Traditional pain relief usually consists of prescribed bolus amounts injected intramuscularly as required or scheduled at regular intervals or of a continuous intravenous (IV) infusion. The prescribed amounts are loosely based on body weight and age. This method does not optimize the usage of current analgesic drugs for several reasons.

In section 2.5.3, it was pointed out that the rate of absorption from intramuscular injections varied greatly, from 10 to 100 minutes. In addition, the peak plasma concentrations of analgesics vary up to five-fold between patients for equal doses injected. Both these factors contribute to erratic and unpredictable drug plasma concentrations using intramuscular administration.

It was also pointed out in section 2.5.3, that the MEAC varied up to 5 or even 10 fold and in section 2.5.2 that the transition from severe pain to near total analgesia was extremely steep. There also seems to be no reliable predictor of a patient’s optimum level of analgesic blood concentration. Weight and body surface area have traditionally been used to predict a patient’s analgesic dosage level, but have been shown to be largely uncorrelated with a patient’s requirements for optimal relief [Bellville et al. 1971, Kaiko et al. 1983, Owen et al. 1990]. The situation is further complicated by the fact that opioids do not have a very large therapeutic index, which means that the amount required to move one patient to MEAC level may produce distressing unwanted effects in another patient. Thus in practice the plasma

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concentration range for adequate analgesia without major unwanted effects is quite small for opioids.

The difficulty in achieving adequate analgesia can be summarized as follows: The exact level at which successful analgesia occurs can vary up to five- or ten-fold between patients while the method of administration does not account for the large variations between patients. This situation is analogous to trying to shoot a small fast moving target with a very inaccurate gun.

Given the variations in patient sensitivity and analgesic requirements it can be seen that some patients may rarely or never reach the window of adequate analgesia shown in figure 2.1, particularly if one bears in mind that the prescribing physician must set the dosage to one that is safe for the more sensitive section of the patient population. The fundamental inadequacy of regularly scheduled injections is further exacerbated by the practice of underprescription and underadministration of opioid analgesics, as well as the time delay involved when the patient requests additional doses.

In studies by Marks and Sachar in 1973 and Donovan in 1979, it was found that physicians regularly underprescribed the amount of analgesics to be given and that nurses further reduced the actual amount to such an extent that patients in the study only received a quarter of the amount they needed for adequate analgesia [Marks & Sachar 1973, Donovan et al. 1979]. The reasons for this are complex but can be traced to deficiencies in skills and knowledge in effective pain relief techniques [Oden 1990]. It was found that the clinical staff expressed a genuine desire to relieve pain as much as possible but the knowledge concerning opioid analgesics and patient variation was not generally appreciated for its practical implications [APMGP 1992].

The general public disrepute into which drugs such as heroin (and to a lesser extend perhaps morphine) have fallen in recent decades may to some extend also play a part in urging clinicians to err on what they perceive to be the safer side, i.e. underprescription. However there is evidence that it is reasonable to administer whatever amounts of morphine will alleviate pain, while avoiding excessive unwanted effects [Fulton 1993].

A further shortcoming of deterministic analgesia administration is that for any additional requests the time from request to eventual administration varies and can often be rather long due to the protocol involved in administering opioids and the workload of nursing staff. The general protocol for conventional analgesic administration is shown in Figure 2.2 below:
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Figure 2.2 The delays associated with conventional analgesic administration. (From: Graves D.A., Foster T. S., Baternhurst R. L., et al, “Patient-Controlled Analgesia”, Ann. Intern Medicine, Vol 99, pp360-366, 1983.)

It will be readily apparent that the procedure illustrated above involves a large number of steps, with times of up to 15 minutes before a dose is given. It may then take from 10 to 100 minutes to reach a satisfactory level of analgesia.

Other than the problems of variations in intramuscular absorption, most of the problems outlined above for interpatient variation using intramuscular bolus injections also apply to intravenously delivered analgesia and continuous infusions.

In the case of intravenous bolus injections, the problem of peak and trough effects from p.r.n. administration and the problem of interpatient variation in MEAC levels remains.

Continuous infusion was proposed as an alternative to PCA in a study by Zacharias but it was almost always necessary to readjust the infusion rate to the patient’s changing needs over time [Zacharias et al. 1990]. These changes were thought to be influenced by circadian variations in receptor sensitivity (chronestesy) and pharmacokinetics (chronopharmacokinetics). Zacharias also found that efforts to predict the morphine dose for individual patients based on age, weight and height

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were unsuccessful and required frequent alteration. In this, he echoes the findings of other studies and highlights the problem of finding the MEAC for individual patients [Tamsen 1986]. From the literature so far, it appears that the subjective perception by the patient is the best judge of pain relief. PCA is based on a recognition of that reality.

2.6 Conclusion

PCA addresses the problems of conventional p.r.n. pain relief in the following ways. By infusing a succession of small amounts of analgesic at the patient’s request, the peak and trough effect commonly experienced with regular injections can be substantially reduced.

PCA also allows patients to adjust the analgesic levels to their individual needs and thus compensate for the considerable variation in pharmacokinetic and pharmacodynamic sensitivity between individuals. Time variations in analgesic requirements can also be more successfully allowed for using PCA.

The delay between the time pain relief is requested and the time it is actually given and takes effect is eliminated using PCA. As PCA is administered intravenously, the time taken for the injected analgesic to take effect is much shorter and more consistent than in the case of intramuscular administration.

Lastly, if desired, PCA also allows the use of analgesic drugs with a shorter half-life, because the patient can easily and frequently request small amounts of additional analgesic.

Some of the disadvantages of PCA are the initial cost of the equipment and the increased complexity of the technology as well as the higher degree of training and skill required from clinical staff. Also, PCA is not suitable for all patients, such as the confused, the hypovolaemic and drug abusers.

When making comparisons between PCA and regular scheduled injections, it is important to remember the point made by White, that with ‘attentive nursing care conventional intramuscular analgesia can become “on demand” and may be as effective as PCA’ [White 1985]. In fact early trials of the PCA concept involved a nurse-observer to provide on-demand analgesia which effectively amounted to PCA [Sechzer 1971].

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Chapter 3  Literature Review

3.0 Introduction

Patient-controlled analgesia (PCA) has developed its own specialist literature over the years. The aim of this chapter is to give an overview of that literature. Within the literature, a number of interest groups have focussed on different aspects of PCA, such as evaluating PCA with respect to other methods of administering analgesia, using PCA for pain measurement or analgesic drug evaluation, and looking at the parameters of PCA systems themselves. This chapter identifies the major groups in the PCA literature and the dominant issues within each group.

3.1 Classes of PCA

Most PCA devices developed to date can be classified into the following four main groups [Norman 1985]:

1) Bolus demand: The size and maximum dose are fixed.

2) Infusion demand: The demand varies a continuous variable infusion.

3) Bolus demand and constant infusion: The constant background infusion aims to provide a minimum level of analgesia and thus avoids the troughs in plasma drug levels when the patient is asleep.

4) Bolus demand and variable infusion: The system monitors the frequency of bolus demands and adjusts the background infusion accordingly.

Most commercial PCA systems belong to groups one and three with only very few in group four, the author is aware of only one prototype in group two [Hill et al. 1993].
3.2 Current Issues in PCA

There are a number of issues currently discussed in the PCA literature. Some of these issues have been identified and treated in the sections below.

3.2.1 Minimum Effective Analgesic Concentration (MEAC)

The concept of minimum effective analgesic concentration (MEAC) which was already alluded to in section 2.5.2, has been the subject of lengthy debate in the PCA literature. Some studies indicate that patients use PCA to titrate to an MEAC level. At this level pain is said to change from being quite severe, at a point called the maximum concentration still associated with severe pain (MCP), to adequate analgesia at the MEAC level. Austin et al. performed a now famous study, in 1980, showing that the difference between the MCP and MEAC level is often only a minute fraction of the total analgesic already given [Austin et al. 1980 b]. In his study, Austin found that as little as 0.05 microgram/ml of meperidine (pethidine) could effect a change from severe pain to near total analgesia, as shown in figure 3.1 below.

![Figure 3.1](image.png)

**Figure 3.1** Blood meperidine concentration response curves for three individual patients, illustrating a typical range of interpatient responses. Pain score of 0 = No Pain, 1= Moderate Pain, 2= Severe Pain. (From: Austin K. L., Stapleton J. V., Mather L. E., "Relationship between blood meperidine concentrations and analgesic response: A preliminary report", Anesthesiology, Vol 53 pp460-466, 1980.)
Austin found that the MEAC between patients varied up to four fold (interpatient variation), but remained stable for individual patients over time. Gourlay reported only a 30 percent intrapatient variation and a five-fold interpatient variation in MEAC [Gourlay et al. 1988]. Tamsen found a four-fold interpatient variation between the plasma drug concentrations achieved by patients using PCA, while Bennett reported a ten-fold variation in ten patients [Tamsen 1986, Bennett 1985]. There are few drugs for which the required dose range between patients is as wide as for the opioid analgesics, yet the opioids have only a relatively small therapeutic index. These mutually conflicting properties make opioid analgesia difficult and have contributed the development of PCA.

Some studies have found that the behaviour of patients does not seem to indicate a definite MEAC. These studies show that patients do not titrate to a definite MEAC level, but rather aim to achieve diminution of pain [Owen et al 1990, 1991]. Owen tested three groups of patients with different demand doses of morphine to establish whether patients demanded an equivalent amount of morphine regardless of the dose size or whether patients made an equivalent number of demands regardless of dose size [Owen et al. 1990]. Owen’s study group found that the number of demands were independent of the demand-dose size and suggests that patients seek diminution of pain rather than aim for a distinct MEAC level. Some of the possible reasons put forward to explain why patients make demands are because 1) pain levels had gradually become worse, 2) pain had suddenly become worse due for example to coughing or 3) pain was anticipated in response to imminent movement such as physiotherapy. (In the opinion of the author this debate highlights the need for a study of the psychology of patients’ button pressing behaviour.) In Owen’s study the group of patients with the lowest demand dose of 0.4 mg showed a slightly lower cumulative morphine level, whereas the groups receiving 0.7 and 1.0 mg demand doses had virtually identical cumulative morphine levels. The lower morphine levels for the 0.4 mg group may be explained as the result of the self-imposed internal demand frequency limit observed by a number of researchers [Keeri-Szanto 1979, McCoy et al. 1993, Mather et al. 1990]. Owen’s study used a 1.5 mg/hr continuous background infusion in order to minimize demands and make any likely differences between demand doses more prominent.

In contrast, a study by McCoy in 1993 compared three patient groups using morphine [McCoy et al. 1993]. The first group received only PCA and no background infusion, while the second group received PCA plus a 1 mg/hr infusion and the third group
PCA plus a 2 mg/hr infusion. The bolus size for all groups was 1 mg. The total dose per hour was kept constant at 6 mg/hr by increasing the lockout time with increasing bolus size. McCoy found that the background infusion did significantly reduce the number of demands, and that the third group (2 mg/hr) recorded an increased incidence of nausea. The patients who received no background infusion did significantly increase their demands but still experienced inadequate analgesia in 9 out of 16 cases in the first 4 hours after surgery. McCoy’s study seems to indicate that patients not only press the bolus request button for diminution of pain, but also aim to reach a definite level of analgesia such as could be found at the MEAC level.

A number of variables must be considered in interpreting these apparently conflicting results. The assumption that patients will press the bolus request button as often or as little as needed to obtain pain relief, while perhaps valid within a range of button presses, is perhaps not valid at the extremes of pain. The extent of this range would be a worthwhile field for future research in the author’s opinion. McCoy found that the patients without a background infusion did not avail themselves of the full amount of analgesia available to them. This could be due to the self-imposed demand frequency limit mentioned above. In Owen’s study the maximum dose per unit time was not constant between groups whereas McCoy staggered the lockout times such that the maximum analgesic available per hour was equal for all groups. The range of analgesic in Owen’s study extended from 0.4 to 1.0 mg with a background infusion of 1.5 mg/hr whereas McCoy’s study used a range of 1 mg to 2 mg with a background infusion of 1 mg/hr.

It may seem obvious to estimate a patient’s blood plasma concentration levels from the amount of analgesic infused, but this assumption cannot always be made. Only actual blood plasma measurements can accurately quantify a patient’s analgesic levels [Gourlay et al. 1988]. In addition the relationship between analgesic levels in blood and the associated pain relief is also subject to unpredictable variation [Owen et al. 1988]. The MEAC level may also vary during the day, and these variations may be masked through averaging during subsequent data analysis. Circadian variations in receptor sensitivity (chronesthesia) and chronopharmacokinetics would be detected only if the data were analyzed on an hourly basis [Lubenow 1991]. In the light of these factors, it seems extremely difficult to come to a definite conclusion regarding the objective existence of an MEAC level at this time. In a study using alfentanil Owen concludes that either patients do not make demands to a definite MEAC level or that the analgesic drug prescription is one of the determinants of the MEAC [Owen et al. 1991]. However as a practical working definition, the MEAC can be thought of...
as the minimum analgesic level at which the patient experiences a definite change to analgesia.

3.2.2 Variations in MEAC and Natural Endorphins in the Cerebrospinal Fluid

In an attempt to explain the large variations in the level of analgesic at which patients experience adequate analgesia, Tamsen has put forward the theory that an individual’s analgesic plasma levels are indicative of his or her sensitivity to opiates and that this is in turn linked to an individual’s endorphin activity in the brain [Tamsen 1986, Tamsen et al. 1982a]. The study by Tamsen showed a significant inverse relationship between individual pre-operative cerebrospinal fluid (CSF) endorphin concentrations and meperidine (pethidine) plasma concentrations using PCA. Thus it seems that patients with higher CSF endorphin levels self-administered less analgesic than those with lower endorphin levels. Tamsen suggests that individual drug differences in drug requirements are mainly due to differences in drug sensitivity. A related study by Cohen, indicates that intra-operative beta endorphin levels in plasma are inversely related to morphine requirements administered by a nurse observer [Cohen et al. 1982]. From the results published thus far, a relationship between CSF endorphin concentration and analgesic requirements does indeed seem to exist, though to what extent this can be used to gauge analgesic requirements in individual cases is open to further investigation.

3.2.3 Background Infusions in PCA

There has been an ongoing debate concerning the use of a fixed rate background infusion to supplement the analgesic the patient receives from bolus requests. The rationale for a fixed background infusion are firstly, that the background infusion provides a maintenance level of analgesic while the patient is asleep and unable to make requests. This is thought to prevent the patient being woken by extreme pain. Secondly the patient should not have to press the bolus request button too frequently because as was already mentioned, there is evidence that patients have a self-determined internal limit above which they will not bother to make any requests (or very few requests) [Owen et al. 1989]. A fixed-rate background infusion is thought to
place the patient just below the analgesic threshold, but the patient is still required to make a reasonable number of bolus requests to obtain proper pain relief. Owen undertook a study of two groups of patients using PCA [Owen et al. 1989a]. The first group received PCA with a constant background infusion of 1.5 mg/hr of morphine, the second PCA without a background infusion. Owen found that the infusion group received twice as much morphine as the non-infusion group yet the infusion did not reduce the number of demands and both groups had similar pain scores. Paradoxically, the infusion group had slightly lower nausea scores. Owen concluded these trials by saying that “the addition of a constant rate infusion to PCA neither improved the effectiveness of the technique nor reduced the number of demands” [Owen et al. 1989]. A further study undertaken by Owen specifically to investigate the use of background infusions showed no decrease in the number of demands made by patients with or without a background infusion [Owen et al. 1991]. The groups with background infusions received significantly more drug (alfentanil) but no differences in sedation were reported. A similar study by Russell confirms Owen’s findings that the addition of a background infusions did not reduce the number of demands [Russell et al. 1993]. Russell investigated the effects of a background infusion on oxyhaemoglobin saturation (SpO2) and found that the background infusion did not cause any difference in the SpO2 levels and the pain scores of the two therapies, but did result in a much higher total morphine dose for the background infusion group. Based on this study Russell does not recommend the use of background infusions in PCA for gynaecological patients. A similar view is expressed in a letter by Wu and Purcell [Wu et al. 1991]. Wu notes that although background infusions did not significantly influence the pain or sedation scores the overall analgesic consumption of patients with background infusions was significantly higher. Parker, Holtman and White examined the use of a constant 1mg/h background infusion (morphine) in abdominal hysterectomy patients and also concluded that the infusion did not improve the post-operative management of pain, sleep patterns or recovery profiles [Parker et al. 1992].

By contrast in the study by McCoy mentioned earlier (section 3.2.1), in which three groups of patients were given PCA, one group without a background infusion and the remaining two groups with background infusions, it was found that the background infusion did significantly reduce the number of bolus requests [McCoy et al. 1993]. In the group without background infusion, 9 out of 16 patients did not obtain satisfactory analgesia despite a higher number of bolus requests.

McCoy was able to show a difference in the number of bolus requests made between the group receiving a 2 mg/hr background infusion and the group receiving the 1 mg/hr background infusion and the group without a background infusion. It
should be noted that the effect of the background infusion was most pronounced in the first four hours of PCA therapy.

Sinatra compared the effects of PCA with PCA plus background infusion and found that the background infusion reduced the pain associated with movement [Sinatra et al. 1989]. When oxymorphone instead of morphine was used, a reduction in the resting pain scores was also recorded. No clear reasons for this finding were apparent. The use of a background infusion was associated with slightly more side-effects such as nausea and pruritus. It would be interesting to study the pain scores and button pressing behaviour of those patients who experienced higher than normal nausea and pruritus to determine whether the background infusion was too high and or whether these particular patients comprised an exceptionally sensitive portion of the population.

Sinatra’s study highlights the need to consider not only resting pain scores but also pain associated with movement. The benefits of a background infusion could be hidden to researchers because of inadequate measurement techniques.

The method used to measure pain intensity must be considered in its context. The visual analogue score gives a measure only of instantaneous pain intensity. McCoy suggests the ratio of requested to given boluses as a way of measuring the patient’s average pain level [McCoy et al. 1993]. When one wants to quantify an inherently difficult and subjective parameter such as pain, it seems reasonable to use all available measurement and indicator techniques. It also seems that the use of only one method such as the VAS is an attempt to temporally reduce a complex subject to an unrealistic level of simplicity.

Some guidelines for the use of background infusions are given by Gaukroger, based on his experiences at the Adelaide Children’s Hospital [Gaukroger et al. 1991]. Gaukroger recommends a small infusion rate of no more than 1mg/hr of morphine and a consideration of the analgesic drugs. He advises against the use of a background infusion in the case of longer acting drugs such as methadone and recommends its use in the case of short-acting drugs such as fentanyl and alfentanil. These recommendations are based on experience in 400 patients over 3 years.

A recent double blind study of abdominal patients using PCA with and without a continuous background infusion found that improved analgesia was obtained in the first 24 hours in the background infusion group but that any positive advantages were absent thereafter and an increased number of complication resulted in day 2 and 3
[Dawson et al. 1995]. There was some evidence of catch-up in the morning of day 1 but none on days 2 and 3. It is interesting that this study has found a temporary use of a background infusion and the question is raised whether a higher bolus dose in the first 24 hours may have had a similar effect.

As a partial answer to the question of fixed background infusions McKenzie suggested a system with a background infusion which increased with increasing bolus demands and automatically decreased with diminishing demands [McKenzie 1990].

In conclusion, it appears that a well-chosen background infusion can indeed be beneficial in some circumstances, such as in the initial post-operative period and if it elevates the analgesic concentration in the patient to a level where adequate analgesia can be obtained with a reasonable number of button presses. The fundamental issue seems to be one of risk to benefit trade-off. Generally the total analgesic consumption seems to be higher for PCA using background infusions with opinion on the benefits as yet unclear.

Some studies conclude that the benefits of undisturbed sleep outweigh the risks of respiratory depression, while others report a slightly higher incidence of side-effects such as nausea. Generally background infusions have involved a higher incidence of human (programming) error and it seems also a slightly increased risk of complications.

### 3.2.4 Opioid Sparing Effects of PCA

Some researchers have reported that the total amount of opioids used in PCA was lower than that used in conventional pro re nata (p.r.n.) administration while also giving more satisfactory analgesia [Bennett et al. 1985, Lange et al. 1988, Ouchi et al. 1991]. This has become known as the opioid sparing effect of PCA and was reported as early as 1971 by Sechzer and by Roe in 1963 [Sechzer 1971, Roe 1963].

Not all research however supports the opioid sparing effect of PCA. The research carried out at the Royal Melbourne Hospital to date has not found evidence of lower opioid analgesic usage and neither have the studies by Tamsen, Kleiman and many other researchers [Tamsen 1986, Kleiman et al. 1987, Ferrante et al. 1988, Owen et al. 1988, Shade 1992].

Bennett claims a 31.5 % reduction in medication required using PCA compared with intramuscular administration [Bennett 1985]. The study involved 19 patients
undergoing gastric bypass surgery. The opioid sparing effect may be supported by a finding in psychology, called the locus of control theory and briefly outlined in section 2.4. Locus of control research has found that people who perceive that they have control over an aversive stimulus endure more severe aversive stimuli and for longer duration. It has even been postulated that dependence on a drug for pain relief may be relegated in favour of control over self in much the same way that patients seem to be willing to endure higher pain levels through the knowledge of being able to control it, should they choose to do so [Egan 1990a].

A study by Zacharias found a lower total dose of morphine consumption using PCA when compared to constant infusion [Zacharias et al. 1990]. It was pointed out in the study itself that this could be explained by the small bolus size (0.5 mg) on the PCA and the longer than usual lockout time of 10 min, such that the patients became tired of pressing the bolus request button repeatedly. It was also conjectured that some patients may have experienced anxiety and fear in making requests using the PCA. In addition, due to the inability to predict dose amounts from age, weight and height, the constant infusion amount had to be periodically adjusted and could have been higher than required for a significant proportion of the time.

One possible reason for the opioid sparing effect is the fact that in the p.r.n. regimen under-prescription of analgesic and further reduction by the nursing staff is common [Marks & Sachar 1973, Donovan et al. 1979]. It is possible that in the special PCA studies the amount given intramuscularly is much closer to the amount the patient should theoretically receive and that the customary further reduction by nursing staff is curtailed in an environment where special attention is focussed on the procedure of intramuscular injections at regular times. Cohen found that one third of nurses would give opioid analgesics ordered every 3-4 hrs p.r.n. only when requested by the patient, in addition to frequent under-administration of actual doses [Cohen 1980]. According to Cohen’s study, only one third of nurses used the severity of pain and only one quarter the patient’s response to the previous bolus as a criterion for determining the next dose. Thus there seems to be some reason to believe that the attention bestowed upon patients in research studies lead to closer adherence to the theoretical protocol for p.r.n. IM injections than is the case in a ‘normal’ clinical setting. This is one possible reason for reports that PCA uses less medication. Solicitously administered intramuscular injections can in principle become a kind of PCA.

The opioid sparing phenomenon can also be approached in the light of the MEAC versus diminution of pain debate. If the diminution of pain theory is correct, then
patients would press the bolus request button only until a reduction in pain is experienced rather than optimum analgesia at the MEAC level. This would then account for a reduced use of opioid analgesics.

If on the other hand the MEAC theory is correct, then one would expect patients to use the same or even slightly more analgesic in order to reach the MEAC level. Patients would then be expected to request boluses until MEAC and or optimum analgesia had been reached.

In a study by Egan et al. it was suggested that patients may be using PCA to treat the anxiety component of their pain and that treatment of the anxiety component seems to reduce the need for analgesic [Egan et al 1990b]. Thus a further variable to consider is the psychological component of PCA use in this regard.

It is very difficult to compare the amount of analgesic used in different methods of administration. The variation in patient parameters such as MEAC, absorption rate and peak analgesic concentration, and the subjective experiences and perceptions of the patients all add to the difficulties of direct comparison. Thus in view of the number of variables involved and the evidence both for and against the opioid sparing effect, it seems that there is no significant underlying principle that allows one to clearly argue for or against the phenomenon of reduced analgesic requirements using PCA. If there is a definite bias in one or the other direction, it seems to be so weak as to be easily obscured, as evidenced by the conflicting reports in the literature. On balance the evidence from most reports in the literature does not indicate an opioid sparing effect. This has also been the experience of trials at the Royal Melbourne Hospital to date.

### 3.2.5 Enhanced Recovery Using PCA

PCA has been credited with enhancing the recovery time from post-operative surgery and reducing post-operative complications. Bennett found that the incidence of post-operative pulmonary dysfunction was reduced in a group of patients using PCA when compared to patients on a conventional intramuscular (IM) regimen [Bennett 1985]. Thirteen patients who had undergone gastric bypass surgery were studied, six being randomly assigned to PCA and seven to regular IM injections. The results obtained from measuring forced vital capacity (FVC) and peak expiratory flow (PEF) indicated a significant (P<0.02) difference between the PCA group and the conventionally
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A treated group on days two and three following surgery. Increased ability to perform post-operative pulmonary exercises as well as less pain and sedation were noted in a report by Panfilli [Panfilli et al. 1988].

Reduced post-operative fever and a significant reduction in pulmonary complications were reported by Lange in a study comparing PCA with intermittent analgesic dosing [Lange et al. 1988]. Fewer post-operative chest abnormalities were also noted in the same study. Lange points out that the control and self-care the patient assumes in PCA are an immeasurable but important factor in the success of PCA in this regard. Other researchers such as Kleiman, noted only less nausea in the PCA group when compared with the group receiving regular IM injections [Kleiman 1987].

A study by Wasylak et al. found that PCA patients experienced less post-operative morbidity than those receiving intra-muscular morphine on a p.r.n. basis [Wasylak et al.1990]. PCA patients recovered faster, minute ventilation returned to normal earlier, ambulation recovered more rapidly, oral temperature became normal one day earlier and patients were able to leave hospital sooner (NB: these are not all independent variables). Wasylak found that the pain scores of patients in both groups were similar and speculates that it may be the actual method of administration rather than lower pain levels which contribute to the observed effect. Another possible interpretation is that the initial experience of pain was less and influenced patients expectations such that they were better able to cope with pain. This point is further enlarged upon in section 4.2.1 and touches upon the psychology involved in pain perception. A study by Finlay claimed a 22% decrease in the duration of the post-operative hospital stay when compared to conventional IM therapy [Finlay et al. 1984]. Reduced hospital stay was also noted in a study by Ouchi [Ouchi et al. 1991].

In some specialized cases PCA has not shown any clear advantages. A study of intramuscular analgesia versus PCA and its possible effects on prolonging post-operative ileus, found that PCA prolonged post-operative ileus but the overall hospital stay was not affected [Stanley et al. 1993].

In 1992 the United States Agency for Health Care Policy issued guidelines urging that doctors treat post-operative pain aggressively and quickly and noted that people with well controlled pain using for example self-medication devices, tended to be discharged earlier and suffer fewer chronic pain problems later [Leary 1992, APMGP 1992].
Research using a prototype of this PCA at the Royal Women’s Hospital, Melbourne, found that women who had undergone caesarean delivery were often able to leave their beds significantly earlier [Cribb 1992]. On the whole, the PCA group showed faster mobilization, however further trials are needed in this area.

In a survey of 116 nurses and 60 doctors at the Royal Melbourne Hospital 97% and 92% respectively believed that patients who received PCA or epidural analgesia were more comfortable than patients who did not and that better analgesia was associated with fewer complications and shorter hospital stays [Libreri 1995].

Enhanced recovery has been noted through psychological support techniques as well. Peck notes that providing patients with support and information about their forthcoming procedure had the effect of patients taking less medication on the second and third post-operative days, swifter recovery and fewer days in hospital [Peck 1986, Schmitt et al. 1973]. However information and support are not always beneficial if the patient is using an avoidant coping strategy [Gill 1992].

Although there are a number of reports that PCA seems to shorten hospital stay and enhance recovery when compared to IM/IV analgesia the evidence for this is tenuous at present, often not statistically significant and lacks double blind trials [Angel et al. 1992]. Enhanced recovery following PCA seems to have been observed often enough in a number of studies (see references this section) to warrant further investigation. any studies in this area are inherently difficult to perform due to the large number of variables such as hospital census, criteria of assessment, differences in nursing care to name just a few. It should also be noted that the precise mechanism for enhanced recovery has not been isolated and is probably not restricted to PCA only but may be a result of superior earlier comfort [Ready 1990b]. It may well be the case that some of the benefits of PCA have their foundations in psychology as well as the dynamics of pharmacology [Egan et al. 1990b]. Enhanced recovery as such seems based on adequate pain relief and PCA is one method which claims to be capable of providing satisfactory analgesia.

### 3.3 PCA and Safety

The experience with PCA has been very positive on the whole. Patients are generally pleased with the system and are generally more alert, mobile and better able to participate in physical therapy and other therapeutic regimens than patients on IM
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pain relief. Nurses gain the benefit of happier patients and reduced time spent administering analgesia, which makes for a more pleasant work environment. Given the large number of PCA systems in use, relatively few problems have been reported. Those problems which do exist can be subdivided into three categories:

1) Side-effects and adverse reactions,
2) Device-related mechanical problems,
3) User-related problems.

3.3.1 Safety: Side-effects and adverse reactions

Although the majority of reports claim no difference between PCA and regular intramuscular injections in the incidence of minor side-effects, such as nausea and vomiting, some researchers such as Welchew have reported increased nausea scores for PCA patients [Welchew 1983]. However, Welchew’s study failed to show any cyclic variations in nausea coinciding with the 4 hourly injections nor any differences in pain scores or sedation scores between the PCA and intramuscular group. More importantly the PCA group received fentanyl, while the regular intramuscular group was given morphine. Increased nausea could have been due to the different drugs used. Callan in a paper on complaints and complications of using PCA points out that most adverse reactions using PCA can be attributed to the drugs used in PCA rather than to the device itself [Callan 1990].

A recent study by Robinson found no significant differences in side-effects between intramuscular regimens and PCA [Robinson et al. 1991]. Bollish specifically studied the attendant side-effects of PCA versus regular intramuscular injections in a crossover study of 20 abdominal surgical patients [Bollish et al 1985]. It was found in this study that the PCA patients experienced less nausea and vomiting and less euphoria than those on regular intramuscular injections. However, the number of patients was too small to allow definitive statements about PCA to be made. There were a number of variables, such as residual anaesthetic, individual surgical differences and positioning of the nasogastric tube, which could have influenced the outcome of a study involving only 20 patients.

The general consensus about PCA seems to be that it does not modify the incidence of side-effects significantly. A small study (2 groups of n =10 each) found that in the case of epidurally patient-controlled morphine this was a safer method with regard to respiratory side-effects when compared with intermittent bolus injection [Nozaki-Taguchi et al. 1993]
Respiratory depression can be a major side-effect of the use of opioids by any method. It is Callan’s opinion that although this risk is always present, it is low in PCA [Callan 1990]. There is no evidence to suggest that PCA as a modality is more likely to produce more respiratory depression than conventional pain regimens.

### 3.3.2 Safety: Device-related mechanical problems

Despite initial fears concerning the reliability of PCA devices, there have been relatively few mechanical failures. The mechanical problems which have occurred include: siphoning, overdelivery, underdelivery and record-keeping errors.

Siphoning has occurred in systems using prefilled glass vials for PCA. When the vial was accidentally cracked, air was able to enter into the system and cause a constant flow of opioid into the patient. Manufacturers have taken various measures to substantially reduce the risk of siphoning [Callan 1990].

Grover reports an incident in which the glass syringe became disengaged from the drive mechanism [Grover et al. 1992]. Grover recommends that PCA equipment be placed at or below the patient heart level to prevent syphoning problems. A further safety measure would be the use of an antisypnoning valve.

Overdelivery has occasionally been reported, often due to a misunderstanding of the method of initiating a loading dose. Software in the pumps has been modified to remove any ambiguities in administering a loading dose. Overdelivery due to corruption of the control program by static electricity was reported by Notcutt [Notcutt et al. 1992].

Underdelivery has usually occurred when the pump aborted an infusion due to an alarm condition and this fact had not been recognized.

Record-keeping errors have usually involved software errors in calculating the amounts administered by the pump.

An automated system for testing the accuracy of PCA pumps has been developed by Hawkins [Hawkins 1992].

The use of antireflux valves in conjunction with PCA devices has become widespread. Antireflux valves prevent retrograde pumping of analgesic agent into to the tubing of a parallel gravity-driven infusion in the event that the intravenous cannula becomes obstructed [Kluger et al 1990b]. The Administration sets incorporating an antireflux valve can achieve a stored volume if occluded and
subsequently release this stored volume as a bolus when the occlusion is removed. Kluger and Owen investigated a number of common administration sets for their stored volume and found that those sets which had low stored volumes significantly hindered the maximum flow of fluid administration and that conversely those sets which presented no significant fluid flow resistance had larger stored volume [Kluger et al 1990b]. They therefore recommend the use of dilute solutions in PCA to minimize the effect of releasing stored volume after occlusion. Kluger et al. argue that with regard to safety the disposables not be neglected but be considered as important as the pumps in PCA therapy.

From the literature it seems that the following safety features are required for disposable PCA administration sets:
1) An antisyphon valve.
2) A one way valve close to the syringe and within the locked part of the PCA to prevent tampering as reported by Stevens [Stevens et al. 1991].
3) An antireflux valve.

One is tempted to speculate whether all these valves could not be combined in one special purpose PCA administration set in the future.

3.3.3 Safety: User-related problems

According to Callan, a review of the American Food and Drug Administration’s (FDA) Medical Device Report (MDR) showed that 67 % of problems with PCA were related to user error [Callan1990]. In his paper on mishaps with PCA, White cites two cases in which user programming errors were responsible for respiratory depression [White 1987]. The user interface has been specially singled out for attention in the University of Melbourne PCA such that no user programming for individual patients is required. The system automatically adapts to individual patient demands and monitors various patient parameters. There is thus no possibility of clinical staff accidentally misprogramming this device. From a nurse’s point of view, this PCA device should require little more than turning the system on, connecting any additional monitoring equipment, and setting the infusion pump. Apart from entering the patient’s name and pressing the PCA program start button on the computer, no actions that are outside standard clinical nursing protocol are required.

Tampering involves the deliberate reprogramming of PCA parameters by the patient. Usually the patient has a history of drug abuse and reprograms the device for
higher infusion rates. Locks and access codes have been used with limited success. Stevens reported a case of tampering in which a patient managed to extract large amounts of opioid [Stevens et al. 1991]. In this particular case the patient used his intravenous tubing to extract opioid using negative pressure and retrograde filling of the syringe with air. To prevent this kind of tampering Stevens recommends the use of a one-way valve between the PCA syringe and the first intravenous access port. The valve should be placed in the locked part of the PCA system.

3.4 Predictors of Analgesic Usage

In order to find the optimum level of analgesic required by a patient, a number of predictive methods have been employed. Some have had limited success in giving a rough indication of the amount of analgesia an individual might require. However individual variations are too great to reliably administer analgesic dosage based on the methods developed so far. Indeed no claims to that effect have been made. Letting patients determine their own analgesic requirements seems to be the best solution to date. It also involves a degree of self-responsibility which may have potential beneficial effects.

3.4.1 Physiological Predictors of Analgesic Usage

Traditionally, body weight and surface area have been used to calculate analgesic dosage requirements, but there seems to little evidence for this practice according to a number of researchers [Bellville et al. 1971, Kaiko et al. 1983]. Parameters such as age, sex, and rate of elimination appear to show little correlation with the therapeutic analgesic concentration levels which patients select themselves using PCA [Tamsen 1986, Tamsen et al. 1982 b]. Zacharias found similar results when trying to predict the morphine requirements for patients based on age, weight and height [Zacharias et al.1990]. This difficulty has substantially contributed to the development of PCA.

3.4.2 Psychological Predictors of Analgesic Usage

An Adaptive System for Patient-Controlled Analgesia
The effectiveness of PCA depends not only on pharmacokinetic and pharmacodynamic factors but also on the psychological complexities of the patient, which can modify and overshadow the purely pharmacological effects. As a result a number of attempts have been made to correlate the wide range in analgesic requirements of patients with psychological parameters.

There has been some limited success in predicting the amount of opioid required by different groups of people based on different methods of psychological classification. One must however keep in mind that these findings only apply to groups of people. Given the current state of knowledge, individual requirements within these groups are still likely to be too diverse to make a dosage regimen based on psychological testing adequate by itself.

Any scheme to predict the analgesic requirements of individuals, must bear in mind the sharp transition between severe pain and analgesia and the often rather small window between analgesia and excessive sedation [Austin et al. 1980]. This places great emphasis on the accuracy of any predictive scheme.

### 3.4.2.1 Coping Style as a Psychological Predictor to Analgesic Usage

Bennett and Wilson found that the patient’s coping style had some influence on the amount of analgesic consumed [Bennett 1985, Wilson et al. 1984]. Not surprisingly, patients with high levels of emotional control and independence required significantly less analgesic than patients with low levels of emotional control. Also patients whose coping style was described as highly aggressive used more analgesic than patients who were classified as more passive in their coping style [Wilson 1984].

Gourlay found that the most successful questionnaire, the Illness Behaviour Questionnaire, accounted for only 19% of the interpatient variation in dose requirements [Gourlay et al. 1988]. Gourlay could not confirm that patients who scored highly on extroversion and neuroticism scales required more opioid.

Psychological questionnaires seem to have some limited predictive ability which seems to vary with different studies and types of questionnaires.

### 3.5 The Control Engineering Approach to PCA

An Adaptive System for Patient-Controlled Analgesia
A number of researchers have used the technology of control engineering to model both the patient and the patient-controlled analgesia pump as one system, in what has been called the ‘patient pain model’. Some noted researchers in this field are Jacobs et al. (1985, 1986) and Feng-Yu et al. (1990). Jacobs models pain relief as a classical control problem, as shown in figure 3.2 [Jacobs et al. 1986].

![Diagram](image)

**Figure 3.2 A control engineering approach to PCA**

The output of the clinical procedure in the form of analgesic "u", aims to control the perceived pain "y" in the presence of discomfort. Discomfort originally consists of pain from surgery, but is made up of physiological, pharmacokinetic, psychological and clinical factors, which are time-varying, patient dependent and situation dependent. In control engineering this situation usually calls for the use of feedback. Jacobs points out that the feedback loop in the conventional 4 hourly bolus injection regimen is based on the nurse’s decision to intervene, which in turn is based on her observation and interpretation of the patient’s pain. Jacobs notes two reasons why this kind of feedback is fraught with problems: "(i) There can be loss of information, or excessive noise, in the feedback path between the patient’s pain and the nurse’s observation. Some patients may not like to complain of pain and others may be overfearful. Most nurses will have many other tasks on hand besides monitoring an individual patient’s pain. (ii) The discrete-time control interval of order 4h is very slow compared to the times over which pain may vary and compared to the pharmacokinetic time constants for many analgesics." [Jacobs et al. 1986]. It may be relevant to point out again that in a study of 121 nurses only one third used the severity of pain and one quarter the patient’s response to the previous medication as a criterion for determining the next dosage [Cohen 1980]. The evidence points to an inadequate feedback path.

The model subsequently developed by Jacobs closely mimics the button-pressing records of actual patients using PCA. Trials on 20 patients and 500 simulated trials on
randomized mathematical models of patients yielded promising results. Proportional, stochastic and hybrid models were evaluated and the hybrid model was recommended in the final analysis. In view of the safety monitoring devices used in the University of Melbourne PCA system, it is interesting to note that Jacobs puts forward the lack of safety monitoring as an impediment to the practical implementation of his algorithms [Jacobs et al. 1986].

Feng-Yu has included a pharmacokinetic model of analgesia and used a modified Smith delay compensator to model the inherent nonlinearity of the system. The system is inherently nonlinear, because there is no button pressing after adequate analgesia has been achieved. Simulations have shown that the pain model developed emulates actual button-pressing records of patients using commercial PCA equipment. The simulated patients obtained good pain relief without undue button pressing or excessive opioid concentrations [Feng-Yu et al. 1990].

In view of the above, it should be pointed out that Gourlay et al. found that large fluctuations in the hourly dose rate of fentanyl do not accurately reflect the constant blood concentration-analgesic effect relationship [Gourlay et al. 1988]. Hence there is danger in using button pressing frequency as a sole criterion by which to judge the appropriateness of a control algorithm.

A sophisticated control system incorporating fuzzy control performed well in simulations in work carried out by Carollo et al. [Carollo et al. 1993]. This system used a 10 point scale to quantify pain and incorporated an algorithm to automatically decrease the infusion if the zero pain setpoint had been maintained for certain stretches of time.

3.6 The Economics of PCA

For PCA to become a more widely accepted modality of pain control, it must be shown to be financially viable and competitive in an increasingly cost-conscious environment. A number of studies have been carried out to show that despite initially higher capital costs, PCA can compete with traditional methods of pain relief such as intramuscular p.r.n. injections, although not always on cost alone. A study by Levi and Osborne in 1986 showed that the average hospital stay including equipment, medication and nursing time with PCA was 1.73 times as expensive as conventional
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pain relief methods [Levi et al. 1986]. A study by Jones in 1989 claimed PCA costs including drug, supply, equipment and labour costs for the first 48 hours were $14.97 versus $8.35 for intramuscular injections, representing a ratio of 1:1.79 [Jones et al. 1989]. In both Levi’s and Jones’ study, patient satisfaction with and preference for PCA was noted, and this was thought to have real, though less quantifiable benefits, for the hospitals concerned. A study using only medical records in a Californian hospital showed a ratio of intramuscular to PCA costs of 3:1 [DeFede et al. 1989]. This study seems to have excluded equipment costs, which may account for the substantially lower cost of PCA.

An analysis by Ready of three hospitals introducing PCA in the Seattle area showed that the daily hospital costs of providing analgesia per patient was generally almost equal for PCA and intramuscular administration [Ready 1990]. Costs in (US dollars) varied between $12.07 to $19.56 for PCA and $13.57 to $20.88 for intramuscular administration. One hospital was reported to generate a revenue of $5000 per month on PCA through a system of leasing PCA pumps. Ready makes the point that the marketing potential through patient preference for PCA must not be underestimated.

It seems that although PCA has undisputable higher initial capital costs than conventional methods, through appropriate management the cost of PCA can be kept within reasonable bounds. There are also a number of non-financial benefits to PCA which ultimately contribute to a more enjoyable stay for patients and less chance for readmission. Thus although hard to quantify in its specifics, good post-operative pain control and superior earlier comfort seem to pay dividends in terms of fewer complications and enhanced recovery which lead to cost reduction [Ready 1990b, MacIntyre et al. 1993].

3.7 Patient and Nurse Satisfaction

Generally speaking, PCA has been well received by both patients and hospital staff and the literature is replete with favourable reports. Some patients are not suited to PCA, such as the hypovolemic, the confused or those with a prior history of drug abuse. Of the patients using PCA, the vast majority expressed a preference for PCA, particularly those who had experienced conventional intramuscular pain relief at some prior stage.

An Adaptive System for Patient-Controlled Analgesia
3.7.1 Patient Satisfaction

As early as 1971 Sechzer noted that patients were “generally satisfied” with PCA [Sechzer 1971]. Bennett et al. found that of the patients who had experienced both PCA and IM injections, PCA was the preferred choice [Bennett et al. 1982]. In an extensive special survey by Kluger of 74 patients who were asked to list their opinions regarding the advantages/disadvantages of PCA, the following responses were collected [Kluger et al. 1990], see Tables 3.1, 3.2 below.
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### Advantages of PCA (n=74). Patient responses.

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Not bothering the nurses. Nurses too busy with others</td>
<td>30 (37.5%)</td>
</tr>
<tr>
<td>2. Rapid onset of pain relief</td>
<td>27 (33.8%)</td>
</tr>
<tr>
<td>3. In control of own pain</td>
<td>16 (20%)</td>
</tr>
<tr>
<td>4. Self-control, not losing autonomy</td>
<td>15 (18.8%)</td>
</tr>
<tr>
<td>5. Titrate exactly to needs</td>
<td>15 (18.8%)</td>
</tr>
<tr>
<td>6. Lack of injections</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>7. No benefit</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>8. Independence</td>
<td>5 (6.3%)</td>
</tr>
<tr>
<td>9. Reduction in the amount of pain</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>10. Reassurance</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>11. Not relying on nurses assessment of pain</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>12. Stable pain relief</td>
<td>3 (3.8%)</td>
</tr>
<tr>
<td>13. Helps research</td>
<td>3 (3.8%)</td>
</tr>
<tr>
<td>14. Mobilisation better</td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td>15. Will not worry other patients</td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td>16. Reduction in amount of drugs</td>
<td>1.1(1.3%)</td>
</tr>
<tr>
<td>17. Privacy</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>18. Control over nausea</td>
<td>1 (1.3%)</td>
</tr>
</tbody>
</table>

Table 3.1 Patient responses to PCA, the advantages. The questions asked were: "We would like to have your opinions on the advantages/disadvantages of using the equipment which allows patients control of their own pain relief (PCA). In the spaces below list any advantages/disadvantages in using PCA from your point of view." (From: Kluger M. T., Owen H., "Forum: Patients’ expectations of patient-controlled analgesia", Anaesthesia, Vol 45 pp1072-1074, 1990)

### Disadvantages of PCA (n=74). Patient responses.

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No disadvantage</td>
<td>36 (45%)</td>
</tr>
<tr>
<td>2. Overdose</td>
<td>9 (11.3%)</td>
</tr>
<tr>
<td>3. Lack of nurse contact, less personal contact</td>
<td>9 (11.3%)</td>
</tr>
<tr>
<td>4. Over use, taking too much</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>5. Machine dysfunction</td>
<td>5 (6.3%)</td>
</tr>
<tr>
<td>6. Inadequate analgesia</td>
<td>5 (6.3%)</td>
</tr>
<tr>
<td>7. Addiction</td>
<td>3 (3.8%)</td>
</tr>
<tr>
<td>8. Insecurity</td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td>9. Over sedation</td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td>10. No compassion</td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td>11. Expense</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>12. Restrict movement</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>13. Needs intravenous cannula</td>
<td>1 (1.3%)</td>
</tr>
</tbody>
</table>

An Adaptive System for Patient-Controlled Analgesia
Chapter 3 Literature Review

Table 3.2 Patient responses to PCA, the disadvantages. The questions asked were:
"We would like to have your opinions on the advantages/disadvantages of using the equipment which allows patients control of their own pain relief (PCA). In the spaces below list any advantages/disadvantages in using PCA from your point of view."

Both the PCA and the IM patients were instructed that pain relief was available at the push of a button, either from the nurse call button or the PCA pendant. It is interesting to note that the majority of patients (37.5%) regarded not having to ‘bother the nurses’ as the main advantage of PCA, with rapid onset of analgesia perceived as the second most important factor (33.8%). A large number, 36 (45%) of patients saw no disadvantages in PCA, while 9 (11.3%) were concerned about overdose and the same number about lack of personal contact. It can be seen that patient-nurse interaction is a major consideration in these patients’ minds and precedes, albeit slightly, their consideration of the actual equipment used.

Kluger mentions that pre-operatively many patients saw a reduction in contact with nursing staff as the main disadvantage of PCA [Kluger et al. 1991]. It seemed that the method of pain control was perceived by patients as equally important as the actual amount of pain alleviated.

From a 1983 study by Donovan it appears that there is a discrepancy between patients’ reports of pain and their satisfaction with traditional analgesic therapy [Donovan 1983]. Eighty six percent of the surveyed patients reported satisfactory pain relief, yet 62 % reported significant pain. Upon closer examination of the patients who reported satisfaction, 75 % said that they were satisfied because they expected pain after an operation and 52 % said they were satisfied because the pain was less than expected [Donovan 1983].

Chronic pain prior to an operation can also influence patients’ use of PCA. There seems to be some evidence that chronic pain sufferers do not use PCA to achieve optimum pain relief, but instead titrate to a moderate pain level. This was shown in a study by Ferrante and co-workers, who found that elderly chronic arthritic patients who had undergone total knee replacement, titrated themselves only to “moderate” pain as opposed to “complete” analgesia [Ferrante et al. 1988]. A study by Magnani also found chronic pain sufferers tended to aim for a ‘moderate’ pain level compared to a ‘mild’ level of pain for acute pain patients [Magnani et al. 1989].
Structured pre-operative education rather than only the usual preparation provided by the physicians in the use of PCA is another factor contributing to patients’ ability to manage their pain [Timmons et al. 1993]. The group of patients who received structured education were able to manage their pain better. This would be expected to result in increased patient satisfaction.

Patients’ general perceptions of recovery and support and their level of anxiety also seem to play an important role in determining patient satisfaction [Jamieson et al. 1993].

Notwithstanding the real psychological benefits of PCA, a study by Moller that investigated the presence of the stress-hormones, adrenaline, noradrenaline, dopamine, cortisol, growth hormone and prolactin, failed to find any significant differences between the PCA and the intramuscular group [Moller et al. 1988]. It seems that somatic stress is not fundamentally affected by the modality of analgesic delivery. This is not a surprising result in view of the fact that the hormone types measured represent the most basic aspect of the body’s stress response rather than psychic or anxiety stress. It is also not clear whether the stress hormones studied respond in a linear gradation to stress or in a step response after a certain threshold has been reached. Claims for PCA and lower stress levels relate mainly to psychological stress and it seems reasonable to presume that after a major stress-inducing trauma, such as surgery, any effects PCA may contribute towards the lowering of stress hormone levels may be masked by the severity of the total experience.

3.7.2 Nurse Satisfaction

PCA has generally been favourably received by nurses, despite the fact that it is still a relatively new modality and suffers from the handicap of technological unfamiliarity and complexity. Nurses’ satisfaction or otherwise is made up of two components, one being PCA as a modality itself, the other the effect of PCA on patients. In a study by Kleiman, comparing PCA with conventional methods, it was noted that PCA was accepted well by nurses, because patients were able to walk sooner after surgery, were more tolerant of repositioning and were better able to cough and breathe post-operatively [Kleiman et al. 1987]. Kleiman also noted that patients seemed enthusiastic about PCA and the personal control over their own medication which
PCA afforded them. Hence nurse satisfaction with PCA stems to a degree from patient satisfaction.

Regarding PCA itself, Falk reports that the consensus of nursing opinion at her hospital, the Brigham and Women’s Hospital, was that PCA is superior to the standard intramuscular (IM) method [Falk et al. 1990]. This seems to be the overall opinion within the nursing profession. Falk sees PCA as contributing in moving health care towards more holistic patient-oriented pain relief [Falk et al 1990].

In a study on patient and nurse satisfaction, Jones attributes to PCA an improvement in the quality of nurse/patient relationships due to 1) more cooperative patients, 2) less time needed to administer analgesics, 3) patient satisfaction, 4) decreased anxiety of patients [Jones et al. 1989]. Thomas found a similarly encouraging response to PCA amongst nursing staff and patients [Thomas 1993].

### 3.8 Alternative PCA Systems

A PCA system in which the patient regulates the continuous infusion rate to meet time-varying needs for analgesia has been reported by Hill and associates [Hill et al. 1991]. In that system, the individual pharmacokinetic profiles using bi- and tri-exponential models of the plasma morphine concentrations are calculated for each patient based on prior measurements by high performance liquid chromatography (HPLC). According to Hill, the system was found to be a safe and effective alternative to only bolus-driven PCA. It was however necessary to use individually predetermined pharmacokinetic parameters.

A system in which the bolus was varied according to the pain intensity has been investigated by Buisan [Buisan et al. 1992]. In this system patients were asked by a nurse to rate their pain on a 5 point verbal pain scale. The verbal scale was then translated into a range of bolus amounts administered by a nurse. Statistically significantly fewer total doses of morphine were claimed for the group in which the bolus demand was varied with pain when compared to two other control groups. The differences were most pronounced in the first 2 to 6 hours of PCA use.

A system using fentanyl in which a continuous background infusion was adjusted as a function of the number of bolus requests in the preceding 16 minutes was trialled by Hull et al. in a paper in 1979 [Hull et al. 1979, Hull 1985]. The system aimed at providing 50% of patients needs as an infusion.
More recently, a PCA system using a handset which allowed patients to request 3 different bolus sizes (0.5, 1.0 1.5 mg morphine) was tested on 10 patients by Owen [Owen et al. 1995]. Preliminary results indicate that the system warrants further investigation and has been well receive.

3.9 Summary

It can be seen from the literature reviewed above that PCA therapy is not a static modality and that there are a number of issues which warrant further investigation. Apparent conflicts regarding enhanced recovery, the opioid sparing effect, as well as the use of constant background infusions and the MEAC debate are some the issues raised by PCA therapy. The temporal variation of pain and the range of pain sensitivities in humans as well as the psychological components of pain have also been highlighted through PCA technology.

Currently PCA is used in three major areas: Oncology, post-operative pain and obstetrics. The principles of PCA are the same in all three cases, although some parameters such as the lockout period, bolus size and the analgesic agents vary. PCA in general has been a very successful modality when compared to scheduled intramuscular or intravenous analgesic administration and looks likely to gain even greater acceptance in the future.

The introduction of PCA represents a shift in thought concerning patient care, in that the patient is placed in charge of a major aspect of the clinical regimen. PCA can be seen as a part of a trend for greater patient participation in health care and a growing emphasis on the patient's responsibility for his or her own health.

The current state of PCA technology represents a definite advance in post-operative pain relief. It has allowed a deeper insight into the field of applied analgesia and has in turn raised many new questions about the human experience of pain.
Chapter 4  Theory of the Adaptive PCA System

4.0 Introduction

This chapter details the proposed PCA system and provides the theoretical framework for that proposal. The need for improvements in conventional PCA was outlined in section 1.2 and discussed more fully in chapter 2.

The proposed PCA system is intended to provide superior pain relief to that obtained with conventional bolus only or bolus plus fixed infusion systems. Four approaches make up the new system, these are:
1) Variable bolus administration and a variable self-adjusting background infusion.
2) A high adaptation feature for safely administering unusually high amounts of analgesic.
3) A specially designed handset allowing the patient to register varying levels of pain intensity and to receive appropriate analgesic amounts.
4) An expert system knowledge base embedded within the control algorithms of the system.

4.1 A Theoretical Framework for the Self-adjusting, Variable Background Infusion

This PCA system attempts to reconcile the apparent conflicts in the infusion debate as well as to make a new contribution to the field by employing a variable self-adjusting background infusion. The background infusion rate in this PCA system varies as a function of the bolus amounts administered and the time since the last bolus was administered.

The theoretical framework for the varying background infusion used in this PCA system rests on three main arguments evidence from the literature, empirical observation and best clinical practice. Each of these arguments is elucidated below.
4.1.1 Arguments for a Variable Background Infusion from the PCA Literature

The use of a background infusion in PCA does not receive unequivocal support in the literature and is considered by some not to be a true part of the PCA philosophy [McCoy et al 1993]. Section 3.2.3 gives an outline of the debate surrounding the use of a background infusion to date.

From the literature it is clear that patients experience analgesia at different analgesic levels and that these levels vary somewhat over time [Hill & Mather 1993]. Time-variation in particular has been a problem in using constant infusion analgesic methods.

The postulate offered here is that it has been difficult to clearly establish the utility of background infusions in PCA because the infusion level neglected to take into account variations in time such as the plasma levels at which individual patients experience analgesia as well as chronesty and chronopharmacokinetics. Four to six fold interpatient variations of the level at which patients experience analgesia have been reported [Hill et al. 1993, Bennet et al. 1985, Gourlay 1988]. The advantages of a background infusion are were also shown to vary over time in a study by Dawson et al. [Dawson et al. 1995]. Dawson found that while a 1mg/h infusion was beneficial for abdominal surgery patients over the first 24 hours there was a definite increase in complications for the subsequent 48 hours.

A major tenet of PCA is the acknowledgment of the large variability of pharmacokinetic and pharmacodynamic parameters affecting opioid analgesic responses between patients [Hill et al. 1993]. Given this recognition it seems reasonable to also recognize this fact in the matter of background infusions; yet most research which compared bolus only PCA to PCA with background infusion used a constant infusion level or at best an occasionally adjusted level for some patients [Zacharias et al. 1990]. It seems more consistent with the underlying philosophy of PCA to also make the background infusion respond to inter- and intra-patient variations in opioid responsiveness.

The button-pressing behaviour of individual patients is unique and reflects various pharmacologic, psychologic and sociologic influences in response to pain. It is
postulated here that, by using the unique button-pressing profile of individual patients as the basis for determining the level of the background infusion, the background infusion may be more effective. This postulate is offered in an attempt to contribute to the current debate regarding the effectiveness or otherwise of background infusions in PCA.

It should be noted that patients’ button-pressing behaviour is the result of complex factors made up as pointed out above of a variety of complex pharmacologic, psychologic and sociologic influences and that the background infusion used in this PCA system is based indirectly through bolus requests on all these factors not only on pharmacologic parameters. Whether patients titrate to a definite MEAC level or not, the background infusion takes its cue from the same factors which affect the button-pressing behaviour of the patient. The proposed infusion algorithm forms an integral part of the whole system.

4.1.2 Empirical Evidence for a Variable Background Infusion

It has been the experience of the clinical staff involved in the development of this PCA that in practice a constant infusion is often used to supplement the traditional PCA pump. Thus, actual clinical practice indicates the desirability for a supplementary infusion. A number of modern PCA machines have the capability for constant background infusions, thus indicating the desirability of at least giving that option to clinicians. The danger of constant infusions is that the patient’s requirements may change over time without the infusion level being adjusted to the changing conditions with the result that the infusion level may either become inadequate or build up to dangerous levels. Furthermore, there seems to be some evidence that constant infusions may be responsible for a slightly increased incidence of nausea and respiratory depression [Owen et al. 1989b, Libreri et al. 1994, Doyle et al. 1993, Wu et al. 1990].

4.1.3 Best Clinical Practice and Variable Background Infusions

A further reason for using a bolus-dependent variable infusion is that this method most closely mimics best theoretical clinical practice in the opinion of the clinical experts involved in the development of the proposed adaptive PCA system. If a nurse
and pain specialist were assigned full-time to one particular patient to provide the best possible pain relief, a low dose, frequently adjusted background infusion would usually be part of the optimal treatment for pain relief. The emphasis here is on ‘frequently adjusted’. The PCA described in this thesis attempts to emulate best clinical practice as closely as possible by making the background infusion self-adjusting as a function of time and the amount of the last administered bolus dose.

4.1.4 Formulation of the Variable Background Infusion Algorithm

Up to this point the main arguments for using a variable infusion per se have been expounded. It remains to clarify the rationale for the development of the particular algorithm decided upon in this PCA system.

The algorithm has been designed to correspond as closely as possible to the strategy used by expert clinicians and is based on existing clinical protocols of what would be expected in a manual non-PCA situation. Thus an infusion algorithm was outlined in which the infusion level increased with higher and more frequent bolus demands, remained stable for some time and decreased over time in the absence of bolus requests.

Determining the exact numerical values for step changes and the length of time the infusion is maintained at various levels involved consultation with the clinicians of the Royal Melbourne Hospital. One of the algorithm constraints was the requirement that the infusion component of patients’ analgesic requirements always be less than 50%. This has led to the infusion increasing only in response to bolus requests greater than half of the maximum available. Assuming a system for IV morphine, a step increase of 0.5mg/hour was decided upon as being a reasonable balance between safety and pharmacodynamics. In the event of the maximum available bolus being chosen the step increase is 1mg/hour.

As there are no negative demands (or negative pain) which could serve as control parameters, the algorithm has been designed such that the infusion never increases except in response to an administered bolus above a certain threshold. In the absence of bolus requests, the infusion rate steps down automatically and after a maximum of three hours the infusion rate reverts to zero. Thus the time interval in which no requests are made is taken as the default control signal to initiate a reduction in the infusion rate. This step-down feature is important in that it ensures that the patient remains in control and prevents the background infusion alone from...
attempting to provide the total analgesic requirements of the patient. The automatic step-down feature was also motivated by safety considerations.

The step-down values of -0.5mg/hour were chosen on the basis of pharmacological considerations and established clinical protocol for similar infusion reduction procedures.

After a period of 3 hours of no bolus requests the infusion ceases altogether. This feature was motivated by safety considerations in that the last indication of analgesic requirements (a bolus request) was deemed sufficiently remote to use for meaningful control purposes other than to suspend further analgesic administration.

The variable infusion algorithm was tested in nine patient trials involving earlier versions of this system. No one ‘best’ solution was possible but rather a compromise/trade-off of a variety of issues resulted in the current solution. Consultation was an ongoing process involving discussion with the clinical staff throughout the project’s development.

Table 4.1 clearly summarizes the background infusion algorithm used in this system. The infusion level depends on the frequency and the size of the requested boluses as well as the time since the last bolus was administered.

<table>
<thead>
<tr>
<th>Time</th>
<th>Bolus size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last Bolus given:</td>
<td>≤ 2.5 mg</td>
</tr>
<tr>
<td>Immediately following</td>
<td>&gt;2.5mg&lt; 5.0mg</td>
</tr>
<tr>
<td>bolus admin.</td>
<td>= 5.0 mg</td>
</tr>
<tr>
<td>60 minutes after last bolus</td>
<td>decrease 0.5mg/hr</td>
</tr>
<tr>
<td>request</td>
<td>continue</td>
</tr>
<tr>
<td>120 minutes after last</td>
<td>decrease 0.5mg/hr</td>
</tr>
<tr>
<td>bolus request</td>
<td>stop infusion</td>
</tr>
<tr>
<td>180 minutes after last</td>
<td></td>
</tr>
<tr>
<td>bolus request</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.1 The normal range background infusion as a function of the previous bolus size and time elapsed since the last administered bolus. Note: for boluses of less than 2.5mg the infusion is unaffected.

4.1.5 Risk Management in the Background Infusion
The point raised by White regarding an adequate risk-to-benefit analysis for a basal background infusion is a valid one [White et al. 1992]. It is suggested that the infusion algorithm proposed in this PCA does indeed provide added benefits while reducing two of the principal risks normally associated with background infusions.

One of the main risks posed by a background infusion concerns manual programming errors. Indeed the majority of PCA mishaps involving the background infusion rate originated from user programming errors [Callan 1990, White 1987]. The background infusion in the proposed adaptive PCA system requires no manual programming for individual patients. The background infusion is a totally integral part of the PCA algorithm and is effectively transparent from the user point of view.

A further risk of fixed background infusions is that a patient’s falling background infusion requirements could push a previously adequate infusion level into the overdose region. In order to reduce this risk the infusion level in the adaptive PCA decays in a series of steps if no bolus request are made for extended time periods. The current rate of decay is that in the absence of bolus requests any background infusion level will reach zero in a maximum of 3 hours. This decay rate has been thought to be higher than the rate at which patients needs and tolerances change over time.

Trials on nine post-Caesarean patients at the Royal Women’s Hospital in Melbourne, using a prototype of the current system and including a similar background infusion algorithm, have reported no incidence of excessive sedation, nausea or vomiting. While many more trials are required to properly test the system, these initial results provided additional confidence in using the background infusion algorithm described in this system.

By removing/reducing the risk of human manual programming errors and using a self-reducing infusion level the major risks of background infusions have been addressed and it is hoped that the benefits will have a better opportunity to manifest themselves.

4.1.6 Conclusion for the Variable Background Infusion Proposition

The original purpose of background infusions was to prevent pain from waking the patient when plasma levels fell too low during periods of sleep. It is thought that the proposed infusion strategy will better fulfil this original purpose by supplying a
maintenance level of analgesic tailored to the level which is most effective for each individual patient.

It should be noted that the background infusion proposed here does not aim to eliminate the need for bolus requests, meaning that the infusion alone is never intended to provide adequate analgesia. The patient is expected to make bolus requests while the background infusion provides an analgesic plateau not only in periods of sleep but continually.

The unique feature of the background infusion in this PCA is that the infusion level is dependent on the button-pressing behaviour of the patient. As such the infusion level reflects each patient’s individual analgesic requirements over time. Given the large variation in the effective analgesic levels between patients, it is postulated that the strategy of tailoring the infusion level to the unique button-pressing behaviour of each patient will go some way towards resolving the current debate surrounding the use of background infusions in PCA.

### 4.2 A Theoretical Framework for the High Adaptation Range

There are two main arguments for the provision of short-term high-level analgesia in the postoperative environment.

The first argument addresses the immediate postoperative period. Good early postoperative analgesia has been found to improve the quality of the overall hospital experience and to reduce a patient’s general discomfort in the days following surgery.

The importance of good early pain relief is stressed in the guidelines issued by the United States Agency for Health Care Policy for the treatment of patients suffering from surgery pain. The guidelines recommended that doctors provide painkillers swiftly and aggressively to decrease suffering and speed recovery [Leary 1992, APMGP 1992]. The guidelines also state that pain once established and severe is more difficult to control. In addition the guidelines show that inadequately managed pain can inhibit recovery, prolong hospitalization and even cause actual physical damage to the patient.

Clinicians involved in this project at the Royal Melbourne Hospital, have also found that a key feature of good early analgesia is the provision of sometimes rather
large amounts of analgesic in the first twelve hours post-operatively in order to ensure adequate early analgesia.

It is generally believed that postoperative pain is easier to control than once it is established. Ready suggests that it may specifically be superior earlier comfort which could be responsible for some of the benefits of PCA therapy such as earlier recovery and fewer complications [Ready 1990b].

Of 116 nurses and 60 doctors survey at the Royal Melbourne Hospital 97% and 92% respectively believed that better analgesia was associated with fewer complications and shorter hospital stays [Libreri 1995].

The second argument addresses the large variation in analgesic requirements between patients. This large variation calls for occasionally higher than normal doses of analgesic in the course of general postoperative recovery.

In recognition of this need, this PCA system proposes a special high adaptation feature which allows patients to self-administer even relatively large amounts of analgesic under expert system control in order to maintain adequate analgesia. The postulate put forward here is that the high adaptation range on this PCA system will contribute towards improved postoperative recovery by ensuring good adequate analgesia immediately following surgery.

Accounts of enhanced postoperative recovery through good initial analgesia come from a number of sources and are presented below.

4.2.1 Enhanced Recovery and Good Early Postoperative Analgesia

In a study by Wasylak et al. comparing PCA with well managed regular pro re nata (p.r.n.) intramuscular analgesia it was noted “..that early relatively high, self-titrated morphine doses may alter the metabolic response to surgery” [Wasylak et al 1990]. The morphine consumption of PCA and p.r.n. patients was virtually identical over the first 48 hours but the pattern of analgesic intake was markedly different. The PCA patients self-administered considerably higher amounts of analgesic within the first approximately 2.5 hours in the recovery room than the average amount received by p.r.n. patients. Subsequent analgesic requirements were slightly lower for PCA patients for the remainder of the hospital stay.

The effects of analgesic management in the first 48 hours only became apparent in Wasylak’s study after the initial 48 hour period and included improved
ambulation, reduction in hospital stay, fewer complications and more rapid recovery of respiratory function. The mean pain levels for the PCA group were slightly lower and patients reported less pain for up to two weeks after discharge as well as less pain when moving about the house in daily activity. The pain scores for PCA patients showed a lower standard deviation which would indicate that the pain fluctuated less over time.

This finding further points to a possible link between the importance of providing early adequate analgesia and enhanced recovery. ‘Early’ in this case refers to the immediate postoperative period or whatever time is required to prevent severe pain from establishing itself. A possible explanation of the importance of early pain relief could also be the conditioning of expectations in the patient’s mind.

A review by Shade notes that PCA patients generally exhibit a high demand rate immediately post-operatively [Shade 1992]. This further highlights the immediate postoperative period as deserving special consideration and further investigation.

In a study by McCoy a group of patients who received the least amount of analgesia in the first 4 postoperative hours showed a subsequently overall higher analgesic consumption and significantly greater pain scores when compared to two other groups [McCoy et al. 1993]. This study was not specifically designed to investigate the consequences of differences in initial analgesic consumption, but the results could also support the importance of the immediate postoperative period in subsequent pain relief efforts.

PCA and enhanced recovery have been discussed in section 3.2.5 and have been reviewed by Angel et al. [Angel et al 1992]. However the role of initial adequate analgesia at sometimes quite high doses in enhanced post surgical recovery has not been clearly identified.

A study comparing p.r.n. IV morphine to PCA IV morphine found a higher initial analgesic consumption amongst the PCA patients [Bedder et al. 1991]. The authors speculate that this initial increased use might reflect self treatment for anxiety in line with findings obtained by Egan et al. who felt that patients may in part be treating their anxiety with PCA morphine [Egan et al. 1990b]. Egan suggests that treating postoperative anxiety could reduce the use of pain medication. Hence it seems that psychological factors in the initial postoperative period may influence the physiological responses of patients.
4.2.1.1 Psychological Factors and the Immediate Postoperative Period

A review by Peck points out that experimental studies [Voudouris et al. 1985] suggest that initial pain relief is an important determinant of future relief because the patient’s expectations may be conditioned at that time [Peck 1986]. The converse may also apply, in that inadequate initial pain relief may also condition the patient’s expectations such that later pain relief is less effective. Anecdotal accounts of the experiences of Royal Melbourne Hospital clinicians bear out such a phenomenon.

It seems that the importance of immediate first impressions post-operatively places PCA in the position of not only providing analgesia but of influencing a major psychological component of the postoperative experience, namely that of the patient’s expectations regarding recovery. Within the PCA modality it may also be the sense of control or otherwise, early in the postoperative period, which influences the expectations of the patient subsequently. It seems that the importance of the patient’s subjective impressions and expectations may have a greater effect than is commonly recognized. In this regard the psychological aspects of PCA may warrant more serious investigation particularly in regard to the concept of ‘locus of control’ as discussed in section 2.4.

Ready lists a number of benefits of PCA therapy and suggests that these benefits may be one instance of the general beneficial effects of superior early comfort, in which PCA is a major factor [Ready1990b].

The high adaptation range has been added to this PCA system in an effort to provide better pain relief for a wider range of pain sensitivities and to enhance a positive impression in the immediate postoperative period.

4.2.2 Formulation of the High Adaptation Strategy for Bolus Requests

In this PCA system, a patient’s bolus requests fall into two ranges the normal adaptation range and the high adaptation range. The normal range consists of a continuous region within which any of ten set amounts of analgesic may be given. The high adaptation range consists of a number of steps, any increase within this range being relative to the previous amount. Figure 4.1 illustrates this scheme.
Under normal adaptation the patient may request various bolus amounts up to a maximum of 5 mg of morphine. Safety monitoring devices are not mandatory in the normal adaptation range but are recommended. Without the monitor(s), it is not possible to enter the high adaptation range. It is proposed to use an Oximeter and a Capnograph as the safety monitors in this system.

Table 4.2 below shows the bolus amounts the patient may request under high adaptation. The high adaptation algorithm is discussed in detail in section 4.2.3.
Adaptation strategy for translating handset button values into bolus infusion amounts

<table>
<thead>
<tr>
<th>Handset button</th>
<th>Normal range 0.5 - 5 mg</th>
<th>High adaptation range (Only if both monitors connected and previous bolus &amp; background infusions &gt;=5 mg) Absolute max. 10 mg bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>5 mg</td>
<td>previous reference level + 1.0 mg</td>
</tr>
<tr>
<td>9</td>
<td>4.5 mg</td>
<td>previous reference level + 1.0 mg</td>
</tr>
<tr>
<td>8</td>
<td>4 mg</td>
<td>previous reference level + 1.0 mg</td>
</tr>
<tr>
<td>7</td>
<td>3.5 mg</td>
<td>previous reference level + 0.5 mg</td>
</tr>
<tr>
<td>6</td>
<td>3 mg</td>
<td>previous reference level + 0.5 mg</td>
</tr>
<tr>
<td>5</td>
<td>2.5 mg</td>
<td>repeat last reference level</td>
</tr>
<tr>
<td>4</td>
<td>2 mg</td>
<td>repeat last reference level</td>
</tr>
<tr>
<td>3</td>
<td>1.5 mg</td>
<td>previous reference level - 0.5 mg</td>
</tr>
<tr>
<td>2</td>
<td>1 mg</td>
<td>previous reference level - 0.5 mg</td>
</tr>
<tr>
<td>1</td>
<td>0.5 mg</td>
<td>previous reference level - 1.0 mg</td>
</tr>
</tbody>
</table>

Table 4.2 The method used to calculate bolus amounts of morphine from handset button values for the two adaptation ranges.

4.2.2.1 Conditions for Entering the High Adaptation Range

The high adaptation range can be entered only if all of the following conditions are met:
1) Both monitoring devices (Oximeter and Capnograph) are connected.
2) Alarm status ‘ALARM OK’ is obtained from both monitors.
3) The previous bolus amount given is equal to the maximum obtainable in the normal adaptation range, which is currently 5 mg for button 10.
4) The background infusion is equivalent to the maximum obtainable in the normal adaptation range. This is currently 5 mg of morphine per hour for under 60 year old patients and half that amount for over 60 year old patients.

If all the above four conditions are met, the normal range is deemed to be insufficient and the patient enters the high adaptation range. The patient will not be aware of this change. No changes in the handset protocol are required.

Once a patient is in the high adaptation range, a new strategy applies. Depending on the handset button-pressed, the patient receives more, the same or less analgesic than the previous time. Table 4.2 gives exact details for each button-pressed.
in both the high and normal adaptation ranges. There is a 10 mg bolus limit and a 10 mg per hr infusion limit. These limits are absolute and were determined through consultation with clinical staff.

The adaptation range remains active only as long as the following conditions are met:
1) The monitors remain connected and report an alarm status of ‘ALARM 1’ or better.
2) The background infusion and last bolus amounts both exceed the maximum obtainable in the normal adaptation range i.e. 5 mg at the time of writing.
Should any one of these conditions not be met, the program reverts back to the normal adaptation range. Some filtering in the data acquisition section of the program has been envisaged to remove motion artefact. False alarms will otherwise be treated as genuine and the system will revert back to the normal range.

4.2.3 High Adaptation Strategy for Background Infusions

The background infusion is a function of the bolus amounts actually administered and the time since the last bolus was requested. Thus, the background infusion depends on two variables. Table A4.3 in appendix A describes the dependence of the background infusion on time and on the last bolus amount administered for both the normal and the high adaptation ranges.

The time-variable ensures that the infusion diminishes in steps if no bolus requests are made within certain time intervals. A more detailed description of the rationale behind the current step-down strategy is given in section 4.1.4.

The background infusion level in the normal adaptation range currently can take any value between 0.5 mg/hr and a maximum of 5 mg/hr. In the high adaptation range the background infusion level takes the same numerical value (in mg/hr) as the bolus value (in mg). Thus, if a bolus of 7 mg were administered, the infusion level would then become 7 mg/hr as well.

If, in the high adaptation range, no bolus requests are received within 60 min, the background infusion level decreases by 1.0 mg/hr in the second hour and by a further 2 mg/hr in the third hour. If no bolus requests have been received by the fourth hour, the background infusion stops altogether and the patient drops back into the normal adaptation range, as shown in table 4.3. Thus, one method of exiting the high
adaptation range is through a lack of bolus requests over time. A special point to note is that in the case where the background infusion has decreased over time due to a lack of bolus requests, the reduced background infusion level is taken as the new reference level for any further bolus requests. Table 4.3 only refers to successive bolus requests separated by less than one hour. For example, if the last bolus administered was 7 mg and no further requests were received for one and a half hours, then the background infusion level would have dropped to 6 mg/hr. Any further bolus requests would then take the current infusion level of 6 mg/hr as the reference level and not the last bolus of 7 mg. If the subsequent bolus request was a button 10 request, then according to table 4.3 the new actual bolus amount would be the current reference level of 6 mg plus 1 mg, i.e. a total amount of 7 mg.

<table>
<thead>
<tr>
<th>Decision strategy of the background infusion as a function of bolus size and time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High adaptation range</strong></td>
</tr>
<tr>
<td>(Only if: Oximeter &amp; Capnograph connected, previous bolus 5mg and current infusion ≥ 5mg)</td>
</tr>
<tr>
<td>Last Bolus given:</td>
</tr>
<tr>
<td>Immediately following bolus admin.</td>
</tr>
<tr>
<td>60 minutes after last bolus</td>
</tr>
<tr>
<td>120 minutes after last bolus</td>
</tr>
<tr>
<td>180 minutes after last bolus</td>
</tr>
</tbody>
</table>

Table 4.3 The high adaptation range background infusion as a function of the previous bolus size and time elapsed since the last administered bolus

4.2.4 Conclusion for the High Adaptation strategy

Good early analgesia seems to have beneficial effects on postoperative recovery but no coherent theoretical framework for these effects has yet been put forward. However there seems to be sufficient evidence for the US Agency for Health Care Policy and Research to strongly recommend a number of measures for early postoperative analgesia [APMGP 1992].

It should be noted that although this new system has a special high adaptation range the higher doses a particular patient requires may well be met by the normal range
without explicitly entering the high adaptation range. Conversely a patient may have such high dosage requirements that the high adaptation range is only an extension of the normal range. The essential point being made here is that the high adaptation range is really only the provision of high analgesic levels commensurate with the patient’s requirements for a limited time and under the constant surveillance to a Pulse Oximeter and a Respiration monitor (Capnograph).

It should be noted that successful application of PCA generally depends among other factors on its early postoperative availability to the patient. A delay in which pain is allowed to establish itself at high levels will make subsequent pain treatment more difficult and has been suggested to produce a variety of negative longer-term effects [APMGP 1992].

4.3 A Theoretical Framework for the Patient Handset and varying bolus amounts

An effective handset rests on a number of theoretical foundations drawn from the areas of psychology, pharmacology and human-machine interface design.

The handset proposed for the adaptive system is intended to allow patients to register a range of pain intensities which result in variable amounts of analgesic being administered by the system. The proposed handset rests on the assumption that patients will be able to use this facility to better match the pain experienced to the analgesic amounts dispensed by the system.

4.3.1 Psychological Aspects of the Patient Handset

PCA is not only a purely physiological method of drug delivery but also has psychological aspects. The transition from the patient as mainly a recipient of medical treatment to the patient as a more active participant in medical treatment represents a fundamental change in approach with very important psychological implications. In psychology the locus of control theory which was briefly outlined in section 2.4 highlights another aspect of PCA and seeks to come to terms with the psychological aspects of patient participation. Studies in pain perception highlight the importance of
the psychological element in pain relief. Peck states that “It is now generally accepted that a considerable proportion of the variance in pain response is accounted for by psychological factors” [Peck 1986]. Perception of pain is also linked to anxiety and the meaning ascribed to the pain [Gill 1992, Melzack 1988].

In the locus of control theory, the perceived sense of control over variables affecting the well being of the person is important. The sense of control may be actual or mainly perceived. How actual control is perceived also depends on a number of complex variables within each person. Thus, although most patients appear to benefit from strategies aimed at providing a sense of control, patients whose predominant coping strategies are avoidant or withdrawal do not tend to benefit as much from increased control [Gill 1992, Paige et al. 1992]. It should be pointed out that there are a variety of ways of providing the patient with a sense of control. Gill points out that “..training in specific coping skills appears to enhance directly the patient’s sense of control and can be quite effective in reducing pain and anxiety and facilitating recovery from surgery or cooperation and coping with painful medical procedures.” [Gill 1992].

The primary argument in this section is that a patient’s sense of perceived control can be increased through the use of a handset which allows the patient to actually indicate various levels of pain intensity. The proposed PCA system aims to increase the sense of control the patient perceives through the use of a handset which allows the patient to select varying amounts of analgesic depending on their pain intensity level. It is thus postulated that allowing patients to give an indication of their pain level increases patients’ sense of perceived control and that this increased sense of perceived control is generally beneficial in the postoperative period.

The actual final implementation of the handset is the subject of the next section on human-machine interface.

4.3.2 Human-Machine Interface Aspects of the Patient Handset

The design of the actual handset is based on general ergonomic guidelines of human-machine interface and tackles the problem of interfacing the PCA system in such a way that the patient can most easily communicate his or her level of pain intensity to the PCA system.
In the design of the handset the following guidelines were considered:
1) The method of indicating pain should be simple and easy to comprehend.
2) Commonly used conceptual icons and cues should be used as much as possible.
   This implies that the handset should build on currently accepted and familiar concepts whenever practical. This guideline also directly supports guideline number 1.
3) Indicating pain and requesting a bolus should take a minimum of time.
4) The handset should be ergonomically well designed and user-friendly.
5) The handset should be safe from accidental triggering while still meeting the need for simplicity and ease of use.

In summary, the guidelines have been formulated to produce a handset which helps the patient externalize his or her subjective pain experience as accurately, quickly and easily as possible in order to obtain relief through the PCA system. In engineering terms, it is desired to have optimal coupling between the patient and the computer controlled pump. In software engineering terms the issue is one of ‘user-friendly’ interfacing.

### 4.3.2.1 Pain Rating Scales

The standard visual analog scale is a commonly used rating scale. Nurses and patients are usually familiar with the system of rating pain on a linear scale by placing a mark on a line. The line is usually 10 cm in length and has the phrases “No Pain” at the left or the bottom and “Worst Possible Pain” placed at the right or the top.

Another method of quickly rating pain is the verbal numeric pain scale. The patient is asked to rate their pain on a scale of 0 to 10 where 0 represents no pain and 10 the worst possible pain. This method benefits from the fact that most patients are familiar with the concept of increasing stimulation being related to increasing numbers [Paige et al. 1992]. Numerical rating scales are used not only in the hospital setting but in many other aspects of life ranging from competitions to market surveys. Thus this rating system uses commonly and culturally accepted concepts.

The handset design uses a mixture of the verbal and the visual analogue pain scales as the main rating scales. The verbal cues are superimposed on the visual analogue scales by adding ‘0’ and ‘10’ to the end points of the analogue scale. Patients may be...
already familiar with one or the other, and this will facilitate use. Routine nursing care at the Royal Melbourne Hospital involves the frequent use of the verbal rating scale, so patients are expected to feel comfortable rating their pain between 0 and 10.

The visual analogue of the verbal rating scale cues was chosen for this system because these scales represent a good compromise between speed and accuracy. Simple descriptive pain scales alone where patients are asked to rate their pain in one of three levels such as ‘mild’, ‘moderate’, and ‘severe’ have been shown not to be as accurate as the visual analog scale [Paige et al. 1992, Chapman et al. 1985].

The visual analogue scales have been criticised for their failure to recognize the multi-dimensional aspects of pain and reducing the pain experience to a single variable [Paige et al. 1992]. This is a valid criticism and has led to a number of more sophisticated rating scales being developed, all of which require a substantial amount of time to administer thus making them impractical in this application. In addition, the pain treatment modality using PCA cannot treat different kinds of pain differently and thus there seems no need to distinguish between different kinds of pain for PCA purposes at this stage.

If the visual analogue and verbal rating scales are used in a traditional setting asking patients to rate their pain too frequently could result in the patient becoming either uncooperative or remembering previous scores without properly evaluating the current situation [Paige et al. 1992, Reville et al. 1976]. This should not be a problem when the scale is used to help the patient select a bolus, as in this setting the patient is internally motivated and makes the decision to request a bolus of their own volition. Another problem has traditionally been the need to standardize the use of the visual analogue scales to obtain reliable results. This problem is also circumvented in the PCA application as the specific need to obtain objective external results in order to administer adequate analgesia is effectively dispensed with. A standardization of a kind is achieved in that all patients are subject to the same maximum analgesic limits.

It is intended that patients simply judge the distance between the end-points which best corresponds to their pain level rather than aim to press for a specific pain score.

It may be worth pointing out here that rating scales are not ratio scales and that comparison between rating scales is difficult if the scales have different numerical ranges [Nielsen 1993]. Nielsen suggests a series of transformations to facilitate comparison between different rating scales. The adaptive PCA handset thus uses a scale of 0-10 to facilitate comparison with the already established pain rating scales.
4.3.2.2 Human-Machine Interface and Conceptual Models

It is through the process of externalizing the subjective experience of pain that some of the psychological and ultimately physical benefits of PCA are thought to be realized. The handset asks the patient to quantify the pain experience introspectively and then with the aid of largely subconscious mental concepts taken from society and embodied in the handset itself to communicate the pain experience meaningfully such that some form of relief can be administered. The proposed handset represents an attempt to aid this process as much as possible.

![Overlay mask (visible)](image)

![Buttons underneath overlay mask (hidden)](image)

Figure 4.2 Top view of the patient handset

Research into cybernetics has found that augmenting cues can have a decisive impact on the mental model a subject makes of the task at hand [Eberts 1988]. “An augmenting cue can be defined as a perceptual event ancillary to the main display that is used to enhance important characteristics of the display.” [Eberts 1988]. It is proposed that the handset use a number of augmenting cues to help patients express themselves. The following is a list of the augmenting cues to be considered in the proposed handset:

1) A wedge shape will be superimposed over the 10 keys of the handset. In effect the line of the visual analogue scale will become a wedge where the thin end corresponds to ‘No Pain’ or the verbal scale equivalent of ‘0’ and the thick end corresponds to ‘Worst Possible Pain’ or ‘10’.

2) 3 distinct colour fields are proposed to form the body of the wedge. This will serve to divide the linear scale into broadly three levels which can be thought of as the...
Chapter 4 Theory of the Adaptive PCA

descriptive phrases ‘mild’, ‘moderate’, and ‘severe’. Here the descriptive modifiers are part of the augmenting cues of more sophisticated scales.
The colours should be chosen to correspond in emotional content with descriptors for their respective pain values. For example, the low end of the scale may be blue the middle yellow and the top red. The colours and the wedge are only intended to be augmenting cues the main rating scales are the combination of the verbal and visual analogue scales.

3) User feedback of the selection made will be given in the form of a row of Light Emitting Diodes (LED’s). There will be 10 LED’s which vary in colour corresponding to the 3 fields described in 2 above. All LED’s up to the point at which the patient presses on the scale will light up. Should the patient change his or her selection the lit column of LED’s should track these changes.
The LED’s will provide direct visual feedback of the level of pain intensity selected and reinforce the patient’s thinking concerning their selection. Thus the row of LED’s can be seen as another augmenting cue which is designed to help the patient externalize the pain experience in a way that the external world can respond to meaningfully.

Tactile feedback buttons will be used in the handset in order to give patients a distinct sense of registering the selection. This would be in addition to the row of LED’s.

4.3.2.3 Externalizing the Pain Experience: “Push the Button when it hurts”

In psychology, the act of verbalising and expressing emotions appropriately is generally considered beneficial and a number of schools of psychology make use of this. A particular aspect of this is thought to be involved in the act of quantifying pain when making a bolus request in the adaptive PCA system.

A very simple conceptual model of the pain experience and the process of quantifying it is given in figure 4.3 below.
The experience of pain reporting itself is subject to a large number of variations [McGrath et al. 1993]. For example it was observed during trials at the Royal Melbourne Hospital that patients’ reports of pain would vary depending on other individuals in the room with the patient and the nature of the relationship with that person (patient trial: 7-7/7/94).

Research into establishing mental models in the area of computer systems has been carried out by Lee and similar work by Doane [Lee et al. 1989, Doane et al. 1989]. Although this work deals with more complex systems similar methods could be used as starting points for investigations into the way patients conceptualize pain. An approach describing the way pictures in childrens’ books can make a complex
information accessible and verify or shape mental models is outlined by Newton [Newton et al. 1995].

4.3.2.4 The Handset Operation Algorithm

Keeping in mind the need for simplicity and ease of use and balancing this with the need for safety to guard against accidental triggering the following system for requesting a bolus from the PCA system has been put forward. Once a patient has decided to request a bolus, there are two steps to be executed:

Step 1: Selecting a place on the three coloured wedge between 0 and 10. This will automatically select one of 10 buttons which best corresponds to the pain intensity experienced. Visual feedback of the choice made is provided by a row of LED’s above the buttons. All LED’s up to the point selected become lit.

Step 2: Press the green bolus request button, hereafter referred to as the ‘GO button’. Pressing the GO button causes an audible tone to sound and all lit LED’s to extinguish themselves. This is intended to indicate to the patient that the PCA system has recognized the request. The value of the button-pressed is sent to the computer serial port and interpreted by the control program.

After step 1, the patient has 8 seconds in which to press the GO button. Beyond that time, all lit LED’s are extinguished and another selection has to be made before GO can be pressed again. If another button is selected during the 8 second interval, the effect is as for step 1 and a new 8 second interval is initiated. A diagram of the button-pressing algorithm is shown in figure 5.12.

The reason for the two-step process is to prevent accidental bolus requests when the handset is lying on or in the patient’s bed. In a study on PCA, Owen laments the passing of the in-built reaction time test which consisted of two button-presses within a short time [Owen et al. 1989b].

A requirement of the two-step process is that the patient must be sufficiently alert to execute the two step sequence within 8 seconds. This is also a safety feature in that a heavily sedated patient will not be able to request further boluses as easily, however it
could also present a degree of difficulty to patients who are in acute pain, but too disoriented for various reasons to master the complexity of the sequence. This would be expected to apply in particular to very old and very young patients. The handset algorithm was tested in preliminary trials at the Royal Melbourne and the Royal Women’s Hospitals. From observations by supervising staff the two-step process did not present any notable difficulties for the patients. It must be noted that PCA of any form is not recommended in any case for confused, disoriented or uncooperative patients.

4.3.2.5 PCA System Feedback to the Patient Handset

There are two design issues which concern the handset and which affect the way a patient uses PCA. The first issue is concerned with whether to give the patient feedback of the cessation of the lockout time. This feedback could be given in simple ways such as a short 'beep' and/or a light on the handset. In the present design, it was decided not to give feedback regarding lockout time, although provision for such future changes have been incorporated in the handset design. It was felt that if feedback was given, the patient might not request a bolus because of lockout time, even though pain was experienced. Without any indication of lockout time, it is hoped that the patient will request a bolus whenever pain is experienced. This is assumed to give a more realistic picture of the patient’s pain profile. Unfulfilled bolus requests, i.e. requests made during lockout, are currently presumed to signal insufficient pain relief or a lack of understanding of the PCA system. These requests thus represent useful information for design modification and/or patient assessment.

The patient is instructed in the use of the PCA system pre- and post-operatively and should be aware of the existence of a lockout period without necessarily knowing the exact duration. The instruction is to the effect that after a bolus there is a period of a few (5) minutes when the bolus is given time to take effect and no further boluses are available. The most significant unfulfilled bolus requests would be those made towards the end of the lockout period, when the patient has had a few minutes to note any effects of the last bolus request and still experiences insufficient pain relief while being unsure of the exact duration of the lockout period. The exact behaviour of each patient will of necessity differ, but in this system the above reasoning has led to the decision to give no indication of the cessation of the lockout time. The exact interpretation of unfulfilled bolus requests will always be subject to uncertainty. Thus, for example, does the patient understand the concept of a
lockout time and therefore wait for the end of the lockout time or is the patient unaware of the lockout time? This aspect of PCA still requires further investigation.

In PCA trials by Guiffre, notifying the patient of the end of lockout was thought to ‘reinforce clockwatching’ and possibly to lead to the patient administering a bolus because it was available and not because it was needed [Guiffre, 1988].

A report from the Royal Cornwall Hospital, UK, mentions a case in which the patient was under the mistaken impression that every time the green light on the PCA system indicated a bolus was available, she should press the button in order to stay pain free [Johnson 1992]. The clinical staff decided subsequently not to draw patients’ attention to the green light but merely to instruct them to press the bolus request button when pain became troublesome. This incident did not result in more than just unusual drowsiness but highlights the need for continued clinical supervision of PCA patients.

The above commercial PCA pump which gave an indication of an available bolus in the form of a green light was evaluated by Jackson and colleagues prior to the above incident [Jackson et al. 1991]. Jackson thought that the green light to indicate an available bolus after the lockout period was generally appreciated by the patients.

The second issue concerns the use of a short beeping tone when a bolus request has been made. Guiffre speculates that this could lead to a placebo effect in cases where a beeping tone is made but no bolus is administered [Guiffre 1988]. White makes a similar comment [White 1990]. Kleiman actually reports finding this effect in trials: ‘Nurses noted that the sound that accompanies pressing the PCA button provided relief to some patients, even when the 15 minute "lockout" period was in effect and no drug could be dispensed’ [Kleiman, 1987].

A special study to investigate the effect of acknowledging successful bolus requests was conducted by Johnson and colleagues [Johnson et al. 1992]. The study found no evidence of a clinically useful placebo effect, however there were other differences between the two test groups. In Group A only successful requests resulted in a beeping tone and in group B every request produced a beeping tone. There were slightly more requests made for group A, although more patients in this group thought that analgesia was at times inadequate, yet the pain scores in group A were no higher than those in group B. Like Owen and colleagues previously, this study found that patients preferred more feedback [Owen et al. 1986]. Nurses also preferred greater meaningful feedback, although this did not result in any quantifiable clinical benefits regarding morphine use, side-effects or pain scores [Johnson et al. 1992].
In this PCA system a beeping tone will be used after every bolus request, because of the more complex nature of the handset and to assure the patient that the request has indeed been recognized by the system. It was thought that the two-step process involved in a bolus request should give the patient some assurance of having successfully completed the request. It is also important to note that the nature of the infusion pump used is such that a bolus infusion can be readily detected by a flashing green light on the pump and clearly audible clicking sounds accompanied by movement of the cassette on the outside of the pump. An observant patient could thus easily discern a successful request from an unfulfilled request by observing the pump.

This issue might benefit from further investigation. It may be possible to use two kinds of distinct tones, one to signal a successful request on the handset and the other to signal a bolus being given. In this case patients would have to learn to distinguish between two kinds of tones. In order to minimize complexity this option has not been implemented at this stage.

4.3.2.6 Variable Bolus Amounts

The pain scores obtained from the handset represent a discretization of an individually discrete analog process in which patients are expected to make an estimate of their pain level on a continuous line segment based on the handset design discussed above. The discretization process is akin to analogue to digital conversion in electronics. This conversion process is the first conversion or translation process that occurs at the PCA system level when the patient requests a bolus. Converting the patient’s analog expression of pain intensity into 10 discrete levels was thought to give sufficient resolution while avoiding excessive complexity.

The second translation process at the systems level consists of converting the pain scores the patient registers on the handset into bolus amounts. The decision regarding the assignment of bolus amounts to the range of ten pain scores consisted of two parts.

The first consists of setting the range of analgesic amounts the patient may request, i.e. fixing the minimum and maximum amounts of analgesic (morphine) a patient can request as a single bolus.

The second part consists of translating the pain scores into bolus amounts according to a definite algorithm. Table 4.2 gives details of the actual analgesic amounts corresponding to each button.
The scheme used at present is a simple linear scale in which the available range of analgesic is divided into 10 equal parts. The current PCA system uses bolus amounts which vary in 10 steps from 0.5 mg to a maximum of 5 mg of morphine in the normal adaptation range. These values were obtained through consultation with clinicians involved with the PCA project at the Royal Melbourne Hospital. The maximum bolus value of 5 mg of morphine corresponding to a pain score of 10 was considered safe under the given situation by the medical team. Other schemes are possible and are discussed in chapter 8.

The high adaptation range is operative only with both safety monitors connected and with an acceptable respiratory rate, Arterial Oxyhaemoglobin Saturation (SpO2) and End-Tidal Carbon Dioxide (ETCO2) values. In the high adaptation range, successive bolus amounts can increase only by a maximum step of 1 mg, subject to expert system approval. The absolute maximum bolus size in the high adaptation range is currently 10 mg of morphine. This dose can only be obtained after 5 successive painscores of 8, 9 or 10 and no contraindications from the safety monitors. Table 4.2 shows the bolus sizes corresponding to pain scores in both the normal and high adaptation mode.

The very first bolus the patient receives is set to 2.5 mg of morphine regardless of which button the patient has chosen. This amount was found to be the average bolus value from previous trials and is a ‘sighting’ dose intended to start the patient with an average amount. The patient is informed of this fact. Subsequent dose sizes then vary directly according to the painscore registered on the handset and shown in table 4.2.

### 4.3.3 Pharmacological Aspects of the Patient Handset

It is postulated that the large interpatient variations in the level of analgesic at which patients find acceptable relief using PCA may be reflected to some degree in variations in the optimum bolus size between patients. This may be one reason for the difficulty in finding an optimum bolus size and lockout time combination. There has been some debate in the literature concerning the optimal bolus size [Owen et al. 1989, Buisan et al. 1992]. It may be possible that the optimal bolus size varies between patients and perhaps even within one patient over time [Owen et al. 1995].

The handset is designed in recognition of the fact that analgesic requirements between patients vary considerably and that it seems reasonable to give patients some degree
of freedom (and responsibility) in finding a comfortable compromise between a bolus size which produces adequate analgesia on one hand and possibly unpleasant side-effects on the other.

### 4.3.4 Summary of the Theoretical Foundations Underpinning the Patient Handset

The handset proposed for this PCA system allows patients to indicate a varying level of pain. The fundamental assumption is that patients will be able to learn to indicate pain intensity on the handset such that the resulting analgesic effect matches the desired analgesic effect. It is postulated that this would have beneficial effects in the majority of patients. From a psychological point of view the patient is given a greater degree of control and an additional degree of freedom with which to express the experience of pain. Taking account of the patient’s experience and attempting to match the machine response as closely as possible to human needs accords with general human-machine interface guidelines and is thought to provide better pain relief.

In a fixed bolus system the patient may not obtain adequate pain relief with a single bolus and may be forced to wait for the duration of the lockout time to request a further amount. This situation may still occur in the present system, however it is postulated that the patient is able to learn to judge the required amount and more successfully request adequate analgesic amounts.

Alternatively the patients may not desire a full standard dose and would prefer a fraction of the standard. This option is also provided by the handset.

From a pharmacological point of view the handset should allow the patient to more accurately titrate the required amount of analgesic and so better find a compromise between the desired and undesirable side-effects of opioids.

### 4.4 A Framework for the Expert System Knowledge Base

This section describes the rationale behind using an expert system, the reasons for implementing it in the chosen way and the process of knowledge transfer from expert to computer system.
A computer has been programmed as an “expert system” to carry out pain control tasks using the same “rules” as are used and taught by skilled clinical staff. This rule-based computer program is designed to embody as closely as possible what is considered to be the optimal clinical management strategy for pain control using an infusion pump. The “rules” for optimal clinical management have been quite well defined and incorporated in the expert system.

### 4.4.1 The Rationale for the Expert System

The overall aim of this PCA system is to be more adaptive and responsive to patients needs in providing analgesia. The complexity of a system represented by a patient’s need of analgesia, the amount of analgesic required and the method of administering the analgesic is too great for strict mathematical modelling. Such attempts as have been made still need to make many generalisations and approximations, as pointed out in section 3.5. As a result in this application an expert system has been used to control and supervise the bolus and infusion delivery of this PCA system. The term expert system is here used to designate a computer program which uses knowledge obtained from experts to make decisions under conditions of uncertainty [Boose 1986].

Expert systems are a branch of Artificial Intelligence (AI). The term ‘expert system’ describes a system which behaves as much as possible as a human expert would in a given field of knowledge. In this case, the PCA system attempts to capture the experience and knowledge of clinicians experienced in pain management and to imitate as closely as possible the actions of a nurse assigned full-time to a patient to provide pain relief. The expert system makes decisions based on new data, heuristic knowledge, facts and constraints as translated from human experts. Expert systems are ideally suited for situations which are nonlinear, time-variant and loosely defined, as is the case here.

The role of this expert system is to make decisions regarding bolus requests and background infusion and to supervise the complete PCA system. In the supervisory mode, the expert facility monitors the state of the system and only intervenes if indications from the data and knowledge base recommend intervention. The close supervisory control exercised by the expert system gives patients increased freedom in determining their own analgesic dosage levels. This is because under constant
monitoring the patient has a greater safe range of analgesic dosage available. The expert system thus also encapsulates a definite philosophy and attitude towards self-responsibility of the patient.

The overriding philosophy underlying the current system is to give the patient as much control over analgesic administration as is reasonably possible, while carefully monitoring relevant physiological parameters. In practice this means the patient is able to request a bolus corresponding to buttons 1 to 10 on the handset whenever necessary, subject to approval by and modification from the expert knowledge base and its data from the safety monitors.

4.4.2 Expert Knowledge Transfer

The knowledge incorporated in the expert system was developed through discussions with doctors, nurses and patients, and subsequently translated into system requirements. In the final development stage, fine tuning of the system required frequent consultations with the medical personnel of the Royal Melbourne Hospital. This resulted in an iterative process involving a gradual progress towards the final form of the knowledge base. Refinement of the knowledge in the system was an ongoing process. In figure 4.4 below the iterative process involved in creating the expert system is shown. The patient is included in the iterative feedback loop after completion of the system. Refinements are expected to take place as the system becomes operational.
The process of eliciting knowledge from the expert and translating it into a usable form for a computer consists of breaking the knowledge in the expert’s mind into smaller units. One method used to do this is to present the expert with a range of sample problems and to ask for justification of the conclusions. If the expert is able to describe how his or her expertise is applied to a specific problem he or she has described an algorithm [Black 1986]. Typically however experts are not able to describe their knowledge in this way. Much of their knowledge has been learnt inductively. It is the job of the designer to elicit the required information from the expert using a variety of strategies. At times it was necessary to observe the expert at work in order to clarify some of the finer points. In the case of this PCA system, the expert’s knowledge consisted of a series of algorithm fragments which could be applied in specific situations, but there was no simple meta-algorithm which determined the use of one or the other algorithm fragment. Intuitive and heuristic knowledge determined the final selection of treatment procedure.

Expert knowledge was particularly drawn upon in the formulation of the background infusion algorithm, the bolus ranges, and the concepts used in the handset. As the proposed system as a whole represents a new concept it was necessary to draw on a wide range of disciplines and to integrate these into a system which satisfied clinical experts at the Royal Melbourne Hospital in terms of established guidelines.
4.4.3 Run-Time Data Processing

During normal operation, the expert system continuously evaluates data received from the external world, processes it with reference to the knowledge base and controls the bolus and background infusion rate of the infusion pump. When circumstances require it, the system also initiates alarms and intervenes by stopping the pump. All these processes are continuously displayed on the clinical staff user interface, i.e. the computer monitor. Section 5.5.2 contains details regarding the computer monitor screen.

The expert algorithm obtains inputs from a number of sources listed below and shown in figure 4.5.

A) The handset relays information regarding bolus requests and may also be used to give indications of bolus availability to the patient.

B) The capnograph supplies the system with data concerning the patient’s respiration rate and end-tidal CO2 level.

C) The oximeter supplies arterial oxyhaemoglobin saturation (SpO2) values.
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D) The keyboard is used to enter patient data such as the patient’s age, at the start of the program. If judged appropriate, all analgesic amounts can be reduced by 50% by selecting the appropriate option from a pull-down menu.

E) Global parameters form an integral part of the program. Examples of global parameters are the absolute maximum bolus and background infusion amounts and the lockout time. Although these are normally thought to be permanent, they can be changed by editing various header text files.

4.4.3.1 External Data Classification Scheme

After discussions concerning the range of possible actions, four discrete status levels were judged to adequately cover the range of possible interventive actions to be taken by the system. The data received from the oximeter and the capnograph is filtered and then passed to the expert algorithm which assigns one of four status classifications to it. The four classifications and the meanings assigned to each in order of increasing priority are:

- ALARM OK: full adaptation possible, no restrictions within normal limits
- ALARM 1: remain at or decrease bolus and background infusion amounts
- ALARM 2: decrease bolus and infusion amounts immediately
- ALARM 3: stop the pump instantly, raise audio and visual alarms to alert clinical staff

Discussion with clinical staff on the evaluation of data received from the monitors yielded table 4.4 below. The table also lists the adaptation strategy adopted depending on the status of the independent variables. For safety reasons the highest priority alarm status has been assigned to any unused variables. The highest priority alarm status is taken to be the governing status state and determines the overall system response.
### Limits for Oximeter and Capnograph parameters

<table>
<thead>
<tr>
<th>Alarm status classification</th>
<th>End-Tidal CO2</th>
<th>SpO2</th>
<th>Ventilation frequency</th>
<th>Adaptation strategy</th>
<th>Background infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status OK</td>
<td>≤50 mmHg</td>
<td>≥90%</td>
<td>≥12 breaths/min</td>
<td>upward adaptation allowed</td>
<td>full adaptation</td>
</tr>
<tr>
<td>Alarm level 1</td>
<td>not used</td>
<td>not used</td>
<td>10-11 breaths/min</td>
<td>stay or decrease</td>
<td>limited adaptation</td>
</tr>
<tr>
<td>Alarm level 2</td>
<td>not used</td>
<td>not used</td>
<td>8-9 breaths/min</td>
<td>adapt downwards</td>
<td>decrease</td>
</tr>
<tr>
<td>Alarm level 3</td>
<td>&gt;50 mmHg</td>
<td>&lt;90%</td>
<td>&lt; 8 breaths/min</td>
<td>shut down system</td>
<td>stop infusion pump</td>
</tr>
</tbody>
</table>

**Table 4.4 Limits for oximeter and capnograph parameters**

At the time of writing only the respiration rate has been subdivided into four distinct ranges. This is primarily because it is the historically most reliable parameter relating to respiratory depression. End-tidal CO2 is a reliable indicator when used with a ventilator, but has yet to prove itself when measured using a nasal cannula as in this application. The method used for sensing SpO2 values is very noise prone and does not warrant distinguishing between more than two levels, in this case between above or below 90\% arterial oxyhaemoglobin saturation (SpO2). Section 5.8.1 contains more details on the importance of SpO2 measurements.

### 4.4.4 Summary of the Adaptive PCA Expert Knowledge System

The description of the expert system has focussed on the need for using an expert system and the knowledge transfer from the clinical experts to the PCA system. The knowledge transfer in particular is not restricted to the expert system itself but has been vital in the design of the total system. Such features as the high adaptation range the variable background infusion and the handset can all be seen as the expression of expert knowledge.

The actual design of the expert system is outlined in section 5.4.
4.5 Summary of the Theoretical Underpinnings of the Adaptive PCA System

The proposed adaptive PCA system incorporates the theoretical concepts discussed in this chapter and endeavours to provide analgesia based on best clinical practice.

1) The proposed PCA system aims to address the issue of the background infusion and interpatient variation by providing a continuously varying background infusion level as a function of the amount of analgesic the patient has received in the form of boluses and the time since the last bolus was requested. It is thought that this will provide an individually tailored background infusion level, which is neither too low to be ineffective nor too high to obviate the need for bolus requests. The issue of PCA and background infusions is further discussed in sections 3.2.3 and 4.1.

2) A high adaptation range is proposed to cater for instances in which an unusually high amount of analgesic is required. This is in recognition of the fact that good early pain relief can have longer term physiological and psychological effects.

3) The adaptive PCA system aims to give the patient an added degree of freedom by allowing the patient to register varying levels of pain intensity. The pain intensity level indicated by the patient is then converted into appropriate bolus sizes by the PCA expert control algorithm. This scheme is proposed to allow patients to register degrees of pain intensity accompanied by correspondingly varying analgesic dosages.

The available analgesic range is thus effectively increased and this is thought to overcome some of the difficulties with conservative PCA prescriptions. In effect the patient is given added responsibility.

It is also thought that a wider analgesic dosage range will diminish any problems of insufficient analgesic due to the self-imposed button pressing limit of a particular patient.

The increased sense of control which is enhanced by giving patients a method of expressing their pain is thought to result in psychological benefits.

4) It was felt that clinical expert knowledge encoded in the control algorithms would best facilitate the variety of functions to be carried out by the system. Expert knowledge will also be used to control the administration of unusually high amounts of analgesic either immediately post-operatively or during the course of subsequent recovery.
Chapter 4 Theory of the Adaptive PCA

Encoded expert knowledge will also be used to both determine the bolus amounts corresponding to various pain intensity levels as registered by the patient and the background infusion level commensurate with each particular patient’s button pressing behaviour.

5) A further aim of the new PCA system is to significantly enhance the user-friendliness of the system by entirely removing any need to program the system for individual patients, by displaying data clearly and by careful design of the patient interface. Operational control should be simple, the system should be robust and should follow general human-machine interface guidelines.

6) Safety of the system as such is of paramount importance and this issue is addressed in two ways. Firstly clinical monitoring devices will form an integral part of the system and secondly the likelihood of human error is presumably lowered through the use of good human-machine design principles and user-friendly interfaces.

The proposed clinical monitoring devices consist of an arterial oxygen saturation monitor and a respiratory capnograph. These devices should increase the confidence in and safety of the system.

Since many PCA mishaps have originated at the human-machine interface level this area has been pinpointed as deserving special effort.

Thus to conclude: The proposed system incorporates a method for patients to express a variety of pain intensity levels, which is intended to tailor the analgesic amount more closely to individual requirements as well as to provide the psychological and emotional benefits a greater sense of control is thought to offer.

The self-adjusting variable background infusion is thought to provide a working compromise between the risks and the benefits of constant rate background infusions in PCA.

Safety has been a major consideration in the design of the system, in that the patient is monitored while using PCA.

A number of theoretical considerations have been omitted in deciding the final system implementation. Thus, for example, it may have been possible to build and test an adaptive bolus only or an adaptive infusion only system first. These steps have been omitted because the philosophy underlying this design has been to imitate the protocol of a skilled nurse assigned full-time to one patient as closely as possible. The system as described here is thought to reflect the best efforts of medical experts in providing what is thought to result in optimal clinical practice in PCA.
Chapter 5  System Design

5.0 Introduction

The objective of any PCA system is to provide patients with control over their own pain relief. This chapter outlines a practical PCA system which is based on the theory outlined in the preceding chapter.

The PCA system has been designed with the following practical guidelines:
A) Safety to patients: All reasonable care should be taken to eliminate as far as possible the danger of malfunction and injury.
B) Robustness. The system must be able to operate successfully and reliably in the demanding clinical environment. It should also record and store data for later analysis.
C) Critical conditions of the patient due to analgesia or other factors, must be reported promptly and swiftly so that appropriate corrective action can be taken.

The PCA system described here uses a handset which allows the patient to indicate pain intensity levels in ten increments. Two external clinical monitors, an oximeter and a capnograph, supply the system with three important parameters of the patient’s respiratory status. An expert system evaluates the available data and decides on appropriate analgesic dosages. The complete system consists of a personal computer (PC), the patient handset, a computer-controlled infusion pump and two respiratory monitors. The computer monitor displays the system status, information for nursing charts and graphs of the background infusion and boluses administered. A block diagram of the complete system is shown below.
Chapter 5 PCA System Design

The philosophy underlying this PCA design has been to give the patient as much flexibility as is reasonably possible to achieve effective analgesia, while at the same time monitoring the patient to ensure safety.

5.1 PCA as a Feedback System

The PCA system can be regarded as a feedback control loop in which the controlled variable is the level of pain and the feedback signal is the number of bolus requests. The patient’s pain sensory system as a whole is the feedback signal generator, the output of which is a series of button presses to the computer controlling the infusion pump.
5.2 Software Design Philosophy

A modular top-down design has been used in writing the control software.

Figure 5.3 Program structure of the PCA system
Figure 5.3 above illustrates the general structure of the program. During the lifetime of the research project, the actual monitoring devices used may need to be changed. The modular approach simplifies the addition or replacement of a hardware unit. For example, in the early stages of the project a Graseby respiration monitor was used and later replaced by a Novametrix capnograph. The Input Output (IO) file dealing with respiration data acquisition was simply expanded to include the capnograph while retaining the capability of the original Graseby monitor should this be required again at a future date.

5.2.1 Design Implementation

![Figure 5.4](image-url) The main program loop and execution sequence

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The main program loop is shown in figure 5.4 above. The program polls four data buffers of the oximeter, capnograph, infusion pump and the handset. The information obtained from these buffers is then processed and placed in a central data store for use by the expert system and the monitoring module. Action is taken depending on the results of the data collected. In the event of a bolus request, the data store is consulted by the expert system to determine the appropriate amount of analgesic to be administered. The program completes a main loop at least every 1.5 seconds.

5.2.2 Programming Practices

Good programming practices are designed to cut down the time spent debugging the program, enable changes to be carried out easily and quickly, detect error conditions quickly, make the program easy to read and contribute to a robust program. The following practices have been implemented in an effort to conform to these programming practices [Radcliffe 1991].

1) Modular design has been implemented. All functions relating to one aspect of the program, such as IO, are grouped together by functionality.
2) Variable and function names are as descriptive and specific as possible, meaning that, for example, instead of calling a variable ‘amount’ it may be called ‘amount_shown_on_pump_this_cycle’.
3) Global variables have been kept to a minimum through the use of local variables wherever possible.
4) All function arguments are type-cast regardless of their triviality.
5) Function arguments are range checked, strings are parsed for legal ASCII characters and length.
6) A universal error handling function is used throughout the program. All errors are logged to a text file with a date and time stamp and the line number at which the error handler was called.
7) The principle of maximum feedback to the programmer has been observed, an example of which is the format in which data variables are saved to an ASCII text file. In this case the text file contains the name of the variable in plain text when a numerical code would suffice.
8) Unused debugging code has been left in place but was cut out of execution using ‘#define’ pre-processing statements or by commenting it out. This enables any future debugging to be carried out quickly.
9) Cross verification is carried out to ensure that expected values correspond to the actual values. The pump for example is interrogated repeatedly by each function that accesses it, and the results of the interrogation are compared with values in the central data store for correctness.

10) All C++ functions which return an error code are checked for error codes and appropriate action taken. All programmer defined functions return an error code whenever possible.

11) All numerical constants are defined in header files. This avoids the much malign practice of ‘magic numbers’ in a program.

12) Functions which are called repeatedly in different parts of the program take the line number from which they are called as one of their arguments. This enables rapid pinpointing of any error sources. The line number is established though the predefined global identifier ‘__LINE__’. Functions which are called extremely frequently also take the filename as a string argument using the predefined global identifier ‘__FILE__’.

### 5.2.2.1 Debugging and Permanent Error Checking

Code used for debugging often serves as error checking code with little or no modification. The error checking implemented in various parts of the program can serve the purpose of debugging if an alteration in one section of the program causes an error in another section. The approach to error detection and debugging is outlined below.

A universal error handling function called ‘error_handler(..)’ has been implemented. This is called in any situation in which a serious error has occurred and the program must be terminated. For the sake of safety this PCA program calls ‘error_handler(..)’ whenever the slightest doubt concerning the validity of a process exists. The function ‘error_handler(..)’ stops the pump, closes down the graphics screen and supplies details of the file name and line number in which the error occurred. In addition a short unique message string is passed to the function and displayed along with an audible alarm. All details are also logged to an ASCII text file accompanied by a time and date stamp.

The practice of rigorous error checking has paid practical dividends in shortening debugging time and making the program safer. The debugging time has been cut...
down, because errors are not able to propagate as far before being detected. Practical experience has shown that often trivial seeming error checking has been of great use in trapping unexpected and subtle errors quickly. As an example, a simple check to ensure that the number of bolus requests is greater than zero has been instrumental in quickly trapping various errors during development of the project. It has been found that all effort expended in error checking has been well worth the debugging time saved.

5.2.2.2 The Testing Phase

Towards the end of code writing, the testing phase consisted of running the program overnight, using automatic random bolus request intervals and sizes to simulate patient button pressing behaviour. A specially developed respiratory monitor simulation program was developed to allow the program to be tested in the most realistic way possible. The monitor simulation program was placed in a second computer and transmitted exactly the same strings to the serial ports of the PCA control computer as the actual monitors themselves.

5.2.2.3 Special Debugging Efforts

During the later intensive testing period, errors which had no obvious cause and only occurred rarely were noted. Below is an account of one particular episode in the testing phase of the project.

After running the program error free overnight for approximately 50 days, a particular error occurred involving inaccuracies and subsequent loss of information reading the real time computer clock. Upon examination it was found that this error had been noted in a comment a few months prior, though again no cause was discernible. This particular error seemed to occur on average once every 700 hours. It was thought perhaps to involve a glitch in the computer system itself. There was no realistic way of quickly debugging this kind of problem. The error involved the loss of real time clock data. The solution eventually adopted was to write code to detect this particular error and to continue program execution as much as possible for that particular cycle.
This particular error was eventually thought to originate in the hardware of the computer itself, triggered by external electromagnetic radiation (EMR).

It should be noted that all errors and all automatic corrections are logged to a specially created ASCII text file. Through the use of this log file, errors with an average low rate of occurrence, can be eventually eliminated even while the program is used in its final form.

The above example is intended to demonstrate that long-term debugging efforts may sometimes be required. To aid in this type of debugging, a number of special support functions were developed.

The author can verify from personal experience that although a program may be logically correct, this does not guarantee it will perform satisfactorily in a real world environment. Electromagnetic interference, supply line ‘glitches’ and other unforeseeable factors can cause malfunction in the operations of the program. Hence, this program was also designed to trap and deal with errors which either have already arisen, or are likely to arise in a real world environment. It was repeatedly found that seemingly superfluous error detection code was essential for the early detection of errors which were unforeseen when the code was written.

### 5.2.3 Software Tools Used

In order to develop a program of the size and complexity of the current PCA system, commercially available libraries were used to implement the user screen interface. The library “Software for Science, Engineering and Industry” by Quinn Curtis was used for all graphics and some communications routines. The graphing functions allow the programmer to place a variety of graphs with appropriate labels anywhere on the screen and to write to the graph using only a single function call. The library “C-Scape” by LIANT was used to implement the pull down menu system.

The program was written in Borland C++. The ‘C’ language was chosen because it is commonly used in industry and a large body of support and information is available for it. Borland C++ was chosen because of its ease of use, good error detection and available support.
5.3 Data Acquisition

This PCA system consists of a Personal Computer (PC) and up to 4 external devices. The PC, infusion pump and the handset comprise the minimum system, with the capnograph and the oximeter completing a fully expanded system. Each of the four external devices need to be controlled and monitored by the computer. The computer uses four asynchronous serial communications ports to collect data from the handset, pump, capnograph and oximeter. Each of these IO devices can send data to the computer at any time in the form of ASCII character strings. To ensure that the data is received and sent reliably, asynchronous communications are implemented as a background activity using interrupts. Interrupts are Terminate Stay Resident (TSR) programs. On the arrival of a character at the serial port a unique hardware interrupt is generated and program control is temporarily passed to a short routine known as the interrupt handler. The character byte at the serial port is read by the interrupt handler and placed in the communications queue corresponding to that serial port. Program control is automatically returned to the foreground program at the point at which execution was interrupted by the arrival of the character at the serial port.

The interrupt handler is able to place characters in the communications queue at the same rate as the transmission rate which ensures reliable data transfer. The foreground program polls the communications queue at its convenience, when the data is required.

After being placed in the buffer the data strings are pre-processed and numerical values are subsequently filtered. The complete IO module is shown in figure 5.5 below.
5.3.1 The Communications Queue

The communications queue provides temporary storage for the characters received from the serial port. It is implemented as a First-In First-Out (FIFO) circular buffer. A circular buffer is implemented by redirecting the end-of-buffer location called the ‘tail’ to the origin called the ‘head’, when the buffer is full.

Characters are pushed onto the head of the queue and popped from the tail of the buffer. The size of the buffer is such that the maximum number of characters which can be received between successive polling of the buffer can be comfortably pushed onto it. The foreground program polls the buffer and pops characters from the tail at a much higher rate than characters were pushed onto the buffer by the interrupt service routines. The average rate of popping data from the buffer must be equal to or greater than the rate at which characters are pushed onto the buffer, otherwise the FIFO buffer overflows, which results in more recent data overwriting older data. Overflow is an error generally flagged at the time of reading the circular buffer and the program has been designed to deal smoothly with this possibility.

Four circular buffers of various sizes are used in this program to hold data received from the pump, handset, capnograph and oximeter. Controlling and monitoring four
Chapter 5 PCA System Design

Separate IO devices is one of the most demanding tasks accomplished in this PCA program. Details of the IO settings used in this program can be found in table A4.1 of appendix A.

5.3.1.1 Polling The Circular Buffers

That part of the program which receives the data from the outside world and places it in circular buffers is made up of the Terminate Stay Resident (TSR) interrupt routines and is referred to as the background program. Once the data has been placed in the buffers it must be read by the foreground program. The foreground program polls the buffers and processes the data received so far. The polling process is asynchronous and has been designed to deal with situations where the foreground program polls a buffer before new data has been received or where no new data has arrived because the external device has been disconnected.

The current scheme allows totally asynchronous polling of the IO buffers at any desired rate. The foreground program must be able to differentiate between new data, old data and a disconnected device at whatever polling frequency it operates. The actual rate at which the IO buffers are polled depends on the speed with which the main program loop is able to call all functions in the loop. This varies with time and the state of the program and has an average of approximately 1 second. There is no upper polling speed constraint. The lower speed constraint is as mentioned previously, that the buffers must be polled before they are filled by the background program. The size of the buffers has been chosen such that the lowest reasonable polling speed does not cause buffer overflow.

5.3.2 Data Integrity

The data transmitted to the computer is subject to a number of corrupting influences. There are three ways in which the data sent by any of the IO devices can be adversely affected:

A) Invalid data
B) Erroneous data
C) Hardware communications path corruption
A) Invalid data.
Invalid data results when a string is received but does not yield a numerical value for that device. For example, in the case of the oximeter, invalid data may be caused through movement of the hand to which the oximeter probe is attached. This will cause invalid data to be sent from the oximeter in the form of messages such as: "Probe off patient", "Insufficient light detected" or "Low quality signal".

B) Erroneous data
Erroneous data is data that appears to genuinely reflect the patient’s condition, but is in fact caused by a complex set of accidental circumstances in which the sensor probe reads a set of parameters unrelated to the true state of the patient. The parameters read are still considered valid by the monitoring device and can be anywhere within the legal range. Data filtering as implemented here cannot detect erroneous data since erroneous data is usually generated at the level of the sensor probe and is a problem inherent in the sensing technique used. A common example is a low SpO2 reading from the oximeter, because the patient has put pressure on the limb to which the probe is attached, thereby reducing circulation and affecting the sensor reading.

A disturbance of the sensor probe can result in either invalid or erroneous data depending on the severity of the disturbance.

C) Hardware communications path corruption
The most common problem in this category is disconnection of the cable or connector problems. Whatever the physical cause of a hardware error, it will affect the actual data by producing invalid, erroneous, or no data at all. These cases are then dealt with by the program in the IO interface routines described below.

5.3.3 Data Filtering

The data from the oximeter and the capnograph is filtered before being used as a basis for actual decision making. There are two kinds of filtering used in this program. The first is defined here as data pre-filtering and deals with data in the form of ASCII strings. It covers valid, corrupt or totally absent strings. The second kind deals with conventional numerical digital signal processing.
After examining the contents of the buffer for a particular monitoring device, it is either classified as present - and its data is considered valid - or it is classified as unavailable. The unavailable classification covers all cases where data is not useable for any reason whatsoever, including actual physical disconnection. In the final analysis, the expert system is not concerned with the details of data acquisition, as it can only use valid data or else must assume the monitoring device is not available and does not exist for purposes of decision making. The absence of a monitor is automatically taken into consideration by the PCA control program.

5.3.3.1 Data Pre-Conditioning/Filtering

Data pre-conditioning/filtering is based on the observation that most short-term invalid and erroneous data is due to the patient’s movements or an accidental combination of patient and sensor position and is not significant in the short-term. Given this situation, it is not desirable that the program respond to every random and accidental fluctuation instantly by raising various kinds of alarms. This is a very important practical consideration, especially for oximetry data, which is very much subject to sensor position and patient movement (movement artefact).
Data pre-conditioning seeks to identify and deal with two specific situations, that of invalid data and that of device disconnection. In either case the system attempts to bridge the period of invalid data or disconnection by outputting the last valid numerical sample for a set time period. Beyond the set time interval, the relevant device is classified as unavailable for the expert system.
Disconnection is sensed by the expert system IO interface routines which poll the circular buffers. If no data at all is received for a time of NO_DATA seconds, that particular external device is classified as unavailable. The choice of the time delay NO_DATA in figure 5.6 depends on the frequency with which the monitoring device transmits a data string and the average rate at which the circular buffers are polled. The oximeter outputs a new data string every two seconds, the capnograph every second. The buffers are polled by the main program at an average rate of approximately once every 1.5 seconds, this being the time taken by the main program to complete a circuit of the main loop. The actual value of NO_DATA was determined to be 8 seconds and was arrived at through empirical observation of the actual program.

The program has been designed such that reconnection of an external device is automatically sensed and the device automatically becomes part of the system. There is no need to issue any commands to the computer via the keyboard. Connecting the operational device to the correct port is all that is required. This applies to both monitoring devices and the pump.

Invalid data is sensed in the situation where a string is received from an external device, but it does not yield a valid numerical value for that device. Reasons for invalid data were outlined in section 5.3.2. If invalid data has been received for less than INVALID_DELAY seconds the last valid data sample is output to the expert system, otherwise the relevant external device is classified as unavailable. The choice of time delay INVALID_DELAY for the filter in figure 5.6 depends on the interaction of the sensor probe and the patient. Given the nature of the sensor, the question is how long does a period of invalid data due to a patient’s movements usually last? At the time of writing INVALID_DELAY has a value of 20 seconds, but this value is constantly being re-evaluated in the light of empirical observations of a wide variety of patients. This area may merit further investigation and could possibly benefit from intelligent adaptation to particular patients with the intent of maximising the valid data collected from each individual patient.

5.3.3.2 Self Modifying Digital Filter for Externally Acquired Data
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The data values for the oximeter and capnograph have been found to fluctuate considerably from sample to sample, even though they are in the legal and valid range.

SpO2 values sent from the oximeter may temporarily dip into the highest priority alarm range while the average is still quite reasonable. Such temporary excursions are usually caused by movement of the limb to which the oximeter probe is attached and are not serious below a certain time interval. In order to overcome this problem, the data values are digitally filtered using a type of low pass Finite Impulse Response (FIR) filter known as a smoothing filter. The filter output consists of the DC average of the last N samples.

One of the major disadvantages of using a smoothing filter is the time delay involved. This time delay is desirable in masking temporary aberrations from the mean, but becomes a problem when a genuine emergency condition has occurred. In such a case a fast response to any change in the patient’s condition is most desirable. The time delay element is no longer needed once a true emergency condition has occurred, instead it has become a liability. Given this situation, the smoothing filter in this system has been made into an automatically adjusting, variable tap filter. Its general structure is shown in figure 5.7 below.

Figure 5.7 Self adjusting variable tap filter for external data samples
The filter has $N$ delay elements which are averaged over the number of elements to become the output. If the output falls into alarm ranges with increasing priorities of 1 to 3, then the output becomes the average of a decreasing number of the most recent elements. This results in decreasing delays for the output sample, i.e. the output sample corresponds more closely to the instantaneous value transmitted by the external device. The decision regarding the filter length for the expert system is always based on the average of all $N$ delay elements in order to preserve overall stability.

This scheme has been devised to satisfy the requirement of immunity from short term chance alarm states while removing the delay element once a genuine alarm state has occurred. The alarm states and their corresponding numerical ranges are shown in table A4.2 in appendix A.

5.4 The Expert System

Expert systems were first used to diagnose and recommend treatment for human physical disorders. An early expert system called MYCIN was one of the earliest expert systems used to diagnose the type of infectious disease a patient had contracted and then make recommendations for treatment [Shortliffe 1976].

There are different types of expert systems each with varying strengths and weaknesses. The three main types considered in this application are evidential reasoning, Bayesian classification or rule-based deduction.

The evidential reasoning approach uses a large knowledge base collected from a number of experts and by a process of assigning probabilities to various hypotheses and calculating measure of belief values, arrives at a conclusion with a certain probability of being correct. This approach is used in the MYCIN system, but is not useful in this particular PCA application, because this system does not contain the kind of complexity that necessitates the use of probability to decide between a number of contending hypotheses.

Bayesian classification is also unsuitable for this application, because it assumes statistical independence of the evidence, something which this PCA cannot guarantee.

One of the most popular types of expert systems uses rule-based deduction. A modified form of this was thought to be suitable in this application, because it is closely related to clinical protocol and the way decisions are made in hospitals. In a
rule-based system, knowledge is encapsulated in rules of the form ‘IF (condition) THEN (statement) ELSE (statement)’. The knowledge base is then scanned for any rules whose conditions are met, those rules which have their conditions met are then said to ‘fire’. The final decision by the expert system is made by repeated scanning. The scanning process is called chaining and both forward and backward chaining can be used. The inference engine scans the conditions of each rule and determines conflict resolution as well as performing cross consistency checks on both the data in the knowledge base and that obtained from the external world. Forward chaining has been used in this case as it is closer to the way decisions are made in a clinical environment. In this application, multiple solutions are not allowed and the system must only ever arrive at only one clear course of action. The final solution arrived at by the system is checked for validity in a manner similar to backward chaining. These checks include range and limit checking for safety reasons.

One of the theoretical advantages of rule-based expert systems is their flexibility. Knowledge can in theory easily be added or changed by editing the knowledge base which usually consists of a text file. The knowledge base text file must however first be translated into a form suitable for execution by a computer. This is done by a lexical analyser and a syntax analyser which together check for correct syntax and legal parameters much like a high level language compiler [Au 1990]. If no errors are found in the knowledge base, the knowledge base is translated into a fact base and a rule base suitable for use by the computer.

This general approach has been modified in this application after considering some of the problems with rule-based programming and also in the interests of simpler programming. Writing a good expert system involves more than just formulating a set of rules which encompass, in general terms, the knowledge used by an expert. Unless the rules have been carefully written and keeping in mind the conflict resolution strategy used by the inference engine, initial runs of the program will most probably fall short of expert behaviour [Jackson 1986]. In practice this means exhaustive tests of all likely contingencies.

Also, representing knowledge in an unstructured way in the form of rules ‘dumped’ into a text file puts the onus on the conflict resolution algorithm to sort out rules which may relate to different functions and aspects of the problem. New knowledge added to the rule base may change the system in unpredictable ways since conflict resolution must sort out when a rule will fire. Thus in practice one cannot simply add a rule and assume that the system as a whole will respond only to this one additional rule and remain the same in all other respects. The result of such a strategy is a need to extensively train the system not only for initial runs but whenever the
knowledge base is altered in some way. This is because the final outcome is the
product of a complex and interactive process not determined by the programmer
[Jackson 1986].

It should also be pointed out that expert systems do not guarantee an optimal
solution to a problem. A rule-based system does not even guarantee a solution at all.
If none of the conditions of the rules are met, none fire and the request falls through
the ‘gap’ of eventualities covered by the rules and their attendant conditions. A
further drawback of rule based systems is their inability to capture essentially subtle
information such as the history of a patient’s progress or decline [Jackson 1986].
There is a danger in blindly applying expert systems to any situation which requires
information processing without fully understanding the subject.

After considering the problems pointed out above and in the interests of
simplicity, it was decided to encapsulate the knowledge base in two clearly labelled
and accessible functions. The expert knowledge has also been structured in a general
way, for example: all alarm states are systematically checked before any further
action is taken. This has the advantage of simpler programming and fewer errors, as
well as more predictable behaviour. No lexical and syntactical analysers are required
as this function is implicit in compiling the program. The disadvantage of such an
approach is that the program needs to be recompiled every time the knowledge base
is altered. Such changes are not expected to be too frequent and those aspects of the
expert’s understanding that are subject to extremely frequent alteration can and have
been incorporated in a pull down menu selection. Those aspects of the knowledge
base which are likely to change only occasionally over the course of time are clearly
identified and their data objects are contained in a specially marked text file.

Fuzzy models were considered as an alternate way of encapsulating expert
knowledge. Fuzzy models are a mathematical way of representing the vagueness of
everyday life, in contrast to the precision of conventional control strategies. Fuzziness
describes the degree to which an event occurs, not whether it occurs. Strict
mathematical modelling of the processes to be controlled is not necessary [Dingli et
al. 1992]. The PCA system described here does not attempt to model a patient’s
analgesic consumption in a strictly mathematical way. Such a task would be far too
complex to be practical, if it were possible at all. In more technical terms, fuzzy
models use fuzzy memberships to represent similarities of objects with imprecisely
defined properties and probabilities which are used to convey information about
relative frequencies [Bezdek 1993]. A patient’s button-pressing behaviour and
physiological parameters would be ideal parameters for a fuzzy model. However,
after due consideration of the clinical environment it was felt that a rule-based expert
system approach would more closely approach the reasoning used in a clinical setting. Also fuzzy control is more applicable in situations where a system is too complex or cannot be easily represented by IF-THEN-ELSE rules [Self 1990].

5.4.1 Expert System Processing Speed Considerations

One common limitation of expert systems has generally been their speed. In this application real time operation is both essential and easily accomplished. It is essential to fulfil its supervisory role on all incoming data; and it is easily accomplished because the processes being monitored are relatively slow compared to the available computing power. In addition the actual knowledge base has been refined and is easily scanned in the available time. To illustrate the above in more concrete terms: On a personal computer running at 20 MHz, it requires approximately one second for the current program to complete one main loop cycle. This includes reading all IO buffers, processing and classifying the data, consulting the knowledge base, making decisions and implementing them. This figure compares favourably with the time constants involved in the human processes being monitored, which are usually in excess of 120 seconds. As speed was not a limiting constraint, it was also possible to implement more time consuming safety checks in the software.

5.4.2 The User Interface

The user interface in an expert system usually performs at least two vital functions. Firstly, it allows the user to enter new data into the system for consideration by the expert algorithm. Secondly, the user interface should display the reasoning process and the conclusions arrived at by the expert algorithm, as well as allow detailed interrogation of any steps employed in the reasoning process on its way to a final conclusion.

New data is entered from two sources: the patient enters data from the handset in the form of bolus requests and the safety monitors transmit data on the patient’s physiological parameters. Human input consists of bolus requests, setting initial parameters, intervening in emergencies and starting and stopping the program. There is no need for continuous human supervision of the decisions made by the system.
is precisely because of the total control exercised by the system that the inference engine described above must ever arrive at only one solution as opposed to multiple solutions. It is also the reason that the program maintains very tight control over all processes. The autonomy of the expert algorithm is another reason for not representing expert knowledge in an unstructured text file but in a form guaranteed to ensure smoothest execution and fewest ambiguities. In a situation where the expert system is employed in an advisory role, these constraints may be relaxed to a greater degree.

The second function of user interfaces has been incorporated in the general PCA user interface. The user interface continually displays the decisions made by the program. One of the aims of the user interface is to make the system as open as possible, that is to make many of the processes within the system visible. This is thought to increase user confidence and allow human monitoring and supervision. A special key has been assigned on the keyboard which triggers a more detailed explanation of the expert system status and decisions.

5.5 User Interface - Software

"The Human-Technology Interface is where most accidents occur. Many in the community who deal with post-accident trauma believe that engineers have not been sufficiently interested in this interface particularly in the physical, physiological and psychological implications; and such people are beginning to see this lack of interest by engineers as negligent."


The purpose of the user interface is to present relevant information to the user and to facilitate input and control operations. The success of this PCA system depends in a large measure on the quality of the user interface. An important part of the brief for the adaptive PCA was the design of a good user interface.

Computer literacy of the clinical staff has not been assumed. Keyboard use has been kept to an absolute minimum, both in the algorithm design of the system and in the operational mode. All graphical information is presented on one screen, eliminating the need to scroll through a number of screen options to find information. There is no
need to use the keyboard at all once the system is running, a feature which decreases the risk of program error and increases safety.

There are four groups of users who must all be satisfied, namely nursing staff, clinicians, patients and researchers. Since the only contact between the patient and the PCA system is via the handset, this aspect of user-interfacing is covered in sections 4.3, 5.7 relating to the handset. For anyone other than the patient, the primary interface with the PCA system is by means of the computer monitor screen. The oximeter, the capnograph and the pump are also part of the interface but in a less immediate way. All salient information needed for running the system is presented on the computer screen.

5.5.1 Pull-Down Menus

Upon startup the program presents a horizontal bar with pull-down menus from which appropriate actions can be chosen. The choice of menus has been kept to a minimum and is as self-explanatory as possible. The format of pull-down menus is well known and is ideally suited to keyboard operation.

5.5.2 The Graphics Screen

The computer monitor screen is divided into three separate areas, namely the system status section, the data section and the graph section. Figure 5.10 below illustrates this.
Figure 5.10 The computer monitor screen and its division into information fields

The current status of the system is displayed by means of three coloured circles in the status section. The circles are large enough to be seen at a distance by passing nursing staff and are modelled on road traffic lights in position and colour. The top circle is green and displays information relating to the background infusion. The middle amber light is dedicated to bolus information, while the bottom light is red and has been reserved for alarm status information. Table A4.5 of appendix A gives a detailed summary of the status screen messages.

The data section has been designed to hold all information needed by the nursing staff for routine record keeping. The aim of this section was to eliminate the need for complex interpretation of graphs.

The graph section has been designed to hold important information covering the preceding 4 hours and is primarily intended for the pain services staff. The top graph displays the history of the background infusion and the middle graph displays the number and size of all bolus requests, where fulfilled requests are shown in blue and unfulfilled requests in red. The bottom graph displays the SpO2, end-tidal CO2 and respiration rate values if these are available.
The professional look of the user interface has been achieved with commercially available software libraries. This has allowed program development to concentrate on refining a more advanced presentation and to focus efforts on the actual control algorithms.

5.5.3 User Interface Features for Nursing Staff

Special attention has been focussed on making the system as ‘friendly’ as possible, especially for the nursing staff who have most direct and frequent contact with the PCA. After consultation with nursing staff, all information needed for routine checking and record keeping has been summarized and tabulated in the bottom left hand corner of the screen. There is no need to search the screen for various pieces of data or to make secondary calculations in order to fill out the standard forms used for clinical record keeping.

5.5.4 User Interface Features for Expert Pain Management Staff

The graphical information is primarily aimed at the pain services specialist. All major parameters are clearly displayed in graphs covering four hours of operation. This is intended to give the clinician a quick overview of how the patient has used the PCA system.

5.5.5 User Interface Features for the System Developer

All the features already covered are obviously of interest to the developer. However in addition, the status window contains a number of lines of text with details of the current status of the monitoring devices and numerical information of the alarm status as seen by the expert system. This information is usually hidden, but can be activated by a designated key on the keyboard. After a fixed time interval this information is automatically erased. The information is intended only for the system developer for
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testing, checking and debugging purposes and comprises a built-in diagnostic function.

5.5.5.1 Data Log Files

For research purposes it is vital that a detailed record of all significant actions by the PCA system is kept. Any changes in the background infusion and every bolus request, are logged to an ASCII text file along with the current alarm status, time and date. This serves as a detailed documentation system for the duration of clinical trials and can be used to check the correct behaviour of the system. It also allows for a reconstruction of the patient’s use of PCA and can be used as a basis for statistical analysis. The log files can be thought of as the equivalent of the black box flight recorders used in aviation.

5.6 PCA System Hardware

The PCA system is controlled by an IBM compatible personal computer consisting of the following hardware configuration:

- IBM compatible personal computer
- Intel 80386 microprocessor
- Four serial RS232 ports
- One parallel printer port
- 640 Kbytes of RAM with 3072Kbytes extended memory
- 1.2 Mbytes 5.25 inch high density floppy disk drive
- 1.44 Mbyte 3.5 inch disk drive
- 105 Mbytes hard disk drive
- Enhanced Graphics Adaptor and Colour Monitor
- Real-time clock with battery backup

The intravenous infusion pump is an Imed 929 Computer Pump. The oximeter is an Ohmeda Biox 3700 Pulse Oximeter and the capnograph is a Novametrix 1260 End Tidal CO2 Monitor. The handset on the patients bedside is a custom designed piece of
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equipment using an MC68HC11 microcontroller, details of which can be found in section 5.7 below.

5.7 The Patient Handset - Design Considerations

The handset is the only direct interface between the patient and the PCA system. The primary requirements for the handset are that it enables the patient to accurately register varying pain levels, be easy to operate and safe from accidental triggering.

The current handset is version three and represents the accumulated experience gleaned from its predecessors. The first version of the handset consisted of a rotary dial and a button, adapted from a games paddle. The patient was required to dial a position corresponding to the pain felt and then press a bolus request button. This design had a number of problems, some technical and others conceptual.

In the technical domain, the handset produced inconsistent values for identical dial positions, and at the extreme ends of the scale the values were non-linear and extremely inconsistent. In practice, it was found that the bolus request button had to be protected by a special shield to guard against accidental triggering.

A second technical problem was that the handset was connected to the computer through the games port which did not have an interrupt and thus required constant polling in order not to miss a button press. There was a definite probability that some bolus requests would be ignored by the system.

The handset relied on a simple push button switch connected to the games port to signify a bolus request. In some cases the EMR in the laboratory was able to trigger spurious bolus requests because the cable of the provisional handset used for testing acted as an antenna. This is no longer possible with the final handset used in the adaptive PCA.

The conceptual problems concerned the way patients used the handset and how the dialled pain scores should be interpreted. The problem was that patients were not forced to select a pain score value, but could simply leave the dial in the last position used and press the bolus request button again. Thus it was not clear to the researchers whether a patient desired the same amount as previously, forgot to adjust the pain scale, did not understand the system, was lazy, or would have selected a slightly different value had a separate choice been required. Conceptual problems concerning the handset design were dealt with in more detail in section 4.3.
Both the technical and conceptual problems were solved in the second version of the handset which was the prototype of the third and current version. The second version differed from the current final version only in that it used discrete logic gates to implement the algorithm and used a combination of the games port and a serial port to implement an interrupt driven system.

5.7.1 Handset Hardware

The handset hardware has been chosen with a view to flexibility, because future changes in the use and operation of the handset were deemed likely. The operation of the handset will depend to some extent on the nature of the clinical trials.

Given the need for flexibility, a small microprocessor system was the logical choice, because software changes are then expected to be able to accommodate all anticipated changes. These possible changes could be the inclusion of a light or tone to indicate the end of lockout time as discussed in section 4.3.2.4. An earlier version of the handset used discrete logic and interfaced to the games port of the computer. This was found to be too inflexible and cumbersome. The current version of the PCA program calls for a handset which can generate an interrupt, which is not possible on the games ports of ordinary PCs.

The Motorola MC 68HC11 E2, hereafter referred to as the HC11, was chosen as the most suitable microcontroller. Ample information and support was available for the HC11, both on location and through the supplier. The HC11 has a number of features which are not used at present but provide room for future expansion. These features include 8 Analog to Digital converters, independent counter timers and various serial and parallel ports. The HC11 has on-board RAM and EEPROM can be programmed from any computer via a serial port. Motorola supplies software for programming and debugging the HC11 as well as an evaluation board for fast prototyping. The ability to program and reprogram the HC11 from a personal computer using a serial port made it an especially attractive choice.
The size of the 4K EEPROM and 256 byte RAM was found to be more than adequate for the handset requirements. Prototype development was carried out on the evaluation board using wire wrapping techniques. The final design was produced as a double-sided printed circuit board (PCB).

The current design of the handset could be used as the starting point for a variety of other applications such as remote data acquisition and pre-processing. It is anticipated that future research projects in the Royal Melbourne Hospital are likely to find the HC11 a useful tool for research purposes.

5.7.2 Handset Prototyping

The construction of the handset can be divided into two stages, namely the construction of the electronic circuitry and associated software, and the construction of the actual case and face plate.

The electronic circuitry was constructed on two double-sided PCBs, one above the other, to enable it to fit into the handset case. The top PCB contained all buttons and LEDs used by the patient. The lower PCB contained the HC11 microcontroller and support components. The lower PCB has been designed as a

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*Figure 5.11 Block diagram of the patient handset*

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general purpose microcontroller board, such that it can easily be used for other microcontroller projects.

The handset was designed and produced by the technical staff at the Royal Melbourne Hospital, the Melbourne University electronics workshop and the author.

The colours of the light emitting diodes (LED) used to light up the buttons on the handset have been graded from green for button one to yellow to red for button 10. These colours have been selected for their subjective value as discussed in section 4.3.2.1.

### 5.7.3 Handset Software

The software for the handset was written in assembly language and compiled using Motorola software supplied with the evaluation kit. A flow diagram of the handset software is shown in figure 5.12 below.
The software interface between the HC11 microcontroller and the keyboard were the most difficult and crucial part of the handset software.

The handset has been designed for maximum flexibility. Only minor alterations to the software in the handset microprocessor are required to eliminate the bolus beeping sound or to include a bolus available indicator, should this be required in the future.

Figure 5.12 Flow diagram of the handset software
5.7.4 Watchdog Timers - a Safety Feature

The computer and the handset both maintain a continual stream of control character information to ensure that the link between them remains intact. The main computer program verifies the presence and functionality of the handset using a loop-back test which consists of sending a handshake character which the handset is expected to echo. If this character is not echoed, the main program will assume that the handset is not functional and sound and alarm signal and display a warning message. The handshake character is sent at least once every two seconds.

Likewise the handset transmits a signal to the PCA computer which the computer is expected to echo. If the character sent by the handset is not echoed within a specified time frame (2 mins) then the watchdog timer in the handset will cause all LED’s to flash and emit a beeping tone to alert staff and patients to a malfunction.

5.8 PCA Parameters

This section covers the reasoning behind the choice of a number of parameters in the PCA system. Deciding the exact values for these parameters involved consultation with the clinicians of the Royal Melbourne Hospital. In many cases no one best solution was possible but rather an engineering compromise of a number of conflicting issues resulted in the current solution. Consultation was an ongoing process involving discussion throughout the project’s development.

The reasoning outlined in this chapter is intended to give an insight into the factors which led to the system in its present form.

5.8.1 Monitoring Parameters

The choice of parameters to continuously monitor respiratory function for possible respiratory depression is somewhat limited by the requirement to make the monitoring as non-invasive and unobtrusive as possible. Fortunately however, some good indicators of respiratory depression can be easily monitored by using both a capnograph to monitor both end-tidal CO2 (ETCO2) and Respiratory Rate (RR) and a pulse oximeter to monitor Arterial Oxyhaemoglobin Saturation (SpO2). Using these three parameters, not only can the patient’s overall respiratory status be reliably
monitored, but also any early warning signs of problems detected. Capnographs and pulse oximeters are standard clinical monitoring equipment and regularly used in hospitals.

In this application the Capnograph is primarily intended for patient’s who are likely to require the high adaptation range and the Oximeter is also intended for more continuous monitoring in the normal range.

5.8.2 Practical Application of Monitoring Parameters

In the context of this PCA system, the primary safety parameters are the respiration rate (RR), finger oxygenation (SpO2) and nasal end-tidal carbon dioxide measurements (ETCO2).

The advantages of capnographic monitoring in general anaesthesia are outlined by Williamson et al. and Webb et al. [Williamson et al. 1993, Webb et al. 1993]. The capnograph is also described as a valuable “backup” monitor when other monitors are not available or fail.

The method of measuring respiratory rate in the adaptive PCA system is by means of a nasal cannula. The respiratory rate is traditionally the most reliable indicator of respiratory depression (although not the only one). Manual monitoring of the respiratory rate is currently used by nursing staff to assess a patient’s level of sedation on at least an hourly basis. Manual monitoring has the advantage of being able additionally to assess the character and nature of the patient’s breathing. In Kory’s opinion, it is important that nursing staff take note of breathing characteristics such as dyspnoea, stridulous breathing and the deep sighs of emotional tension [Kory 1957]. Mechanical monitoring has the advantage of being continuous, but it does not attempt to classify the character of breathing.

The pulse oximeter monitors a further important parameter, finger oxigenation from which inferences with regard to brain oxygenation are drawn. This parameter is less sensitive to the fine gradations of respiratory depression but is a reliable indicator of severe depression. The oximeter thus provides further safety monitoring in addition to respiratory rate measurements. Pulse oximetry is currently used in a variety of situations to monitor patients for decreased oxygenation and has been highly recommend in anaesthesia [Runciman et al. 1993].
Thus two separate machines and distinct methods are used to obtain the two most important parameters of respiratory depression. This provides an added degree of safety. A capnograph and oximeter together were found to provide a good degree of monitoring in an anaesthetic environment [Webb et al. 1993].

In this context and application the ETCO2 value is considered to have the lowest priority of the three monitored parameters. Although the value and the reliability of ETCO2 measurements in ventilator applications is well established, it needs to be validated in the context of a nasal cannula as used in this PCA system. The nasal cannula has been found to be very effective for respiratory rate measurements, but it has not yet proven sufficiently reliable for ETCO2 measurements on a PCA patient. It is hoped that the data collected from trials of this system will allow some conclusions as to the suitability of ETCO2 measurements for PCA to be made.

5.8.3 Choice of Respiration Monitor

Initially, the small portable Graseby 108 respiration monitor was used to obtain respiratory rate. However, in the course of development and through discussion with physicians, it was decided to replace the Graseby respiration monitor with the Novametrix 1260 capnograph for two compelling reasons.

Firstly, the capnograph was chosen because it also provides end-tidal CO2 values which are the most sensitive of the easily obtainable parameters for respiratory depression [Jennett 1968]. According to Jennett, respiratory frequency is the next most sensitive parameter.

Secondly, the capnograph provides data samples at its serial port every second as opposed to every 60 seconds for the Graseby respiration monitor. A 60 second update interval was thought to be unacceptable in view of the fact that the data values were filtered for spurious values which could delay remedial action by a few minutes. A sample interval of one second comfortably allows data filtering for spurious effects while still giving adequate time to respond in the event of respiratory depression, see section 5.3.3 for details concerning data filtering. It should also be kept in mind that the Graseby monitor is primarily designed to be a portable bedside monitor and is not specifically designed to be an integral part of a computer monitoring system. The capnograph used in this PCA system was designed to be part of a computer monitoring system.
5.8.4 The Purpose of the Lockout Time Interval

The principal purpose of the lockout time interval is to prevent the patient from over-administering analgesic. Although opioid analgesics administered intravenously provide very fast pain relief compared to intramuscular injections, there is still a time delay of several minutes for the medication to produce its analgesic effect. The lockout time forces the patient to wait for an appreciable effect to take place before requesting a further bolus. The full effect of morphine takes approximately 20 minutes to occur, but the lockout time is sufficiently close to peak analgesia for the patient to make an informed choice about further bolus requests. In this system the lockout time has been set to 5 minutes, during which time 75-90% of the full effect of the requested bolus should be felt by the patient. The lockout time also includes the time to administer the bolus. An average bolus requires approximately 2 minutes to administer.

In a recent article Hill and Mather point out that they believe the lockout time should be as short as practical to enhance patient confidence in the PCA system [Hill et al. 1993]. Naturally the lockout time should be balanced with the bolus size to limit the overall analgesic consumption to acceptable levels.

5.8.5 Choice of Lockout Time

The actual choice of a lockout interval is determined by trading off the requirement for safety from overadministration against the requirement to give the patient access to pain relief as much and as often as required.

The lockout interval must be long enough so that, coupled with the maximum bolus size being requested as often as possible, the patient is still within safe dose limits. On the other hand, the lockout interval must be short enough to allow a patient who has fallen to a subtherapeutic plasma drug concentration, through for example sleep, to catch up in a reasonable time. In addition, pain intensity varies over time and the PCA must be able to respond adequately to changing demands.

The maximum bolus size and the trailing background infusion rate also influence the choice of lockout time, as all three parameters govern the maximum hourly amount available to a patient. However as this system aims to provide a broad
range of analgesic dosages and has intelligent computer control it was felt that the
lockout interval should not primarily be used to limit the total maximum dose but that
patient confidence and the pharmacodynamics of the analgesic agent were considered
of more importance in this case.

Patient confidence in the system is thought to depend to some extent on the
duration of the lockout interval. An interval judged subjectively ‘too long’ by patients
is thought to undermine the principle of PCA and erode the benefits of a sense of
control in the patient [Hill et al. 1993, Owen et al. 1989a, Mather 1994]. Hence the
argument for patient confidence PCA is one for a relatively short lockout interval.

The lockout interval should also be of sufficient duration to permit patients to
judge the analgesic effect of their most recent bolus request. Thus the lockout interval
must force patients to delay further requests until the pharmacodynamics have had
sufficient time to establish themselves to a degree which permits a reasonable
judgement as to the most recent bolus request to be made.

A 5 minute interval was considered the appropriate time interval for the
adaptive system by the clinical staff of the Royal Melbourne Hospital involved in this
project.

5.8.6 Drug Choice for the Adaptive PCA

This PCA system was designed primarily for morphine but also pethidine (if diluted
to equianalgesic levels as morphine), because the principles involved in the use of
these two drugs are generally similar. Morphine is one of the most widely used
analgesics, with a reasonable therapeutic index amongst the available choices
[Drasner et al. 1992]. The therapeutic index alone however should not be used as a
sole criterion for selecting a particular drug for PCA. After recounting a number of
factors which affect the action of an analgesic drug in practice, Hill and Mather
conclude that “...although quoted values for therapeutic indices may make one drug
appear more attractive than another, none emerges as being outstanding, nor is it
likely that pain laboratory investigations will offer much help in making the choice of
drug for postoperative analgesia” [Hill et al 1993].

In 1992 the United States Agency for Health Care Policy recommended morphine as
the first drug of choice to treat postoperative pain because it was relatively easy to use
for continuous dosing [Leary 1992, APMGP 1992]. The final choice for this system
was morphine and was made by the medical staff involved in this project. Morphine is a commonly prescribed opioid analgesic.

5.9 Summary

This chapter has given an outline of the actual design of the various components of the proposed adaptive PCA system. The system as a whole aims to implement the theoretical propositions put forward in the preceding chapter.
Chapter 6  PCA Safety

"...we are not really concerned about risk itself, but the acceptance of risk."

6.0 Introduction

Safety, in particular in software engineering, has become a major issue in recent times as software assumes greater control in daily life. Amongst others, the IEE has addressed the issue of safety-related systems in a recent brief with particular attention being paid to systems using computers or other programmable elements [Kemp 1992]. The brief is not specifically concerned with medical electronics but covers all engineering applications in which the failure or malfunction of a system might result in personal injury, death or damage to the environment.

In the IEE brief, ‘safety’ is defined as the likelihood that a system will NOT lead to the endangerment of human life or the environment. A ‘hazard’ is defined as something that may go wrong. The concept of ‘risk’ combines the amount of damage a hazard might do with the probability of its occurrence. Finally, a ‘safety’ argument consists of arguing that the risk involved in a particular system is ‘acceptable’. One of the main points of the brief is that it is never possible to claim that all risks have been eliminated.

An introduction to the psychology of human error in the context of anaesthesia has been outlined by Runciman [Runciman et al. 1993]. Errors are defined by Runciman as a ‘flawed’ plan of action such as a planned sequence of mental or physical activities which result in an unintended outcome such as an incident or an accident. An incident is defined as an unintended outcome which reduced the safety margin of the patient and an accident is defined as an adverse or ‘negative’ outcome. Runciman describes ‘active’ errors such as rule-based, skill-based, and technical errors and goes on to stress the neglected category of ‘latent’ errors which include environment,
psychological state, equipment, work practices, personnel training, social and cultural factors.

This section addresses the topic of safety in PCA and the steps needed to ensure patient safety at all times. The focus will be on the adaptive system presented here and in particular the aspects of adaptive PCA which are different from conventional PCA.

6.1 The Dangers of PCA

Initial proposals for PCA were greeted with a certain degree of apprehension and scepticism regarding the safety of the pumps themselves and the possible consequences of pump malfunction. There was also a reluctance on the part of physicians and nurses to give patients control of their own therapy [Kluger et al. 1991].

The journal ‘Health Devices 1988’ holds up the safety issue as one of the most important concerns in purchasing PCA equipment [Health Devices 1988]. Safety not only addresses the traditional areas of reliable electronic and mechanical control but also ergonomics and potential for programming errors.

The main risk in PCA is posed by the fact that the opioid analgesics used will cause respiratory depression if given in sufficiently large doses. Untreated respiratory depression can lead to apnoea, coma and death. To prevent deliberate or accidental overdosing, a number of safety and risk-reducing features have been incorporated in the design of this particular PCA system. The safety features discussed here will cover deliberate and accidental overdosing, whether through equipment failure, accidental misuse or ignorance.

6.1.1 PCA Safety to Date

Respiratory arrest due to PCA has been found to be extremely rare. Kluger cites a report from the Cleveland Clinic Foundation which surveyed 3299 patients receiving PCA [Kluger et al. 1991]. There were 42 mishaps reported (1.3%), of which 22 were operator related, 15 due to equipment malfunction and 5 cases of adverse drug
reaction. Kluger also mentions a survey of 1000 patients using PCA, which showed that there were respiratory problems in only 2.5% of the patients and that in more than half of these it was possible to continue PCA therapy. The survey also found that technical problems were more common than clinical problems.

### 6.2 Inherent Safety

When the concept of PCA is first expounded to lay-persons, often the unspoken assumption is that given free access to morphine a patient would want to have as much as possible. This is simply not the case. In clinical trials it has been found that almost all patients exercise restraint in the use of analgesics. The only exception is a patient with a history of drug abuse and in such patients PCA is contra-indicated in most of the literature. Such patients have also usually been excluded from trials. Keeri-Szanto describes drug abusers as people who have ‘. . administered narcotics to the brink of unconsciousness, “coming up for air” only long enough to trigger the administration of more drug’ [Keeri-Szanto 1979]. In trials at the Royal Melbourne Hospital, some patients had to be encouraged to increase their usage of the PCA, as these patients were excessively concerned about overdosing themselves.

Callan points out that there is increasing evidence for the existence of a biological negative feedback control system [Callan 1990]. As pain decreases, the demand for analgesics diminishes thus reducing the probability of respiratory depression. In addition, increasing amounts of analgesics produce unpleasant side-effects, including nausea, vomiting, drowsiness and respiratory depression. More details of side-effects are covered in section 2.5.1. Other than intravenous drug abusers, most patients aim to stay as alert as possible, reaching a point of compromise between pain and sedation.

The adaptive PCA uses a background infusion which decays to zero in the absence of further bolus requests. Inherent safety has here been extrapolated to include the time decaying background infusion of adaptive PCA. In effect a bolus request on the adaptive system can be seen as a bolus request with a decaying infusion component. The infusion component decreases in order to maintain inherent safety and place the patient in control. The maximum length of time for the infusion to reach zero is 3 hours barring intervening bolus requests (Table 4.1, 4.3). Thus despite the infusion component adaptive PCA the concept of patient control is maintained [Hull 1985].
Thus, the patients themselves generally exercise restraint in the use of analgesics. This can be called inherent safety. While not sufficient by itself, inherent safety is nonetheless an important consideration in PCA safety.

6.3 Software Safety

The underlying philosophy for software safety used in the adaptive PCA program is that ‘every process must be within its legal range at every step’. If the slightest doubt concerning program correctness exists, the program is terminated in an orderly fashion. The program has been written in such a way that unless execution stays within very narrowly defined limits, an error will be reported and the pump shuts down. The effect of this philosophy has been an increase in the code of the program by over 50%, because almost every function and every step performs its own independent error checking. The program has been written with safety considerations foremost. Further practical out-workings of this philosophy are detailed below.

6.3.1 Data Protection

The variables used to control the pump are protected from accidental corruption by two means, firstly, by the concept of ‘data protection’ as implemented in the programming language "C++", and secondly, by automatic range checking used to access the protected variables. ‘Accidental corruption’ refers to altering the value of a variable through mistakes in programming, hardware errors, glitches and illegal accessing.

Data protection in C++ is a method whereby variables in a class can be declared ‘private’ and are only accessible by certain functions declared ‘public’ in the same class.

6.3.2 Range Checking
To prevent corrupt data from entering the data store legitimately through public functions, each variable is checked every time it is written to or read. The nature of the check depends on the variable in question, however every variable is range checked. Range checking consists of ascertaining whether the variable has a reasonable value for that particular variable. For example, the value of the SpO2 variable is screened for the range 50 to 100 percent, any other values are clearly erroneous and cause an error to be logged to a file and the program to terminate.

In addition to range checking, a variable can be checked for a number of different properties such as the change in value it underwent since it was last accessed. Some variables are also checked for monotinicity, such as the variable holding the amount of analgesic infused by the pump. The exact type of check carried out depends on the particular variable and the permissible range of values it may take.

Range checking is not only carried out for access to the central data store but also for every function which takes arguments. A valid range of the arguments is determined and any value outside this range flags an error. This practice in particular has been instrumental in preventing error propagation as well as assisting with debugging. Strings which are passed as arguments are a particularly common source of errors and are usually checked for length and valid character range. The power of range checking function arguments is illustrated in the experience of the Microsoft software company. A large number of the initial problems with Microsoft’s Windows program version 3.0 were eliminated by range checking all functions parameters, and this resulted in a more reliable subsequent version.

Program loops which receive data from the outside world, often depend on conditions external to the computer to terminate or exit and are therefore provided with a time out fail-safe mechanism. If for example, the Oximeter should malfunction, the loop reading the value of the Oximeter buffer might never exit unless the time out feature forced an exit from the loop.

One of the benefits of almost fanatical error checking has been faster debugging during development. As the program grew, subtle errors which were not noticed at the time were caught by error checking routines which seemed trivial or redundant at the time. For many ‘if’ statements, the ‘else’ statement is used to check for errors regardless of the apparent likelihood of actually obtaining an error at this point. The same applies to ‘switch’ statements and their attendant ‘default’ statements. In this
sense the program can be said to be actively looking for errors and opportunities to terminate.

### 6.3.3 Bolus Delivery

The danger of overdosing the patient is particularly large at the time of bolus delivery. At this time the pump is set to infuse at a high rate of over 300 ml per hr until the set bolus amount has been rapidly delivered. Should the pump continue infusing at the bolus delivery rate, the patient would be in imminent danger. The software safety features to prevent this are as follows:

1) The time it should take to infuse a particular bolus is calculated and if exceeded the pump is shut down and an alarm is raised.

2) If a bolus infusion exceeds the absolute maximum time for any bolus infusion, pump shut-down occurs.

3) The amount infused by the pump within consecutive 2 second intervals is checked periodically. Any amounts above a preset limit result in the pump being shut down and an alarm raised.

After a bolus amount has been infused, the amount delivered and the amount intended to be delivered are compared and if the difference is significant an error is reported and the program terminated.

A potential threat of overdosing the patient exists if the serial communications cable to the pump is disconnected while the pump is delivering a bolus in the high infusion mode. The computer is then unable to stop the pump. The pump used in this PCA system has a time out safety feature for just such a case. The time-out feature is based on the same principle as the ‘watchdog timer’ found in most computer systems, i.e., under computer control the pump must be addressed via its serial cable at least once within a certain time period, and if this does not occur, it will shut down and raise audio-visual alarms. The time-out period for the Imed 929 pump used in this system is 26 seconds.
6.4 Hardware Safety Features

According to Kluger, malfunction of equipment was one of the biggest concerns of the pioneers of PCA. This concern has proven itself unfounded in practice as judged by the paucity of articles regarding equipment mishaps in PCA [Kluger et al. 1991].

The equipment used for this PCA consists of the actual pump, the controller in the form of a personal computer (PC), two respiratory monitoring devices and accessories such as tubing, a drug reservoir and anti-reflux valves. The infusion pump has its own independent alarms and safety system, including alarms for occlusion, air-in-line, low fluid volume, time out and low battery. Any alarm condition is also relayed to the controlling computer. The pump always ceases operation on registering a serious alarm condition. Any hardware/software failure on the part of the controlling computer which prevents the pump being polled at regular intervals will cause the pump to shut down after a maximum delay of 26 seconds by activating the time-out alarm.

The pump communications protocol has built-in redundancy to verify and check the communications link. Data sent by the pump must be echoed by the receiving device, in this case the computer. Commands issued to the pump are echoed back by the pump. This protocol ensures correct and valid communications between the pump and the computer.

Each monitoring device retains its own alarm features and will detect and initiate an alarm regardless of the fact that it is connected to a computer. The controlling computer does not in any way change or modify the built-in alarms of the oximeter, the capnograph or the pump. The patient thus enjoys the safety features of each of the instruments separately and the system as a whole. This is reasonable given the increased complexity of the system. The computer monitors the data from the oximeter and capnograph and will itself also decide alarm limits based on the data. These computer alarm limits are usually stricter than the limits on the individual monitoring devices.

It should be noted that the monitoring devices provide an extra degree of safety, in that the patient is monitored not only with respect to PCA-related problems, but with respect to any other life-threatening complication which could be detectable by an oximeter and/or a capnograph.
The safety features of the accessories include an anti-reflux valve. The valve is designed to prevent the analgesic solution travelling into the main intravenous line in the event of an occlusion in the common line. Anti-reflux valves are mandatory when PCA is used with a concurrent infusion [Kluger a]. The experimental trials use a concurrent saline infusion, and thus an anti-reflux valve is required.

The two-step process involved in using the handset to obtain a bolus is a further safety feature and guards against accidental triggering.

It can be seen that the PCA hardware features a considerable number of safety considerations.

### 6.4.1 Infusion Pump Accuracy

Drug infusion pumps in normal conventional clinical use are usually accurate to within ±5% of the set volume. Under computer control and with frequent rate changes this accuracy was recently shown to remain at the nominal ±5% for three common commercially available drug infusion pumps [Connor et al.1992]. Based on results of previous trials and the results reported by Connor, the accuracy of the pump used in this system has been judged satisfactory.

### 6.5 Patient Selection for PCA

Safety is considerably enhanced by screening patients. Some patients are unsuitable for PCA, in particular those with hypovolaemia, labile cardiovascular parameters, a history of drug abuse and the confused [Tamsen et al.1982 c]. The very young and those unable to operate even simple handsets are also unsuited for PCA.

The psychological make-up of the patient may also render them unfit for PCA therapy. The psychological concept of ‘locus of control’ was discussed in section 2.4 and has been developed into the Multidimensional Health Locus of Control (MHLC) scale. Briefly, those patients with an ‘external locus of control’ attribute positive reinforcement to other people or events, with subsequent loss of control, reliance upon others and a more frequent failure of the PCA technique [Kluger et al. 1991]. To
date no uniform, reliable and simple assessment for screening patients for suitability in terms of psychological parameters is available. The judgement of the physician and nurse is the most important aspect of patient selection in all respects.

6.6 Patient Errors and Education in PCA Therapy

Appropriate education in the use of PCA also contributes to PCA safety. Education prevents failure to understand PCA therapy and ensures that patients do not put themselves at unnecessary risk. The patient should receive pre-operative instruction in PCA use and should be made fully aware of the safety features and goals of PCA. Such pre-operative education not only allays any fears the patient may have about PCA, but can also reduce general anxiety about the impending operation, thus contributing to a less traumatic experience overall. Pre-operative education is being carried out for all patients using this PCA system.

6.6.1 Tampering with the PCA Device

Tampering with the PCA device usually involves drug abusers who modify the system for additional analgesic. If the patient selection process fails to identify drug abusers, the system must withstand attempts to modify it for higher analgesic rates. Direct reprogramming for additional amounts is not possible with the Melbourne University PCA as there is no user programming for bolus sizes and background infusion involved in this system. The only way an additional amount could possibly be obtained would be to disconnect the infusion pump from the computer and to reprogram the pump manually. However, the computer would raise an alarm should the pump remain unresponsive for longer than a preset time interval. Modifications of this kind require a high degree of sophistication and knowledge, and the risk of its occurrence has been judged small, particularly in view of the fact that patients are carefully selected and screened in the trials for this system.

6.7 Operator Errors
White lists the following possible operator errors: mis-programming the PCA device, failure to clamp or unclamp tubing, improperly loading syringe or cartridge, failure to respond to safety alarms and misplacing the PCA pump key [White 1987]. In the same article, White also gives details of two mishaps involving PCA. In one case, the nurse changing the cartridge containing the analgesic neglected to cross clamp the tubing connecting the cartridge to the IV catheter which caused the patient to receive a sizeable bolus, resulting in seizure-like motor activity. It should be noted that this kind of human error is not uniquely PCA related but is possible in any situation involving an electronic infusion device. In the second case, the PCA was mistakenly reprogrammed at a very high bolus amount by the ward nurse. In both cases, the patients were successfully resuscitated with no lasting ill-effects. A more recent respiratory arrest using PCA was reported in correspondence by Simes et al. [Simes et al. 1996].

The University of Melbourne PCA system has been designed using a constant analgesic concentration such that there is no need for the clinician to enter instructions for individual patients, which eliminates one of the major sources of operator-induced mishaps. If there was a need for this system with variable analgesic concentrations, such as in a commercial application, some programming would be required. In this particular case as well as in all cases of PCA systems needing extensive programming, it may be advisable to include a basic screening algorithm which performs various cross checks to ensure that the bolus and infusion amounts have reasonable values. The analgesic concentration would have to constitute a pivotal piece of information without which the system should not operate at all.

Adequate education on the principles and aims of PCA is especially important for all operators of PCA devices. It is also important that the operators (nursing staff) keep the patient under close observation at all stages of PCA use.

6.8 System Tests

The PCA system was continuously tested during development. The latest changes were incorporated into a working program, and the program was run almost every night for five months, giving in excess of 1500 test hours.
The complete system was tested exhaustively using a specially developed program to simulate the oximeter and the capnograph. The simulation program was resident in a second PC and sent exactly the same string to the serial ports of the PCA computer as the oximeter and the capnograph. As far as the PCA system was concerned, there was no difference between the actual patient monitors and the simulated monitors. The advantage of the simulation program was that it allowed exploration of the widest possible spectrum of possible patient parameters (SpO2, RR, ETCO2). This ensured the system reacted appropriately at all levels. It would be very difficult to obtain these parameter values from the monitors themselves. The simulation program can also be used at any time to retest the system.

A complete operational system is shown in figure 6.1 below.
Figure 6.1 The complete PCA system
6.9 Summary of Adaptive PCA Safety

The PCA system described here has been designed with safety as a top priority. Safety considerations have guided the development of the system as such, the operational protocol and the actual software. The system uses two clinical monitors to enhance patient safety. The system has been tested under a wide range of simulated patient conditions and has reacted correctly in all cases.
Chapter 7 Clinical Trials

7.0 Introduction

This chapter gives an outline of the hospital trials using the PCA system developed at the University of Melbourne and the Royal Melbourne Hospital.

The trials aim to establish whether the proposed current system is able to provide substantially better pain relief by addressing some of the shortcomings of conventional PCA listed in section 1.2.1.

A further aim of the trials is to practically evaluate many of the theoretical assumptions made in the process of developing this PCA and to re-evaluate the choice of PCA parameters in the light of clinical experience.

7.1 Previous Trials at the Royal Melbourne and Royal Women’s Hospitals

A prototype of the current PCA system was designed at The University of Melbourne by the author’s predecessor Mr Zheng-Ming Xu and trial tested in the Royal Women’s Hospital on 23 patients who had undergone Caesarean section. The results of these trials inspired the development of the current PCA system.

The prototype system used the same background infusion algorithm as the current system, but did not include the expert system or high adaptation range. The prototype handset consisted of a rotary dial to indicate various pain intensity levels and has been described in section 5.7. There was provision for an optional oximeter. The prototype verified the feasibility of the bolus and time-dependent background infusion algorithm and of using a handset capable of registering a range of pain intensity levels.
7.1.1 Results of Previous PCA System Trials

The results of trials on ten patients, using the PCA system prior to the current version, are shown below in figure 7.1.

Figure 7.1 Trial results from the previous PCA system at the Royal Women’s Hospital
The figure shows the average results obtained from 24 hours of operation of the PCA system when used by ten different patients. The pain scale refers to the average of the button number pressed for ten patients on an hourly basis. Button numbers ranged from 1 to 10, with 10 representing the highest pain intensity level. The dose and the number of demands also refer to the average for ten patients per hour. Over the first 4 hours the level of pain experienced by the patients declined rapidly and dosage fell. Between 5 to 12 hours into the trials, many of the patients slept and pre-programmed reductions of the dosage levels occurred in the absence of demands from those patients. Over the 13 to 16 hour period postoperatively the patients awoke, registered increased levels of pain and reactivated the demand for analgesic. Figure 7.1 shows that the PCA system is effective in matching dosage levels to levels of pain experienced by the patients [Rudolph et al. 1993].

From favourable observations of these exploratory trials it was decided to proceed to the current PCA system.

In the preliminary trials, there also seemed to be some indication of earlier mobilisation for women who had Caesarean births and used the PCA system. This observation was however not published in the literature but reported in the popular press [Cribb 1992].

### 7.2 Trial Structure

The clinical trials for the current adaptive PCA system were structured as follows. A double-blind, crossover design was planned and is shown schematically in figure 7.2 below.
Each patient used the two PCA systems simultaneously, the first being the new system developed at The University of Melbourne and the second being an Abbott Lifecare® 4200 PCA system. One PCA system delivered an active analgesic solution, whilst the other delivered a placebo solution (normal saline). Upon a bolus request, both systems simultaneously infused a dose into the patient. The nursing staff were not aware of which system contained the active solution. The solutions were prepared independently by a third party. A random sequence was used to determine which system was first assigned the active solution. Every 12 hours the active and the inactive solutions were interchanged, to produce a crossover trial.

The patients were unaware of which system delivered the active analgesic solution. The University of Melbourne PCA ten button handset was used to trigger both the University and the Abbott systems. The infusions from both PCA systems were combined using a ‘Y’ connector and an anti-reflux valve, so that the patient only had a single intravenous cannula as for single system operation.

Recording of data consisted of automated data logging by the adaptive PCA system and regular questionnaires administered by the research nurses and the author. The ward staff were not required to perform any additional documentation compared to regular conventional PCA.

### 7.2.1 The Rationale Behind the Trial Structure

The rationale for using two PCA systems for the same patient was to provide a trial structure with its own built-in control and to eliminate as much as possible the psychological differences that would be expected if a conventional PCA was trialed separately from the University of Melbourne system. As was pointed out in sections 2.3, 2.4, 3.3.2, pain and pain perception have a large psychological component and can be modified by a range of as yet incompletely understood factors. It was thought that the equipment used and the subsequent attention focussed on the University of Melbourne adaptive system could influence the experimental results if separate trials were conducted. The equipment used for the adaptive system involved a personal computer, an oximeter and a capnograph as well as a handset with numerous buttons. The patient was furthermore required to wear a cannula and to tolerate an oximeter probe attached to a finger. Such an array of equipment was thought very likely to...
leave a subjective impression of an unpredictable nature on the patient when compared to the much more simple and compact commercial models. (The capnograph and its cannula were deleted from the adaptive system after the 4th of April 1995)

The increased attention bestowed upon patients using a new experimental PCA system is another factor which would be expected to influence the results of separate trials.

A further reason for using a structure in which patients provide their own control is the difficulty in comparing data across patients even for the same kind of operation. Individual differences are hard to eliminate and require a large test population in order to obtain statistically significant results. The above trial structure allowed the system to be tested in the varied environment for which it is ultimately intended.

The trials were designed to provide their own control, in the sense that the only major difference between the two PCA systems as seen by the patients consisted of their control algorithms. It was the control algorithms which were therefore tested in the double blind crossover protocol.

7.3 Issues Addressed in the Royal Melbourne Hospital PCA Trials

The trials aimed to establish whether the features of the PCA system developed at the University of Melbourne provided better pain relief compared to fixed bolus and or fixed background infusion PCA. The following issues were addressed in the trials.

The question outlined in section 3.2.1 concerning whether patients titrate analgesic for diminution of pain or make demands to essentially consistent MEAC levels was addressed in the trials. If patients generally titrate up to and slightly beyond a minimum effective analgesic concentration (MEAC), the number of button presses should reflect this as the active PCA switches between the Abbott system and the University of Melbourne system. On average a different hourly button pressing rate would be expected for an active Abbott system, because the bolus size was fixed.

If patients press only for diminution system, then the number of button presses would be expected to be the same regardless of which system was active. This assumes that the bolus dose of each system results in approximately the same pain
diminution. The blood analgesic levels would also be expected to vary largely between the two groups. It should be noted that the number of requests, or even the amount of analgesic administered, does not always accurately reflect the blood plasma levels of analgesic [Gourlay et al. 1988].

The trials also sought to substantiate the rationale behind the third objective which is to provide analgesic at increased amounts early in the postoperative period where high amounts for a short time are sometimes needed and also to possibly aid postoperative recovery. This is based on the observation of physicians at the Royal Melbourne Hospital that early adequate postoperative pain relief, at whatever dosage level the patient requires it, seems to ensure greater continuous comfort and enhanced recovery. In a recent study of three patient groups by McCoy, the group which experienced early inadequate analgesia continued to experience insufficient pain relief for the remainder of the postoperative stay, despite an eventually higher total analgesic consumption [McCoy 1993].

7.4 Adaptive PCA Trials at the Royal Melbourne Hospital

As the patient population using PCA in hospitals is heterogenous and the trials were designed to provide their own control, all patients deemed eligible for conventional PCA were candidates for the adaptive PCA trials. Thus the trial population for the adaptive PCA trials is mixed and trials vary in their starting times and type of operation. The trials were designed to test the adaptive system in the environment for which it is eventually intended.

The ultimate aim of these trials has been to test the robustness and effectiveness of the system in a large cross section of the patient population and to ascertain whether the system deserves further development with more extensive and rigorous clinical trials.

The table below outlines the patient trials undertaken at the Royal Melbourne Hospital from December 1993 until July 1995.
### Royal Melbourne Hospital Patient Trials

<table>
<thead>
<tr>
<th>Date</th>
<th>Patient Code</th>
<th>Observations &amp; Notes</th>
<th>Patient’s response</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Dec 93</td>
<td>1-2/12/93</td>
<td>Too confused to use patient handset, unsuitable for PCA of any type.</td>
<td>No trial</td>
</tr>
<tr>
<td>22 Feb 94</td>
<td>2-22/2/94</td>
<td>Technical problems coupled with low analgesic requirements led to abandonment of the trial</td>
<td>No trial Patient placed on conventional PCA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Actual trials commence from this time onwards</td>
<td></td>
</tr>
<tr>
<td>13 Apr 94</td>
<td>3-13/4/94</td>
<td>Adaptive PCA only - no crossover trial</td>
<td>Patient very enthusiastic and satisfied</td>
</tr>
<tr>
<td>20 Apr 94</td>
<td>4-20/4/94</td>
<td>First formal double-blind crossover trial History of nausea following morphine</td>
<td>Patient volunteered for trial based on observations of previous patient</td>
</tr>
<tr>
<td>4 May 94</td>
<td>5-4/5/94</td>
<td>Total hip replacement</td>
<td>Patient used PCA before painful manoeuvres</td>
</tr>
<tr>
<td>21 Jun 94</td>
<td>6A-21/6/94</td>
<td>Conventional PCA inadequate - Non trial Adaptive PCA only</td>
<td>Extremely high analgesic demands</td>
</tr>
<tr>
<td>24 Jun 94</td>
<td>6B-24/6/94</td>
<td>Special request for adaptive PCA</td>
<td>Very high analgesic requirements</td>
</tr>
<tr>
<td>7 Jul 94</td>
<td>7-7/7/94</td>
<td>Patient enrolled in PCA trial following failed epidural.</td>
<td>Experienced nightmares and nausea</td>
</tr>
<tr>
<td>9 Aug 94</td>
<td>8-9/8/94</td>
<td>Patient used the PCA system well</td>
<td>Good use of PCA to control pain</td>
</tr>
<tr>
<td>19 Sep 94</td>
<td>9-19/9/94</td>
<td>High analgesic demand, conventional system unable to meet requirements in 12-24 hour period</td>
<td>Formal trial discontinued after 24 hours and adaptive PCA only used</td>
</tr>
<tr>
<td>20 Sep 94</td>
<td>10-20/9/94</td>
<td>Patient made regular use of PCA for first 12 hour period only</td>
<td>PCA discontinued through lack of use after 24 hours</td>
</tr>
<tr>
<td>26 Oct 94</td>
<td>11-26/10/94</td>
<td>Motorbike accident: surgery to arm and leg.</td>
<td>First instance in which both safety monitors were connected.</td>
</tr>
<tr>
<td>4 Nov 94</td>
<td>12-4/11/94</td>
<td>Orthopaedic surgery (leg)</td>
<td>Prior drug experience some hallucinations</td>
</tr>
<tr>
<td>4 Nov 94</td>
<td>13-4/11/94</td>
<td>Lumbar laminectomy Patient strongly encouraged by nursing staff to use PCA</td>
<td>Excessive nausea called for cessation of trial after 14 hours.</td>
</tr>
</tbody>
</table>

*An Adaptive System for Patient-Controlled Analgesia*
Table 7.1 Part 1 All patient trials in chronological order

<table>
<thead>
<tr>
<th>Date</th>
<th>Day</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 Nov 94</td>
<td>14-8/11/94</td>
<td>Patient had experienced PCA previously</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Preferred adaptive PCA handset however criticized the weight</td>
</tr>
</tbody>
</table>

An Adaptive System for Patient-Controlled Analgesia
## Royal Melbourne Hospital Patient Trials (continued)

<table>
<thead>
<tr>
<th>Date</th>
<th>Patient Code</th>
<th>Observations &amp; Notes</th>
<th>Patient’s response</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 Nov 94</td>
<td>15-9/11/94</td>
<td>Chronic pain sufferer (angina)</td>
<td>Moderate use of PCA Preferred single button system</td>
</tr>
<tr>
<td>2 Dec 94</td>
<td>16-2/12/94</td>
<td>PCA trial following failed epidural analgesia</td>
<td>Preferred PCA when compared to previous non-PCA experience</td>
</tr>
<tr>
<td>12 Jan 95</td>
<td>17-12/1/95</td>
<td>Placed on PCA following failed epidural analgesia</td>
<td>Initial frequent use PCA</td>
</tr>
<tr>
<td>18 Apr 95</td>
<td>18-18/4/95</td>
<td>Patient initially hesitant to use PCA, some clarification and information given</td>
<td>Eventual full use of PCA made to achieve good analgesia</td>
</tr>
<tr>
<td>28 Apr 95</td>
<td>19-28/4/95</td>
<td>Chronic pain sufferer (arthritis)</td>
<td>Sparing use of PCA</td>
</tr>
<tr>
<td>10 May 95</td>
<td>20-10/5/95</td>
<td>Patient with professional medical knowledge</td>
<td>Patient reduced PCA use following initial nausea</td>
</tr>
</tbody>
</table>

Table 7.1 Part 2 All patient trials in chronological order

The first two patients who were consented for the trials never participated in an actual trial. The first patient (No 1-2/1293) was found to be too confused and disoriented upon recovery to use any form of PCA. The second patient (No 2-22/2/94) was unable to use the adaptive PCA system because of technical difficulties and was placed on conventional PCA instead. Thus actual patient trials effectively start with the third patient, No 3-13/4/94.

Data was gathered in a number of ways: Quantitative data was written to file on a continuous basis throughout the trial period by the personal computer used for the adaptive system. Primarily qualitative data was obtained from questionnaires administered by the research nurses at the time of changeover from one system to another. These questionnaires are called ‘12 hour questionnaires’. In addition, from trial number 11 onwards, an ‘end of trial questionnaire’ was administered by the author at the cessation of the official trial period. The complete questionnaires can be found in appendices D and E as well as in condensed form in the key of appendix G. Full details of all data for each trial can be found in appendix G.
Chapter 7 Clinical Trials

Throughout a clinical patient trial the author and the research nurses maintained close personal contact with the patient and the nursing staff responsible for the patient.

7.4.1 Ongoing Refinements of the PCA System

The initial patient trials served to test and refine the PCA software and hardware in ‘the field’ in a way earlier laboratory tests could not. The PCA software was modified in minor ways continually as the trials proceeded. Most of these modifications were related to user interfacing and data logging for analysis purposes.

Minor adjustments included changes in the startup menu, additional message boxes to warn users of common errors and extra functions to write data to text files in a format suitable for use in a spreadsheet application program.

Below is a list of major modifications and adjustments made over the course of the trials.

1) The algorithm made provision to reduce all bolus and infusion amounts by half for patients aged over 60 years. After trial number 3 and 4 it was found that the background infusion level for the over 60 year old patients decayed to zero after 2 or 3 hours into the trial and did not rise again with increasing bolus doses. It was found that the infusion thresholds had not been adjusted to respond to half of the normal levels for over 60 year olds. The infusion was set to respond to double the bolus levels for under 60 year old patients.

The effect of this was that for these first three trials (up to patient No:5-4/5/94) the adaptive PCA had become bolus only PCA with no background infusion, except for the decaying infusion at the start of a new PCA run. The effect of this may be seen in the graphs of patients 3,4 and 5 in appendix G.

2) The background infusion algorithm was designed to start at 2.5mg/hr following the first ever bolus request made by a patient in a trial. The PCA program made provision to exit the PCA mode and enter into a waiting state. It was then possible to continue at the previous levels later. It was found that if the program was exited completely or the computer was turned off, a starting background infusion level of 2.5mg was again infused for the first bolus following startup. In other words the program did not “remember” that a startup background infusion had been given previously. If the program was put into the wait mode without exiting this problem did not occur. The problem was rectified after patient number 10-20/9/94.
The effect of the above problem was that some patients were given an average startup bolus and background infusion rather than the actual infusion level from the time before the program was fully exited. The difference between the actual analgesic infused and the amounts intended to be infused according to the infusion algorithm were found to be small. The difference is thought to have only a negligible effect on the early trials especially in view of the fact that the trials as such vary in many other ways and were often beset by unplanned medical or technical disruptions.

From ongoing trials the capnograph was found to be impractical as a monitoring instrument and was excluded from the adaptive system from the 4th of April 1995 and patient trial 18 onwards. A full discussion of the monitoring equipment and reasons for this decision can be found in section 7.4.2 below.

7.4.2 Evaluation of the Safety Monitors: Intelligent Data Acquisition for the High Adaptation Range

The PCA system was tested and refined in the normal adaptation range for the first 12 patients. Subsequently it was felt that the high adaptation range warranted more detailed investigation and thus the Oximeter and the Capnograph were connected for some of the following patients. The high adaptation range was in fact not required but a number of problems were uncovered in the process, the most significant of which was the unreliability of the sensing techniques used in the high adaptation range.

The high adaptation range required both monitors to be connected and to furnish a constant stream of data. Any period of invalid data in the data stream would cause the system to reset itself to the normal adaptation range. It was found that the data stream was frequently interrupted by the patient’s movements to the extent that it was impossible to enter or remain in the high adaptation range for any significant period of time. The interruptions to the continuous stream of data were of such duration that the filtering and compensation mechanisms described in section 5.3.3 were inadequate. The data filtering software was designed to deal with short term data loss however the extend of actual disturbances to the data stream was beyond the limits of meaningful filtering. Figure 7.3 below shows the trace of the oximeter for patient 17-12/1//95 for the 12th of January 1995.
The oximeter probe was easily moved and movement of the limb to which it was attached would frequently result in erroneously false readings, trivial alarms, or no valid SpO2 data. While this was acceptable for general monitoring purposes it was not acceptable for the high adaptation range algorithm used in the trials. In practice this would mean that the patient would drop out of the high adaptation range whenever the data stream was interrupted for more than a certain time period. While this would not pose a safety risk it would make effective use of the high adaptation range as implemented so far impossible.

Pulse Oximetry is well known for its susceptibility to motion artifact. Wiklund found that more than 75% of Pulse Oximeter alarms were trivial [Wiklund et al. 1992, Wiklund et al. 1994]. Attempts at reducing the impact of motion artifact using neural networks have been made by Egbert et al. [Egbert et al. 1993b].

A similar situation to the problem described for the Pulse Oximeter was encountered with the capnograph monitoring the respiration rate (RR) and the ETCO2 levels. A small nasal cannula was used to obtain the expired CO2 levels and an oxygen mask was fitted over the patient’s nose. This arrangement was found to be more sensitive to disturbance than the oximeter. The flexible nasal cannula was subject to movement...
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and if not positioned properly in the patient’s nostrils would frequently elicit a “line blocked” alarm condition from the capnograph.

Thus the monitoring system originally intended for the high adaptation range was found to be inadequate and an alternative data evaluation algorithm for monitoring the patient in the high adaptation range was devised.

Using intuitive human evaluation as a guideline for evaluating irregular Pulse Oximeter readings the following algorithm was used to evaluate the data coming from the monitors.

A moving window containing the filtered monitor values of the last X minutes was examined for a continuous Y second interval of valid data. The longest continuous data interval exceeding Y seconds was used as the basis for deciding the alarm status for that monitor.

Consultation with clinical staff resulted in an initial value of 5 minutes for X and 10 seconds for Y. These values were empirically determined, drawing on the expert knowledge of clinicians. 5 minutes for X was thought to be the maximum practical time limit for a moving average window in which the patient was thought to be safe, however 3 minutes was chosen as a reasonable value which would give an added margin of safety. It was thought highly unlikely that a patient’s condition would deteriorate drastically in less than 3 minutes due to PCA use.

The above algorithm was tested on patients in the ICU who most closely approximated PCA patients in terms of mobility and level of arousal. Testing of the Oximeter and the Novametrix Capnograph took place in the first half of 1995. From these tests and the formal PCA trials the following results were obtained.

The Novametrix Capnograph was found to be especially difficult to use in practice on two counts:
1) The nasal cannula required to take measurements was unreliable and uncomfortable. Even when fitted properly patients would frequently remove it or reposition it resulting in movement artifact and possible dropout from the high adaptation range if applicable.
2) The particular Capnograph used was very sensitive to mechanical disturbance of the cannula and the associated pneumatic system as well as the CO2 sensor. This made the system extremely sensitive.

It was found that the Capnograph used in this application was intended for monitoring of critical care conditions where patients are usually not mobile and often

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unconscious. For these extreme conditions the sensitivity and complexity involved in monitoring are justified and indeed mandatory. The PCA patients with which this monitor was used were however far more mobile and not in the kind of critical condition for which this monitor was intended.

Considering the fact that measuring the ETCO2 values presented the bulk of the difficulties in using this monitor and that the ETCO2 values are not of primary importance in this application it was considered advisable to forego the measurement of ETCO2 values and concentrate on the oximeter as the primary monitoring tool. Although it is conceptually proper to use CO2 and respiration rate monitoring it was found not feasible for bedside practice in this application. The decision to eliminate CO2 monitoring was made on April 4th 1995 by the medical staff responsible for the PCA trials.

The Oximeter used in this PCA system was an Ohmeda Biox® 5000. Definite improvements in eliminating short term artifacts were noted after implementing the above algorithm.

A further method for eliminating motion artefact from oximetry data using a template is described by Jones [Jones et al. 1992]. The template uses the fact that signal amplitude from the plethysmograph increased prior to episodes of desaturation caused by movement artefact to filter out episodes of movement artefact. Retrospective identification of signal amplitude preceding artefactual desaturation allowed a reduction of 25% of absolute incidents. A similar method using two oximeters was used in a study by Visram [Visram et al. 1994]. None of these methods were used in the adaptive PCA system however future trials may benefit from these techniques and could be combined with the methods already described above.

The principal difficulty in monitoring PCA patients with existing equipment lies in the fact that these patients are usually quite mobile whereas the monitoring equipment used in this PCA system was primarily intended for more critical situations in which the patient is not usually mobile enough to interfere with the monitoring process.

One of the principal practical requirements of the high adaptation algorithm lies in the need for a continuous uninterrupted data stream. Movement artifact generated by patients was a major impediment to entering and remaining in the high range. Thus it may be advisable to change the high range adaptation requirement for a continuous uninterrupted data stream by changing the high range algorithm itself to a more robust one. It may be possible to use a high range algorithm in which the range of available boluses is increased by a certain percentage subject to a number of shorter term
monitoring constraints. Alternative algorithms are briefly discussed in chapter 8 section 8.3.1.

A simple low cost and relatively non-invasive nasal catheter for capnographs is discussed by Jones et al. who describes a modified Benjamin Jet Anaesthetic Tube™ (Tuta Laboratories, Australia) which provided satisfactory respiration data was easy to insert and and did not cause any discomfort in 77% of patients [Jones et al. 1996]. A laryngeal mask and facemask were compared in a study by Ivens, and the laryngeal mask was found to be more reliable in estimating arterial carbon dioxide partial pressure by monitoring end-tidal carbon dioxide [Ivens et al. 1995]. Whether either of these methods, especially the modified Benjamin Jet Anaesthetic Tube, are feasible in the more mobile PCA patient population would need to be trialed in a clinical setting but was not tested in the trials described here.

A new acoustic air flow sensor using differential multi-point air-flow detection in the nose and mouth region is described by Hok and was found to be a good patient monitoring sensor in clinical trials [Hok et al. 1993, Wiklund et al. 1994]. Such new methods may well be worth investigating for respiration rate monitoring for adaptive PCA. Hok also found that oximetry monitoring had a “low sensitivity to respiratory disorders.” [Hok et al. 1993].

From the patients point of view, the oximeter and capnograph probes were found to be inconvenient. Prior to deletion of the Capnograph the number of connections from the patient to the PCA system came to 4 for the high adaptation range as opposed to 2 in the normal range. Patients interviewed in these trial series generally disliked large numbers of connecting lines, which were felt to be intrusive and bothersome.

Other methods for monitoring respiration rate and or arterial CO2 concentrations may need to be considered in the future. Transthoracic impedance monitoring using ECG leads and transcutaneous CO2 measurements were both rejected at this stage for being too invasive and costly. The Graseby 108 respiration monitor mentioned in section 5.8.3 may be worth reconsidering in view of the difficulties encountered thus far.

7.5 Evaluation of the PCA Handset

The handset was one of the elements of the PCA system that was tested in the clinical trials. This section outlines the changes and improvements made to the handset during
the course of the trials, gives details of patients’ criticisms of the handset and concludes with an overall evaluation. Details of the handset design can be found in sections 4.3 and 5.7.

7.5.1 Modifications During Clinical Trials

The handset was modified and improved during the course of the trials. A particular problem with the first two successful trial patients (3 and 4) was the difficulty of finding and using the handset at night. The patients would call for the nurses and ask for the light to be turned on so in order to be able to see the handset face plate and press the button of their choice. This problem was rectified by installing a small light globe inside the handset which made it easy to locate and illuminated the semitransparent face plate of the handset from the rear. The patients were 74 and 81 years old and had no other difficulties using the handset.

All digits from 0 to 10 were initially printed next to the 3-coloured wedge covering the 10 buttons. The numbers from 0 to 10 created confusion because the patients felt a need to press specific buttons and yet the buttons themselves were not visible under the wedge overlay. The difficulty lay in the fact that the patients seemed to decide on a number and then tried to find that number on the scale. It became clear that education in the use of the handset should either teach patients to select a number and aim for that (on a modified handset) or no numbers should be shown and only the analog sliding approach should be taken. It was decided to only show the numerals 0 and 10 at either end of the scale as anchoring points, since in the verbal analogue scale patients are asked to rate their pain between 0 and 10. Using these two numbers as reference points draws on the principles of the verbal analogue/numeric scale. Section 4.3.2.1 gives more details of the rationale behind this.

Subsequent adaptive PCA education asked patients to rate their pain on an analogue scale rather than attempt to quantify their pain level by giving it a number and then seeking to find that number on the handset. The original intention was always to use an analogue approach. This episode highlighted the importance of not mixing the type of augmenting cues employed.

7.5.2 Simplicity Versus Complexity of Handset Use

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End of trial questionnaire questions designated as A1 to A8 in the key for appendix G were designed to explore the patients’ use of the handset. The following questions quoted from the end of trial questionnaire were designed to probe for any difficulties patients might have had using the handset.

A2) Did you have difficulties requesting pain medication from the PCA system?
   A) No    B) Yes - please explain the nature of the difficulties:

A3) How long did it take you to fully understand how to operate the handset buttons?

A5) Did you find the handset:  A) Easy and simple to use          B) Complex and difficult to use.            C) Difficult to use at the beginning and easy to use after that

### Table 7.2  End of trial questions relating to the ease or otherwise of handset use

<table>
<thead>
<tr>
<th>Trial No</th>
<th>Qu: A2</th>
<th>Question: A3</th>
<th>Question: A5</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>A) No</td>
<td>Easy - not long at all</td>
<td>A) Easy and simple to use, - Initially hard to use with only one hand</td>
</tr>
<tr>
<td>12</td>
<td>A) No</td>
<td>“Straight away”</td>
<td>A) Easy and simple to use</td>
</tr>
<tr>
<td>14</td>
<td>A) No</td>
<td>“Simple”</td>
<td>A) Easy and simple to use</td>
</tr>
<tr>
<td>15</td>
<td>A) No</td>
<td>“Two minutes, it’s a simple thing”</td>
<td>A) Easy and simple to use</td>
</tr>
<tr>
<td>16</td>
<td>A) No</td>
<td>N/A (No answer)</td>
<td>“Awkward” - (handset was too heavy, sat directly on patient’s wound)</td>
</tr>
<tr>
<td>18</td>
<td>A) No</td>
<td>“Fairly quickly”</td>
<td>A) Easy and simple to use</td>
</tr>
<tr>
<td>19</td>
<td>A) No</td>
<td>A few explanations</td>
<td>A) Easy and simple to use</td>
</tr>
<tr>
<td>20</td>
<td>A) No</td>
<td>“Not long at all”</td>
<td>A) Easy and simple to use</td>
</tr>
</tbody>
</table>

Patient 19 expressed some concern about how to change an initial selection. Patient 16 found the handset “awkward” and too heavy as it was positioned directly over the patient’s wound.

The use of the handset was explained pre- and post-operatively. No patient required more than a few minutes to grasp the concept of handset use. The two-step algorithm for requesting a bolus did not present any difficulties for the trial patients. It is particularly noteworthy that patients from a range of educational and social backgrounds seemed equally adept at using the handset.
7.5.3 Specific Criticisms of the Handset

The following questions quoted from the end of trial questionnaire were designed to investigate patients’ reception of the handset in terms of the ability to register varying degrees of pain and to choose the bolus dose as well as the overall design of the handset.

A1) Have you ever used a PCA device before? A) No B) Yes, and for how long?

A4) Would you have preferred a single choice single button system or a multi-choice multi-button system? A) Single button, single choice B) Multi-button, multi-choice Would you like to give reasons why?

A6) What did you like least about the system?

A7) What did you like best about the system?

A8) Is there anything you would like to change about the handset if you could? A) No B) Yes: What?

<table>
<thead>
<tr>
<th>No</th>
<th>A1</th>
<th>Question: A4</th>
<th>Question: A6</th>
<th>Question: A7</th>
<th>Question: A8</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>No</td>
<td>B) Multi-button</td>
<td>Problem of running out of morphine</td>
<td>Ability to control pain relief and choice of gradient</td>
<td>B) Smaller, lighter, chord annoying, one handed operation</td>
</tr>
<tr>
<td>12</td>
<td>No</td>
<td>B) “If only need a little. Good no real issue”</td>
<td>“Nothing to say against it. Nothing wrong, it was there”</td>
<td>Simple control, own administration, “a top system”</td>
<td>A) NO</td>
</tr>
<tr>
<td>14</td>
<td>Yes</td>
<td>B) Liked choice, but handset too big”</td>
<td>“Handset too big”</td>
<td>“For pain, this (adaptive) PCA is better”</td>
<td>N/A</td>
</tr>
<tr>
<td>15</td>
<td>No</td>
<td>“10 buttons all right. Probably one button would make it much easier”</td>
<td>N/A</td>
<td>“Very simple, absolutely simple... One button would be even simpler”</td>
<td>“Too heavy and clumsy, better: smaller and lighter”</td>
</tr>
<tr>
<td>16</td>
<td>No</td>
<td>A) Single button. “Oh I don’t know I’m not very cluey about computers”</td>
<td>N/A</td>
<td>N/A</td>
<td>“Lighter...” (Patient’s hands were swollen, buttons difficult to press)</td>
</tr>
<tr>
<td>18</td>
<td>No</td>
<td>B) “Good to be able to express the variance in pain”</td>
<td>Restricted movement. Handset too bulky.</td>
<td>“Setting own pain reduction- not by someone else”</td>
<td>B) Yes: Not so bulky</td>
</tr>
</tbody>
</table>
Table 7.3 Questions 1, 4, 6, 7, 8 from the end of trial questionnaire relating to the concept of the handset.

Some of the patients criticised the buttons on the handset for being hard to press and feel. Some patients found the “Go” button in particular difficult to locate under the membrane overlay. This was in a large part due to the fact that the surrounding cover plate was positioned at the same level as the buttons which were in effect buried a little too deeply in the face plate. It is recommended that future versions should aim at making the buttons beneath the overlay bigger and raised above the level of the face plate. The “Go” button could be made larger and perhaps faintly illuminated. Raising the buttons above the face plate should enhance tactile recognition. The buttons on the trial handset were positioned so as to avoid false triggering. From observation of patients the handset was usually kept well clear of all bedding, uncovered and face up, thus reducing the danger of accidental triggering.

The size and weight of the handset was most frequently criticised by patients. One potential trial patient refused consent on these grounds after being shown the handset. This patient had previously used an Abbott single button handset. It should be pointed out that the handset used in the trials used a custom-built plastic moulded case. The case contributed approximately 70% of the total weight but future designs would considerable reduce this percentage.

7.5.4 Multi-Button Versus Single Button Handset

This section covers questions and answers relating to the central issue of giving patients a method of expressing pain intensity. Questions 1A, 4A and 8A in table 7.3 from the end of trial questionnaire were designed to investigate patients’ reception of the multi-button multi-choice handset. Although questions 6A and 7A are not directly concerned with the issue of the multi-button handset this issue was touched upon in
the answers to these questions. The answers in table 7.3 indicate that the choice of buttons was well received by most patients.

Patient 15 was the only patient of those completing the end of trial questionnaire who suggested a single button and did not seem to see any advantage in the trial handset. Patient 16 seemed to be indifferent to the issue of the handset. Similarly patients 12, 19 and 20 seemed to simply accept the element of choice offered by the trial handset with no marked opinion on the subject. In contrast patient 11 had identified both the choice “gradient” and the ability to control the pain himself as the advantages of the system. Likewise patients 14 and 18 clearly preferred the choice offered by the handset.

All patients were able to operate the handset without difficulty. From personal contact during the course of trials it was also noted that patients of their own volition identified the concept of being able to express a range of pain levels as important.

7.5.5 Overall Evaluation of the Handset

The major criticisms of the handset relate to the size and weight of the unit. Much of the size and weight can attributed to the fact that the handset was manufactured as a prototype within the constraints of a research project. It is envisaged that any future versions would address these problems through the use of specialized technology. It should be noted that the handset used in the clinical trials described in this thesis is the third version and has been the product of progressive refinement.

Nurses involved in the trials observed that some patients did not like to have equipment of the size of the handset in their beds. Patients also seemed to feel somewhat ‘territorial’ about their bed space. This was a generally observed phenomenon not confined to the handset used in this trial. This is also a further reason for reducing the size and weight of the handset as much as possible for any future versions.

The electrical cable connecting the handset to the PCA was at times rather inconvenient by restricting movement and placement of the handset. The unit could be improved through the use of wireless technology. The absence of an electrical lead would make the handset more user-friendly and less intrusive. This idea was greeted with enthusiasm by patients.

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A possible future version of the handset could be a wireless light-weight unit the size of a video remote controller which could be pinned to clothing or the bed linen without undue disturbance.

The end of trial questionnaire was always administered by the author. In addition the author maintained close contact with patients throughout the trial period and gained subjective impressions of how patients responded to the handset. From all this, it can be said that the handset has been well received among the trial population.

From answers to question 7A (Table 7.3) it is worth noting that patients identified the concept of self-administered pain relief as important. This finding is also supported by anecdotal evidence gleaned by nursing staff and the author during the trials.

The two-step algorithm for requesting a bolus did not present any noticeable difficulties for any of the patients in the trials. No patient was forced to abandon a trial because of an inability to operate the handset. The very first patient enrolled in the trials was however too confused to operate any kind of PCA device, a conventional single button device was proposed but also judged to be unsuitable.

Patients made full use of the possible ranges to express their pain over the course of a trial.

It appears that an interactive design of the handset is in order which integrates the above noted points from the clinical trials carried out thus far. It has been suggested that generally user interface design passes through at least three version in order to achieve substantial improvements in usability [Nielsen 1993]. (A new iteration of the handset has been developed in the second half of 1995 following the trials and a sketch can be seen as a matter of interest only in appendix J.)

7.6 The Psychology of Pain Relief in Patient Trials

This section presents speculative ideas concerning possible mental models and psychological factors underlying patients’ use of the adaptive PCA system and PCA technology in general. A number of ideas and issues will be raised to provide possible new directions for further research.

It may be worth investigating the predominant conscious or subconscious model by which patients operate when using the adaptive PCA handset. An interesting question

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is whether patients generally seek only diminution of pain or aim to achieve a balance between analgesia and the inevitably more or less palpable side-effects of opioid analgesics. Also zero pain may not be a necessary goal for comfort for all patients. For example, some patients may be satisfied with a diminution in pain either because they believe that the optimum has been reached for them, or for a variety of other reasons, such as fear, learned helplessness, chronic pain, nursing attitudes, social attitudes to pain, or reluctance in taking control of their own analgesia, to mention just a few. Other patients may need to be more certain that optimum analgesia had been reached and may feel the need to go beyond the optimum to experience some of the more unpleasant side-effects of opioid analgesics. (Refer to section 2.5.1 for details on side effects.) Not all patients may be, for lack of a better word, ‘adventurous’ enough to test the limits of optimal analgesia in this manner. The psychological equivalent of ‘adventurous’ would presumably influence patients’ actions. It may be possible to divide patients into those who test the limits by slightly ‘overshooting’ into the side-effects region and those who are satisfied with a diminution of pain, in the sense of “If there is less pain, that’s good enough”.

In addition, environmental factors such as the attitude of visitors may also affect the way patients view and use PCA and thus modulate underlying behavioural patterns. Evidence of this was noted in a number of instances in these trials, in particular in patient trial 7, where the patient reported widely varying verbal pain scores depending on which member of the family was in the patient’s presence.

End of trial questions C1-5 were designed to provide material to address the above issue.

C1) What were your expectations of pain relief after the operation?  
A) No pain at all  
B) Some pain  
C) Moderate pain  
D) Tolerable pain  
E) Severe pain

C2) In actual fact did you experience  
A) more  
B) less pain than expected?

C3) Did you press the button every time you felt pain?  
A) No - Why not?  
B) Yes

C4) Were you ever afraid you might get too much medication from the machine?  
A) No  
B) Yes When?

C5) Did you ever feel you had given yourself too much medication?  
A) No  
B) Yes How did that feel?
As the number of respondents is very small, the actual answers given may provide more insight into the thinking of the patients and have been included in the table below.

Of the 8 patients questioned (C1,C2) above, only one (16) experienced more pain than expected. In this case the epidural block had failed and the patient was later placed on PCA. Four patients (12,14,18 & 20) experienced the expected pain intensity or less, or did not consider this an issue. Three patients (11,15,19) experienced very much less than expected pain.

Four patients indicated pressing the button every time pain was felt (C3). Interestingly all of these patients answered ‘No’ to the question of whether they ever felt they had given themselves too much analgesic (C5). The same four patients also indicated not being afraid of too much analgesic (C4), the only exception of a kind being trial 19 where once the patient was unable to deal with the situation of having accidentally pressed a higher dose than intended.
### Expectations and Mental Models

(Handset use: A Meta-analysis)

<table>
<thead>
<tr>
<th>Trial No</th>
<th>Question C1</th>
<th>Question C2</th>
<th>Question C3</th>
<th>Question C4</th>
<th>Question C5</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>E) Expected that there would be a bit, a fair bit.</td>
<td>B) Felt less, a lot less than expected</td>
<td>A) No, “A few times No” B) Yes, when couldn’t bear it</td>
<td>A) No- 5 mins delay felt safe, self control, hang back.</td>
<td>B) “Dozy. First night a little bit only hard to differentiate”</td>
</tr>
<tr>
<td>12</td>
<td>Not an issue</td>
<td>N/A</td>
<td>B) Yes</td>
<td>A) No</td>
<td>A) No</td>
</tr>
<tr>
<td>13</td>
<td>No questionnaire completed, trial ceased after 14 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>No expec’tn</td>
<td>B) “Not much pain”</td>
<td>B) Yes - “Never into red region”</td>
<td>A) No</td>
<td>A) No</td>
</tr>
<tr>
<td>15</td>
<td>E) Severe</td>
<td>B) “…did not get any”</td>
<td>B) Yes “Pressed when I thought the pain was going to come on”</td>
<td>A) No</td>
<td>A) No</td>
</tr>
<tr>
<td>16</td>
<td>B) not much</td>
<td>A) More because of failed epidural</td>
<td>A) No “Didn’t bother, didn’t want to get used to it”</td>
<td>B) Yes “That’s why I didn’t take it much, I didn’t like taking drugs”</td>
<td>B) “Making me sleep a lot but still pain sometimes if I moved”</td>
</tr>
<tr>
<td>17</td>
<td>No questionnaire completed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>“Spasmodic” hear that this operation was very painful</td>
<td>B) “Not so bad in first 3 days”</td>
<td>A) “If space it out the better off I’d be. Better if I could accept the pain”</td>
<td>B) “Yes when the machine went haywire” (a number of false alarms)</td>
<td>A) No (patient was aware of pain VS sedation tradeoff)</td>
</tr>
<tr>
<td>19</td>
<td>E) “Tremendous amount”</td>
<td>B) “Practically I had no pain at all”</td>
<td>B) “…it helped with the arthritis too”</td>
<td>B) “When all the lights came on I got scared and didn’t want the highest amount”</td>
<td>A) No</td>
</tr>
<tr>
<td>20</td>
<td>C) moderate</td>
<td>No more than expected</td>
<td>A) felt a bit nauseous and sleepy (1st day)</td>
<td>A) No</td>
<td>B) A couple of times felt sleepy when most pain</td>
</tr>
</tbody>
</table>

#### Table 7.4 Conceptual frameworks and expectations of pain of patients using the Adaptive PCA system.

Four patients responded with: not pressing the PCA button every time they felt pain (C3). Two of these two (11,18) gave the impression that they used PCA only when they had reached a certain level of endurance. One patient with professional medical knowledge (20) refrained from button pressing because of nausea and sleepiness. The answers to C3 and C4 for the patient for trial 16 seem to indicate that the patient did not want to use analgesic drugs for fear of dependency, “That’s why I didn’t take it much, I didn’t like taking drugs (C4).” “…didn’t want to get used to it (C3)”. All of the four patients who indicated not pressing the PCA button every time they felt pain (C3), also indicated having felt that they had given themselves ‘too much’ medication in answer to question C5.
Five patients indicated not being afraid of “getting too much medication from the machine” (C4). Of the three who answered as being afraid of too much medication one (16) was afraid of dependency, one (18) was afraid because the PCA system “...went haywire” and one(19) did not know how to change an accidentally higher than intended amount on the handset. This latter situation differs from a general fear of overdose in that it relates to one specific bolus request in which the patient did not know how that the initially selected amount could be changed or that it would automatically time out. The instance in which the system ‘went haywire’ occurred when the error checking on one part of the software was tightened and legitimate occurrences triggered false alarms and shut down the adaptive PCA system. From the patient’s viewpoint his unease would seem justified in this case.

From the answers listed above, it seems that many patients have some conceptual framework within which requests for analgesia are made. Generally speaking, about 50% of the patients had some belief which cautioned them in the use of PCA, whether this was a distrust of ‘drugs’ per se (16), or a belief that it would be “…better it I could accept the pain” as for 18. These patients also all reported experiencing side-effects such as sleepiness and drowsiness.

None of the patients who pressed the PCA button every time they felt pain reported feeling that they had given themselves too much medication. 

From this is may be possible to identify two broad groups. The first group consists of patients who request relief every time pain emerges and who are not concerned about overdosing and also do not seem to experience many side-effects. The second group does not request pain as readily, is fearful of overdose and reports experiencing the effects of too much medication.

The two groups are very small and no definitive conclusion can be drawn at this stage. Further analysis using larger samples could yield better understanding of the psychology of self administered pain relief but is outside the main scope of this thesis.

A study of patient satisfaction and pain relief using PCA has been made by Jamison et al. and would be a useful reference for further trials [Jamieson et al. 1993].

7.6.1 Patient’s Perceptions: Matching Pain to Presumed Dosage Amounts
A further issue for future research in this area would be to investigate how patients view the adaptive PCA handset range. Do patients have a concept of a standard or normal amount? Patients may view the range 0 to 10 as one ‘standard’ bolus from which they select a fraction or they may view the middle of the scale as the ‘standard’ amount. In trial 14 the patient’s answer to question C3 was: B) Yes, “Never into to the red region”, the red region being the higher end of the pain scale. This would indicate an aversion to using the higher end of the scale.

A further point with regard to the element of choice offered by the adaptive system handset is the way patients view the amounts dispensed by a single button system. The patient in trial number 13 had prior experience with a single button system and commented that he felt an increased feeling of control with the adaptive system. His concern with the single button system was whether the amount dispensed by the system was appropriate to the pain intensity level he experienced. In the patient’s opinion the adaptive PCA handset gave him options such as only requesting a small amount if the pain was not severe in his estimation. It seems that the issue of matching the appropriateness of a request to the pain level being experienced was an issue in this patient’s mind.

The common instruction given to PCA patients to “press when there is pain” leaves the patient to decide which level of pain is appropriate to press the PCA button for. It is likely that patients will assume that there is a pain threshold for which the dose given in a single button system is appropriate. It is then left to the patient to make assumptions about what level is appropriate to the unknown bolus dose programmed into the system by the “experts”. For some patients this may be a source of stress.

In both systems patients do not know the absolute amount being given in a bolus, nor would this information be useful to the majority of patients. However it seems that some patients are concerned about matching the bolus dose as they perceive it to the pain experienced. It is suggested here that the adaptive PCA handset gives patients finer control and removes the element of “all or nothing” that may be perceived with single button systems. From the trials it was found that patients generally sought to match their pain intensity to the handset scale.

It could also be useful to investigate how closely patients associate the pain intensity as expressed on the handset scale with the amount dispensed from the PCA system. This issue relates to the question of whether patients view the handset primarily as a way of registering pain intensity (with an indirect bearing on the analgesic amounts) or whether patients clearly associate the handset as a way of determining the

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analgesic amount they desire for their particular pain intensity. It may be that the two viewpoints are linked in such as way as to be essentially the same.

The role of patient education in handset use is thought to be of importance and would need to be scrutinized more closely in future trials. A system of checking patient comprehension of handset use both pre- and post-operatively would seem appropriate as well.

7.7 Qualitative Evaluation of the Adaptive PCA system

This section deals with qualitative data related to the whole PCA system. Much of the clinical trial data is descriptive and is derived from questionnaires, nursing/medical records and direct personal contact with patients.

Data for statistical analysis was primarily derived through automated electronic data logging from the personal computer used for the adaptive system. Appendix G contains both the descriptive and quantitative raw data for each trial. A summarized form of the data in appendix G is presented in appendix H in tabular form.

7.7.1 Patient Evaluation of the Trial PCA System

This section gives an overview of patients’ perception of the PCA system. Perceptions of the handset discussed in section 7.5 also made reference to the systems as a whole.

The following end of trial questions from Parker, Holtman and White (Anaesthesiology, Vol 76, No 5, Mar 1992) were primarily used in these trails to evaluate the total pain management experience using PCA. Although the same questions were also used by Parker et al. to gain insight into the effects of a constant background infusion, this was not their primary purpose here.

D1) Have you slept well at night since the operation? A) No B) Yes

D2) The most common cause of difficulty sleeping after the operation was:
   A) Pain and discomfort B) Activity in the room C) Unfamiliar surroundings D) Need to push the PCA button E) Other (specify)
Chapter 7  Clinical Trials

D3) Did you ever awaken from sleep at night because you were in pain and needed additional doses of pain medicine?  
A) No  
B) Yes

D4) Was self-administering pain medicine from the PCA device at night inconvenient?  
A) No  
B) Yes

D5) Were you able to rest comfortably at night?  
A) No  
B) Yes

D6) Excluding the day of your operation, which of the following best describes how sleepy you felt during the daytime?  
A) Wide awake  
B) Slightly drowsy  
C) Moderately drowsy  
D) Very sleepy/drowsy

D7) How would you describe the pain treatment since the operation?  
A) Excellent  
B) Well  
C) Adequate  
D) Fair  
E) Poor

D8) If you had to undergo the same operation in the future, what method of pain relief would you chose? - Why?  
A) Definitely chose the self-administered (PCA) device  
B) Some other method such as nurse administered pain relief.  
C) Do not care which pain method was used. Would you like to give reasons for your choice?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Qu: D1</th>
<th>Qu: D2</th>
<th>Qu: D3</th>
<th>Qu: D4</th>
<th>Qu: D5</th>
<th>Qu: D6</th>
<th>Qu: D7</th>
<th>Qu: D8</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>B) &quot;OK&quot;</td>
<td>B) activity</td>
<td>A) No</td>
<td>A) No</td>
<td>N/A</td>
<td>N/A</td>
<td>A) Ex.</td>
<td>A) PCA</td>
</tr>
<tr>
<td>12</td>
<td>B) Yes</td>
<td>N/A</td>
<td>??? (No)</td>
<td>??? (N/A)</td>
<td>N/A</td>
<td>??? (N/A)</td>
<td>A) Ex.</td>
<td>A) PCA</td>
</tr>
<tr>
<td>13</td>
<td>No questionnaire completed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>B) Yes</td>
<td>N/A</td>
<td>B) Yes</td>
<td>A) No</td>
<td>N/A</td>
<td>C) mod.</td>
<td>C) Adequ.</td>
<td>A) PCA</td>
</tr>
<tr>
<td>15</td>
<td>B) Yes</td>
<td>B) activity</td>
<td>A) No</td>
<td>A) No</td>
<td>N/A</td>
<td>N/A</td>
<td>A) Ex.</td>
<td>A) PCA</td>
</tr>
<tr>
<td>16</td>
<td>B) Yes</td>
<td>N/A</td>
<td>B) Yes</td>
<td>A) No</td>
<td>B) Yes</td>
<td>B) &amp; D</td>
<td>A) Ex.</td>
<td>A) PCA</td>
</tr>
<tr>
<td>17</td>
<td>No questionnaire completed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>A) No</td>
<td>A) &amp; C)</td>
<td>B) Yes</td>
<td>A) No</td>
<td>N/A</td>
<td>N/A</td>
<td>B)</td>
<td>A) PCA</td>
</tr>
<tr>
<td>19</td>
<td>B) Yes</td>
<td>B) noise</td>
<td>A) No</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>A) Ex.</td>
<td>A) PCA</td>
</tr>
<tr>
<td>20</td>
<td>A) No</td>
<td>B) activity</td>
<td>A) No</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>A) Ex.</td>
<td>A) PCA</td>
</tr>
</tbody>
</table>

Table 7.5 Answers to questions to evaluate the pain treatment using PCA. From the end of trial questionnaire. Answers which cannot be placed into any of the given alternatives are designated as ‘???’. Appendix G contains the original full answers in such cases. Suggested categorizations are given in braces.

Six of the eight respondents stated sleeping well (D1). The main difficulty in sleeping (D2) was given as noise or activity in the room by 5 patients with 3 not responding to this question. For none of the patients questioned was pain or discomfort the main difficulty in sleeping. When asked directly in question D3, only 3 of 8 patients...
answered that they awoke because of a need for more ‘pain medicine’ and none found this inconvenient (D4). Question D5 was thought to be a rephrasing of the first question D1 and was thus found to be redundant. Thus the above answers seem to indicate that the patients questioned experienced satisfactory analgesia at night and that the principal source of disruption to sleep was noise and activity in the room.

Three of the patients reported feeling moderately or slightly drowsy during the daytime with the majority not responding to this question (D6).

Six patients rated their pain treatment since the operation as ‘excellent’ with one responding ‘well’ and another patient responding ‘adequate’ (D7). All patients stated that they would choose PCA again as their preferred method of pain relief for any future operations (D8).

Regarding the appropriateness of a background infusion, answers to questions D1-8 collected in table 7.5 (D1-8) are by themselves insufficient to allow any meaningful conclusions regarding the use of a background infusion to be made. In addition, trial protocol required that the adaptive system dispense placebo solution for alternate 12 hour intervals thus effectively making the above data collected over 48 hours inappropriate for this kind of evaluation.

Question B1 of the end of trial questionnaire specifically asked patients to comment on the advantages and disadvantages of using a PCA system.

B1) “We would like to have your opinions on the advantages/disadvantages of using the equipment which allows patients to control their own pain relief (PCA). In the spaces below list any advantages/disadvantages in using PCA from your point of view.”

Only patients 12, 18, and 20 specifically answered question B1 of the end of trial questionnaire regarding the advantages and disadvantages of the PCA system. This question was the same as in the survey by Kluger and Owen discussed in section 3.7.1 [Kluger et al. 1990].

Patients’ responses were as follows:

<table>
<thead>
<tr>
<th>Trial No</th>
<th>Perceived advantages/disadvantages of PCA</th>
</tr>
</thead>
</table>
| 12       | **Advantages:** Not rely on someone else, not press buzzer and wait for the nurse  
|          | **Disadvantages:** Others (patients) could overdose - (patient perceived a potential danger for other patients) |
Table 7.6  Patient perceptions of the advantages/disadvantages of PCA

It was felt that the low response rate to question B1 was mainly due to the fact that the preceding questions A6-7 were often seen by patients as essentially asking for the same information. Table 7.3 lists the answers to A6 and A7 which will be considered here were relevant in conjunction with those to B1. In addition the length and the formal tone of question B1 coupled with the perceived repetitive elements to A6 and A7, resulted in a paraphrased version of the question being asked in practice. For these reasons B1 cannot really be considered identical to the format used in the survey by Kluger and Owen [Kluger et al. 1990]. However the essential meanings and impression elicited from patients do bear further discussion.

Although limited to a very small sample the recurring positive theme in answers to questions B1 and A7 is the element of control and self determination offered by PCA. This element only featured in third place (at 20% of respondents) in Kluger’s survey, with “Not bothering nurses...” and “Rapid onset of pain relief” being considered as the two most important advantages seen by the patients. It is interesting to note that these sentiments were not mentioned in this series of trials. It would seem reasonable that the significance of “Not bothering nurses...” would depend in part on the attitude of patients and nursing staff in a particular ward and hospital. However the small number of responses in this category in this series of trials makes any more direct comparison with Kluger and Owen’s findings extremely tenuous.

Criticism was more varied and not focussed on one topic although the sample was very small. In Kluger’s survey the principal disadvantages listed in descending order were “No disadvantages”, “Overdose”, and “Lack of nurse contact”. The first two sentiments were also mentioned in one form or another in this trial series.

7.7.2 The Background Infusion
The background infusion is an integral part of the PCA system proposed here. However the trials were not specifically designed to evaluate that part of the system by itself but rather to evaluate the system in its totality.

Although the background infusion in these trials reached values of up to 5mg of morphine per hour, this infusion was never constant for at most a few hours, frequently dropping to zero while the adaptive PCA was active. This kind of variation was expected as part of the initial design. A background infusion was never used/prescribed for the Abbott system.

A speculative idea for further investigation may be the possibility that some patient’s sensitivity to opioids varies over the postoperative acute pain period and thus the risk of respiratory depression may also vary. Hence a low level constant infusion may be more hazardous over a longer time period than a time-varying patient-driven infusion which although it may reach quite high levels does so only while these levels are supported by the patient’s bolus demands. This idea is speculative and is proffered as a possible direction for future research only.

Patients controlled the background infusion through their button pressing behaviour. Pain relief provided by the adaptive system was always a combination of bolus doses and any background infusion and would have been perceived as a whole by patients.

The wide fluctuations in background infusion levels observed in these trials (including zero infusion) would seem to indicate that the background infusion has a definite purpose in this system and in particular suggests that the element of variability in the infusion level under indirect patient control is to some extent justified.

Dawson et al found background infusions to be beneficial in the first 24 hours and to produce more complications thereafter in abdominal surgery patients [Dawson et al. 1995]. The variable background infusion used in the adaptive PCA system may be a realistic alternative to either no or fixed background infusions.

### 7.7.3 Patients’ Perspectives of Pain and Complications

Regular questionnaires were carried out following the 12 hourly changeover from one active system to another and at the end of a trial period. These questionnaires were called ‘12 hour questionnaires’. The original questionnaire can be found in appendix D, appendix G lists the full replies given by patients. Appendix H presents an
intermediary summary which forms the basis of the further reduction of data in table 7.7 below.

Questions 1 to 5 were concerned with patients’ level of pain and how this pain affected post-operative activities, physiotherapy and sleep.

Approximately one third of patients reported no pain (Qu 1) or being unaffected by pain in their post-operative activities (Qu 3) and as being able to carry out all aspects of physiotherapy (Qu 4).
## 12 hourly questionnaire summary

<table>
<thead>
<tr>
<th>Qu No</th>
<th>Category</th>
<th>Adaptive PCA first</th>
<th>Abbott PCA first</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adap active</td>
<td>Abbott active</td>
</tr>
<tr>
<td>1</td>
<td>No or Nil pain</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Pain other than None or Nil</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>Pain scores (verbal &amp; or visual)</td>
<td>2.03 ± 1.73 (0-6.1)</td>
<td>1.95 ± 1.60 (0-5.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.21 ± 2.45 (0-7.4)</td>
<td>4.46 ± 3.08 (0-10)</td>
</tr>
<tr>
<td>3</td>
<td>Did pain affect post-op activities? Yes</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>Did the pain affect physiotherapy?</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>a) Unable to do any of it</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>b) Unable to do some of it</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>c) all aspects but with some difficulty</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>d) all aspects with minimal to no pain</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Sleep without being woken by pain? Yes</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Average pain score of ‘No’ respondents</td>
<td>4.9 ± 1.7</td>
<td>3.9 ± 1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 only</td>
<td>1 point</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.25 ± 2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>6</td>
<td>Have you been bothered by:</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>a) nausea</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>b) Vomiting</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>c) Both</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>d) None</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>Affected by nausea/vomiting:</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>a) all the time</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>b) Frequently</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>c) Occasionally</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>Is Qu 7 assoc with button presses? Yes</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Unsure</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>Do you know if received medication? Yes</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>Relieved by medication?</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>a) completely</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>b) partly</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>c) not at all</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>More itchy than normal?</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>12</td>
<td>If so, is itching assoc. with a rash? Yes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>13</td>
<td>Aware of being given medication? Yes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>14</td>
<td>Staff</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Was sedation a problem?</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>a) Excessively</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>b) Somewhat</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>c) Not at all</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>
Table 7.7 Summary of the questionnaires following a 12 hour trial period on either the adaptive or the Abbott PCA active. (Original data in appendix G, intermediary summary in appendix H)

Approximately two thirds of patients reported being able to sleep without being woken by pain (Qu 5). Pain scores for question 2 will be discussed more extensively in section 7.8.4.1. At this point it will only be pointed out that the pain scores following adaptive PCA (2.03 & 2.21) are less variable than the scores following Abbott PCA (1.95 & 4.46). Not surprisingly the average pain scores for patients who were woken by pain are higher than for the verbal pain scores and the scores obtained from the 12 hourly questionnaires. Of the respondents 69% indicated that they were able to sleep without being woken by pain. There was no significant difference between groups. From the end of trial questionnaires it was found that noise and activity in the room were given as the major reasons for sleeping difficulty.

Questions 6 to 10 investigated nausea and vomiting which are the most common side-effects of morphine administration. Approximately half (47%) the respondents were bothered by nausea and or vomiting (Qu 6) but 77% were only affected occasionally (Qu 7). To the question whether nausea or vomiting was associated with PCA button presses 20% responded ‘Yes’, 44% were not sure, and 36% responded ‘No’ (Qu 8).

67% of respondents were aware of being given medication to control nausea (Qu 9) and for 39% this relieved the problem completely, for 44% only partly and 17% not at all (Qu 10).

Questions 11 to 13 concern itchiness, which is a side-effect of morphine use. 33% of respondents felt more itchy than normal (Qu 11) and none of the respondents knew if they were being given medication to relieve the itching (Qu 13). Itching was associated with a rash by only one of 21 respondents to question 12.

Questions 14 and 15 were asked of the nursing staff responsible for the patient. Excessive sedation was not seen as a problem by any of the staff respondents, while 15% thought that sedation was ‘somewhat’ of a problem and 85% answered the question whether sedation was problem with ‘not at all’ (Qu 14). To the question of whether the patient was too sleepy to comply with requests (Qu 15) only 95% responded with ‘No’.

<table>
<thead>
<tr>
<th>Staff</th>
<th>Was patient too sleepy to comply?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Number of questionnaires in each category</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>(Not all completed for every question)</td>
<td>9</td>
<td>16</td>
</tr>
</tbody>
</table>
7.8 Quantitative Analysis of Clinical Trial Data

The comparison of the new proposed adaptive PCA with an existing PCA is analysed for various parameters using the t-test for continuous variables and the chi-square test for discontinuous variables, with conventional levels of probability ($p = 0.05$) using 2-tailed tables. There was insufficient pre-trial information to permit a realistic estimate of the power of the study and thus any potential type II error.

The basic unit for data analysis is the average of that parameter for the approximately 12 hour interval during which a particular system was active. The approximately 12 hour intervals are here referred to as 12 hour blocks. A trial was considered closed for analysis purposes once the 48 hour limit was reached or the patient made no requests for a full 12 hour interval or medical staff decided to discontinue the trial. Eight patients were enrolled in the adaptive-first trial category and 9 in the Abbott-first category.

It should be noted that the trial PCA system was treated as a conventional PCA system as far as discontinuation of PCA and replacement by oral analgesics was concerned.

Numerical data in tabular form shows the standard deviation following the ‘±’ symbol and the range in round ‘(min-max)’ braces.

Table 7.8 below summarizes the trial patient demographics. There is no significant difference in the population variables.
## Chapter 7 Clinical Trials

### Trial Patient Demographics

<table>
<thead>
<tr>
<th>Category</th>
<th>Adaptive PCA first</th>
<th>Abbott PCA first</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>2 Females, 6 Males</td>
<td>4 Females, 5 Males</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>76.5 ± 10 (65-91)</td>
<td>74.5 ± 13 (54-88)</td>
</tr>
<tr>
<td>Age [years]</td>
<td>49 ± 19 (17-74)</td>
<td>57 ± 24 (27-83)</td>
</tr>
<tr>
<td>Intra-op Morphine [mg]</td>
<td>8.1 ± 7.9 (0-20)</td>
<td>7.6 ± 7.7 (0-24)</td>
</tr>
<tr>
<td>Intra-op Fentanyl [µg]</td>
<td>103 ± 83 (0-200)</td>
<td>69 ± 70 (0-200)</td>
</tr>
<tr>
<td>Time in theatre [hour]</td>
<td>4.3 ± 2.3h (1.5-7.8)</td>
<td>3.8 ± 2.7 (1-8)</td>
</tr>
<tr>
<td>Time surgery to PCA &lt;12h</td>
<td>3 trials 2.6 ± 0.7 (2.0-3.4) h</td>
<td>7 trials 2.8 ± 0.9 (1.4-4.1) h</td>
</tr>
<tr>
<td>Morphine post-op to PCA</td>
<td>3.8 ± 4.7 (0-9) [mg]</td>
<td>4.7 ± 7.2 (0-20) [mg]</td>
</tr>
<tr>
<td>Time surgery to PCA &gt;12h</td>
<td>5 trials 22.3 ± 3.2 (18.9-27.5)</td>
<td>2 trials 22.6 ± 0.64 (22.1-23)</td>
</tr>
<tr>
<td>Failed epidural ICU post-op &gt;12h</td>
<td>2 trials (22.2, 18.9)</td>
<td>2 trials (22.1, 23.0)</td>
</tr>
<tr>
<td>Surgery to discharge [day]</td>
<td>14.6 ± 6.1 (3-25)</td>
<td>24.3 ± 21.1 (4-68)</td>
</tr>
<tr>
<td>No of trials/12h blocks</td>
<td>8 Trials/ 29 12 hour blocks</td>
<td>9 Trials/ 29 12 hour blocks</td>
</tr>
<tr>
<td>Procedures:</td>
<td>Abdominal: 6</td>
<td>Abdominal: 4</td>
</tr>
<tr>
<td></td>
<td>Major Ortho.: 2</td>
<td>Major Ortho.: 5</td>
</tr>
</tbody>
</table>

**Table 7.8 Trial patient demographics**

1) This patient was admitted to ICU, experienced a failed epidural block and has also been included in the Failed epidural category above.

In the adaptive PCA first group only 3 trials commenced within 12 hours of surgery with an average delay of 2.6 hours after surgery compared to 7 trials commencing with an average delay of 2.8 hours for the Abbott PCA first category. Three patients in the adaptive PCA first category were transferred to the ICU for ventilation immediately post-operatively (Trials: 6B, 8, 14). These patients commenced adaptive PCA trials upon reaching the wards. Two trial patients in each category experienced failed epidural block and were subsequently enrolled in the adaptive PCA trials. These and the ICU patients all experienced delays between 19 to 28 hours after surgery before being able to use the adaptive PCA trial system. In the case of failed epidural block the patients were usually experiencing considerable pain prior to PCA.

For this reason it is difficult to use the trial results to quantitatively evaluate the success of the adaptive system in providing good early pain relief immediately...
post-operatively and any of the benefits commonly attributed to good early pain relief

There is no statistical significance in the length of hospital stay (surgery to discharge). The trial structure did not seek to investigate this aspect and the use of alternating systems would obscure any definite trends in either direction. None the less the average stay for the adaptive PCA first trial category was 14.6 days as compared to the 24.3 days for the Abbott PCA first category. This difference may in part be caused by the higher percentage of orthopaedic procedures in the latter category, in particular trials 4 and 5 which involved repeat operations and prolonged stays of 68 and 43 days.

Trial 16 in the Abbott PCA first category was conducted successfully but the nursing observation chart for Acute Pain Drug Infusion was not filed in the patient’s record file. This trial was thus excluded from data analysis involving hourly verbal pain, respiration and sedation scores. All other data remains unaffected. Alternate respiration rates for the trial period were however available from the daily observation charts and revealed respiration rates in the normal range. Sedation scores of 0 and 0-1 were recorded for the first two 12 hour blocks in the nursing notes. No reversal agents for sedation or nausea were administered. Pain scores of 1-5 and 6 (“high”) were also recorded in the nursing notes for the first two 12 hour blocks.

An overview of complications is given in the table below. There is no statistically significant difference in the values shown for sedation, respiration and verbal pain scores as grouped in the table. (These parameters will be examined more closely at a later stage.)
Complications During 12hour Active System

<table>
<thead>
<tr>
<th></th>
<th>Adaptive PCA active</th>
<th>Abbott PCA active</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verbal pain scores:</strong></td>
<td>Scale of 0-10</td>
<td>Scale of 0-10</td>
</tr>
<tr>
<td>Adaptive PCA first:</td>
<td>2.63 ± 1.54</td>
<td>1.87 ± 1.15</td>
</tr>
<tr>
<td>Abbott PCA first:</td>
<td>3.51 ± 1.70</td>
<td>4.03 ± 2.13</td>
</tr>
<tr>
<td>All trials:</td>
<td>3.04 ± 1.65</td>
<td>2.95 ± 2.01</td>
</tr>
<tr>
<td><strong>Sedation scores:</strong></td>
<td>Scale of 0-6 (6 max)</td>
<td>Scale of 0-6 (6 max)</td>
</tr>
<tr>
<td>Adaptive PCA first:</td>
<td>0.4 ± 0.4</td>
<td>0.4 ± 0.3</td>
</tr>
<tr>
<td>Abbott PCA first:</td>
<td>0.4 ± 0.4</td>
<td>0.6 ± 0.5</td>
</tr>
<tr>
<td>All trials:</td>
<td>0.4 ± 0.4</td>
<td>0.5 ± 0.5</td>
</tr>
<tr>
<td><strong>Respiration scores:</strong></td>
<td>Breaths per minute</td>
<td>Breaths per minute</td>
</tr>
<tr>
<td>Adaptive PCA first:</td>
<td>18.0 ± 1.2</td>
<td>18.2 ± 1.4</td>
</tr>
<tr>
<td>Abbott PCA first:</td>
<td>18.1 ± 1.2</td>
<td>18.3 ± 2.1</td>
</tr>
<tr>
<td>All trials:</td>
<td>18.1 ± 1.2</td>
<td>18.3 ± 1.7</td>
</tr>
<tr>
<td><strong>Recorded nausea:</strong></td>
<td>Incidents ≥ 1 per 12hr</td>
<td>Incidents ≥ 1 per 12hr</td>
</tr>
<tr>
<td>Adaptive PCA first:</td>
<td>4 blocks - some nausea</td>
<td>3 blocks - some nausea</td>
</tr>
<tr>
<td>Abbott PCA first:</td>
<td>3 blocks - some nausea</td>
<td>2 blocks - some nausea</td>
</tr>
<tr>
<td>All trials:</td>
<td>7 blocks - some nausea</td>
<td>5 blocks - some nausea</td>
</tr>
<tr>
<td><strong>Recorded vomiting:</strong></td>
<td>Incidents ≥ 1 per 12hr</td>
<td>Incidents ≥ 1 per 12hr</td>
</tr>
<tr>
<td>Adaptive PCA first:</td>
<td>2 blocks some vomiting</td>
<td>0 blocks some vomiting</td>
</tr>
<tr>
<td>Abbott PCA first:</td>
<td>1 block some vomiting</td>
<td>1 block some vomiting</td>
</tr>
<tr>
<td>All trials:</td>
<td>3 blocks some vomiting</td>
<td>1 block some vomiting</td>
</tr>
<tr>
<td><strong>Metoclopramide</strong></td>
<td>10 mg doses</td>
<td>10 mg doses</td>
</tr>
<tr>
<td>Adaptive PCA first:</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Abbott PCA first:</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>All trials:</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td><strong>Prochlorperazine</strong></td>
<td>12.5 mg</td>
<td>0 mg</td>
</tr>
<tr>
<td>Adaptive PCA first:</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abbott PCA first:</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All trials:</td>
<td>12.5 mg</td>
<td>0 mg</td>
</tr>
</tbody>
</table>

Table 7.9 Indicators of complications and side-effects

Incidents of nausea and vomiting were usually recorded in the ‘Nursing/Medical Progress Sheets’ but such recording was not always rigorous. Nausea and vomiting have only been entered in the table if these events were definitely recorded in the patient’s history.

There was no statistical difference in the number of antiemetics (Metoclopramide and Prochlorperazine) administered between the trial categories.

Numerical data for the trials derived from the automatic data logging process in the adaptive PCA system is shown in the following 3 tables.

An Adaptive System for Patient-Controlled Analgesia
For patients on adaptive PCA and over 60 years of age the algorithm was programmed to dispense half the amounts of analgesic of those under 60 years.

### 7.8.1 Pilot Trial and Adaptive Only Trial

The patients in table 7.10 below were trialled using only the adaptive PCA. Trial 3 was the first successful trial of the adaptive system and served as a pilot trial prior to full double blind crossover trials.

<table>
<thead>
<tr>
<th>Trial number</th>
<th>Time Blocks</th>
<th>Hset pain score</th>
<th>Sdev pain score</th>
<th>Boluses given</th>
<th>Lock-out request</th>
<th>Bolus amount mg</th>
<th>Infusion amount mg</th>
<th>Total Bolus + Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0-12h</td>
<td>7.6</td>
<td>2.4</td>
<td>11</td>
<td>0</td>
<td>22.25</td>
<td>5.43</td>
<td>27.68</td>
</tr>
<tr>
<td></td>
<td>12-24h</td>
<td>5.2</td>
<td>3.9</td>
<td>16</td>
<td>0</td>
<td>20.75</td>
<td>0</td>
<td>20.75</td>
</tr>
<tr>
<td></td>
<td>24-36h</td>
<td>4.9</td>
<td>2.9</td>
<td>8</td>
<td>0</td>
<td>9.75</td>
<td>0</td>
<td>9.75</td>
</tr>
<tr>
<td></td>
<td>36-48h</td>
<td>4.3</td>
<td>2.3</td>
<td>8</td>
<td>0</td>
<td>8.5</td>
<td>0</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>48-60h</td>
<td>1.6</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>12.25</td>
<td>0</td>
<td>12.25</td>
</tr>
<tr>
<td></td>
<td>Totals/ Average</td>
<td>5.98</td>
<td>2.5</td>
<td>57</td>
<td>0</td>
<td>85.75</td>
<td>5.43</td>
<td>91.18</td>
</tr>
<tr>
<td>6A</td>
<td>0-12h</td>
<td>8.1</td>
<td>2.8</td>
<td>27</td>
<td>11</td>
<td>51.5</td>
<td>18.25</td>
<td>69.75</td>
</tr>
<tr>
<td></td>
<td>12-24h</td>
<td>8.7</td>
<td>1.6</td>
<td>18</td>
<td>1</td>
<td>39.5</td>
<td>17.25</td>
<td>56.75</td>
</tr>
<tr>
<td></td>
<td>24-36h</td>
<td>8.4</td>
<td>2.8</td>
<td>18</td>
<td>3</td>
<td>34</td>
<td>15.75</td>
<td>49.75</td>
</tr>
<tr>
<td></td>
<td>36-48h</td>
<td>8.1</td>
<td>1.5</td>
<td>13</td>
<td>6</td>
<td>18.5</td>
<td>7.75</td>
<td>26.25</td>
</tr>
<tr>
<td></td>
<td>Totals/ Average</td>
<td>8.34</td>
<td>2.2</td>
<td>76</td>
<td>21</td>
<td>143.5</td>
<td>59</td>
<td>202.5</td>
</tr>
</tbody>
</table>

**Table 7.10** Numerical data for trials using only the adaptive PCA system. Note that regardless of age the bolus and infusion ranges for both trials are those used for over 60 year old patients, i.e. 0.25-2.5 mg morphine.

The patient in trial 6A was a 17year old male, pre-operatively placed on conventional PCA programmed at 1mg boluses, no background infusion using morphine as the analgesic agent. The patient was in extreme pain, breathing shallowly and sweating as well as complaining vocally about his level of pain.

Following closer evaluation medical and research staff recommended using the adaptive PCA system (non-crossover) and the patient was able to obtain adequate analgesia. Medical progress sheets record: “#1. PCA - changed to Adaptive PCA this
afternoon with good effect -> pain rating (approx) 0 since. Able to inspire deeply, moving a bit more than prev.”.

It should be noted that the Abbott PCA could in theory also have provided the required higher analgesic amounts however medical staff at the time were reluctant to explicitly prescribe a higher bolus dose. The adaptive PCA was suggested and accepted after representation from the research staff involved in the adaptive PCA trials. Medical staff were concerned that the patient would obtain excessive analgesia if the button pressing frequency observed with the Abbott system was translated to the adaptive system. For this reason the adaptive system was used at half strength by programming the system as for over 60 year old patients. This was the only case in which a patient under 60 years was placed on the range for over 60 year old patients. The maximum bolus size the patient was able to obtain on the over 60 year range was 2.5mg of morphine. Post-operatively the same patient was enrolled in a formal crossover trial in trial 6B and it was decided to continue this patient on the dosage range for over 60 year old patients in trial 6B.

7.8.2 Full Double-Blind Crossover Trials

The data logged to the computer hard disk by the adaptive PCA system is summarized in tables 7.11 and 7.12 below. These tables are based on the data in appendix G. Appendix H contains additional data beyond the official 48 hour trial period shown here.
### Adaptive PCA first: Clinical trial data for 48 hours

<table>
<thead>
<tr>
<th>Trial number</th>
<th>6B</th>
<th>7</th>
<th>8</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>17</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott bol (mg)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Age:</td>
<td>17</td>
<td>37</td>
<td>57</td>
<td>33</td>
<td>56</td>
<td>74</td>
<td>71</td>
<td>47</td>
</tr>
<tr>
<td>A H-set pain score</td>
<td>8.5</td>
<td>6.7</td>
<td>6.4</td>
<td>8.4</td>
<td>4.7</td>
<td>4</td>
<td>5.3</td>
<td>5.3</td>
</tr>
<tr>
<td>D Sdev. pain score</td>
<td>2.0</td>
<td>1.4</td>
<td>2.8</td>
<td>1.8</td>
<td>2.1</td>
<td>1.9</td>
<td>1.2</td>
<td>1.6</td>
</tr>
<tr>
<td>A Bolus given</td>
<td>27</td>
<td>18</td>
<td>9</td>
<td>12</td>
<td>10</td>
<td>6</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>P Lockout requ.</td>
<td>12</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T Bolus amount</td>
<td>57.25</td>
<td>53</td>
<td>28</td>
<td>49</td>
<td>12.5</td>
<td>5</td>
<td>17.75</td>
<td>19.5</td>
</tr>
<tr>
<td>I Infusion amt</td>
<td>29.25</td>
<td>64.5</td>
<td>17.25</td>
<td>45</td>
<td>12</td>
<td>4</td>
<td>14</td>
<td>13.75</td>
</tr>
<tr>
<td>V Total (Bol+Inf)</td>
<td>86.5</td>
<td>117.5</td>
<td>45.25</td>
<td>94</td>
<td>24.5</td>
<td>9</td>
<td>31.75</td>
<td>33.25</td>
</tr>
</tbody>
</table>

### Table 7.11 Numerical data for trials starting with the adaptive PCA system
Trial patient 13 on average requested high pain scores (average 8.4) which resulted in a considerable amount of morphine being administered and causing severe nausea, vomiting, an episode of incontinence which resulted in the eventual discontinuation of PCA. This patient had received the third highest bolus amount in any 12 hour block in the trials and the second highest total morphine amount when the infusion component is included. Some doubt remains as to whether the patient was post-operatively inappropriately instructed in the use of PCA. It seemed that some of the nursing staff may have encouraged the patient to frequently press high pain scores immediately post-operatively. The patient had received 94mg in 12 hours from the adaptive PCA system. This is high when compared to the average of approximately 48mg for the adaptive system and 16mg for the Abbott system in the first 12 hours respectively.

In trial 15 the patient required an additional 2.5mg morphine bolus to alleviate pain in the 24 to 36 hour period. This patient also suffered from severe angina pain.
# Chapter 7 Clinical Trials

## Abbott PCA first: Clinical trial data for 48 hours

(12 hourly averages)

<table>
<thead>
<tr>
<th>Trial number</th>
<th>4</th>
<th>5</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>16</th>
<th>18</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott bol (mg)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Age:</td>
<td>81</td>
<td>77</td>
<td>28</td>
<td>76</td>
<td>32</td>
<td>27</td>
<td>63</td>
<td>48</td>
<td>83</td>
</tr>
<tr>
<td>A H-set pain score</td>
<td>5.5</td>
<td>4.8</td>
<td>9.9</td>
<td>6.3</td>
<td>9.5</td>
<td>6.8</td>
<td>6.8</td>
<td>7.9</td>
<td>5.9</td>
</tr>
<tr>
<td>B Sdev. pain score</td>
<td>3.6</td>
<td>1.3</td>
<td>0.3</td>
<td>0.5</td>
<td>0.8</td>
<td>1.7</td>
<td>2.2</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>B Bolus given</td>
<td>2</td>
<td>12</td>
<td>23</td>
<td>6</td>
<td>13</td>
<td>11</td>
<td>20</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>O Lockout requ.</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>7</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>T Bolus amount</td>
<td>2.0</td>
<td>12.0</td>
<td>23</td>
<td>6</td>
<td>19.5</td>
<td>11</td>
<td>7</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>T Infusion amt</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total (Bol+Inf)</td>
<td>2</td>
<td>12</td>
<td>23</td>
<td>6</td>
<td>19.5</td>
<td>11</td>
<td>7</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>A H-set pain score</td>
<td>5.3</td>
<td>4.9</td>
<td>9.1</td>
<td>8.7</td>
<td>9.4</td>
<td>6.3</td>
<td>5.6</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td>D Sdev. pain score</td>
<td>1.4</td>
<td>2.4</td>
<td>1.4</td>
<td>3.3</td>
<td>1.3</td>
<td>2.6</td>
<td>2.9</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>A Bolus given</td>
<td>11</td>
<td>22</td>
<td>22</td>
<td>5</td>
<td>16</td>
<td>11</td>
<td>14</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>P Lockout requ.</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>11</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T Bolus amount</td>
<td>14.5</td>
<td>26.75</td>
<td>97</td>
<td>21</td>
<td>77.5</td>
<td>13.75</td>
<td>31</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>I Infusion amt</td>
<td>0</td>
<td>0</td>
<td>36.75</td>
<td>5.25</td>
<td>19</td>
<td>11</td>
<td>1</td>
<td>2.75</td>
<td></td>
</tr>
<tr>
<td>V Total (Bol+Inf)</td>
<td>14.5</td>
<td>26.75</td>
<td>133.75</td>
<td>0</td>
<td>26.25</td>
<td>96.5</td>
<td>24.75</td>
<td>32</td>
<td>12.75</td>
</tr>
<tr>
<td>A H-set pain score</td>
<td>5.9</td>
<td>8.0</td>
<td>9.1</td>
<td>7.9</td>
<td>9.5</td>
<td>6.8</td>
<td>6.4</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>B Sdev. pain score</td>
<td>0.9</td>
<td>2.4</td>
<td>2.5</td>
<td>2.5</td>
<td>1.2</td>
<td>2.3</td>
<td>1.0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>B Bolus given</td>
<td>12</td>
<td>14</td>
<td>8</td>
<td>8</td>
<td>4</td>
<td>20</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O Lockout requ.</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T Bolus amount</td>
<td>12.0</td>
<td>14.0</td>
<td>12</td>
<td>8</td>
<td>4</td>
<td>20</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T Infusion amt</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (Bol+Inf)</td>
<td>12.0</td>
<td>14.0</td>
<td>0</td>
<td>12</td>
<td>8</td>
<td>4</td>
<td>20</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>A H-set pain score</td>
<td>5.9</td>
<td>6.6</td>
<td>7.9</td>
<td>9.3</td>
<td>6.2</td>
<td>5.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D Sdev. pain score</td>
<td>1.1</td>
<td>2.3</td>
<td>1.5</td>
<td>1.5</td>
<td>0.8</td>
<td>0.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Bolus given</td>
<td>15</td>
<td>14</td>
<td>17</td>
<td>20</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P Lockout requ.</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T Bolus amount</td>
<td>22.0</td>
<td>23.25</td>
<td>76.5</td>
<td>61.5</td>
<td>1.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I Infusion amt</td>
<td>4.75</td>
<td>2.5</td>
<td>21.75</td>
<td>29.25</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V Total (Bol+Inf)</td>
<td>26.75</td>
<td>25.75</td>
<td>0</td>
<td>98.25</td>
<td>0</td>
<td>90.75</td>
<td>1.25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| T H-set pain score | 5.64 | 6.07 | 9.51 | 6.33 | 8.67 | 8.73 | 6.59 | 6.52 | 6.05 |
| O Sdev. pain score | 1.75 | 2.11 | 0.85 | 0.52 | 2.17 | 1.42 | 2.33 | 1.37 | 0.57 |
| T Bolus given | 40 | 62 | 45 | 6 | 26 | 52 | 35 | 91 | 20 |
| A Lockout requ. | 2 | 2 | 7 | 0 | 2 | 22 | 8 | 8 | 0 |
| L Bolus amount | 50.5 | 76 | 120 | 6 | 52.5 | 173 | 24.75 | 149.5 | 23.25 |
| S Infusion amt | 4.75 | 2.5 | 36.75 | 0 | 5.25 | 40.75 | 11 | 30.25 | 2.75 |
| Total (Bol+Inf) | 55.25 | 78.5 | 156.75 | 6 | 57.75 | 213.7 | 35.75 | 179.75 | 26 |

**Table 7.12** Numerical data for crossover trials starting with the conventional (Abbott) PCA system.

Trial patient 9 was unable to obtain adequate analgesia from the prescription for the active Abbott PCA in the 0 to 12 hour period (23mg morphine used). His morphine

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consumption in the 12 to 24 hour period when the adaptive system was active rose to 133.75mg which is 5.8 times that of the 0-12 hour period for approximately the same number of bolus requests. The patient had been in severe pain in the 0-12 hour period (average pain score 8.4) but the pain abated in the following 12 hours to 6.2 (average). For this reason medical staff decided to discontinue the trial after 24 hours on humanitarian grounds and to continue with the adaptive system only. The patient was able to achieve improved analgesia in the 24 to 48 hour period with average 12 hour pain scores of 3.9 and 4.0.

The only recorded incidence of respiration less than 8 breaths per minute (bpm) was recorded for trial patient 9 in the adaptive PCA active period, at 11:00 and 17:00 hours of the 20/9/94, 30 and 36 hours after the commencement of the trial.

The recording at 11:00 was of 7.5 bpm and was preceded by a recording of 18 bpm at 10:00. The next recording of 16 bpm was at 13:00.

At 17:00 a respiration rate of 7 bpm was recorded. This was preceded by 18 bpm at 16:00 and followed by 16 bpm at 18:00. Some ambiguity exists in the interpretation of the chart concerning the value of 7 bpm at 17:00. The actual notation on the chart could be interpreted as a respiration rate of 16 bpm and a verbal pain score of 7, however nursing notes for the 20/9/94 at 21:00 hours, state: “Resp. Rate a little low when sleeping (b/w 5-8) - however patient probably tired/exhausted due to lack of sleep previous night. Resps. b/w 16-20 when awake.”

No reversal agent was thought necessary in the judgement of the medical staff and PCA therapy was continued uninterrupted for a full 48 hours.

Trial 10 was discontinued after 12 hours because the patient made very little use of the PCA both in the amount of analgesic used (6mg of morphine) and the number of bolus requests (6 requests) in the first 12 hours. Oral analgesics were deemed sufficient for this patient according to medical opinion.

Trial patient 11 was taken off PCA after 36 hours as this patient’s opioid needs diminished and oral analgesics were sufficient.

Trial patient 16 did not make use of the PCA system for the 36-48 hour period and like trial patient 11 had reached a natural end-point of diminished pain as shown by low analgesic consumption.
7.8.3 High Range Use of the Adaptive PCA

The high range could not be evaluated at this stage primarily because of difficulties with the monitoring equipment (section 7.4.2) and secondarily because 7 patients experienced a delay of more than 19 hours before being placed on adaptive PCA.

The patient in trial 18 was the last patient to be connected to the original monitoring configuration of oximeter and capnograph. This patient entered the high adaptation range twice for approximately one hour each time at 02:20 and 06:15 in the 30 to 36 hour interval after PCA commencement. During this time the Abbott PCA was active. The patient only entered the high adaptation range by 0.5mg/hr above the normal range maximum of 5mg. The records indicate that the patient would have entered the high adaptation range again at a later stage while the adaptive system was active but this was prevented by the monitoring equipment not being fully connected.

Trials 6A, 6B, 7, 13 and 9 showed high initial analgesic consumption and may have been possible candidates for the high adaptation range. This was despite the fact that 6B and 7 experienced a delay of 27.5 and 22 hours respectively during which time the patients experienced considerable pain. Of the initial high consumers only trial 9 commenced with the Abbott PCA first and this patient was unable to obtain adequate analgesia from the trial system. The patient was withdrawn from the trials after 24 hours and placed on adaptive only PCA on humanitarian grounds as mentioned above.

It was originally envisaged that the high adaptation range would only be useful for a certain fraction of the patient population in the immediate post-operative period. From the trials it seems that the majority of patients would be comfortable using the normal range.

Before proceeding with more thorough future investigations of the high range, the problem of reliable monitoring and or a more robust high adaptation algorithm as discussed in section 7.4.2 would have to be addressed.
7.8.4 Evaluation of Endpoints: Pain Scores as a Reflection of Patient Comfort

Pain scores were obtained from 3 different sources, the handset, the questionnaire following a change-over in active systems and the hourly verbal pain scores recorded in the Acute Pain Infusion charts (also referred to as the nurse charts). The pain scale for all methods and sources was 0-10.

![Nurse charts: hourly verbal pain scores](image)

Figure 7.4 Verbal pain scores recorded in nurse charts (Acute Pain Medication Infusion Chart) on an approximately hourly basis.

The graph above (figure 7.4) shows the average pain scores derived from the Acute Pain Infusion charts for both trial categories separately and pooled. The charts were used to record patients’ verbal pain scores, respiration rate and sedation scores on an approximately hourly basis.

The graph shows that the average pain scores over 12 hours blocks in the adaptive-first PCA category were lower than for corresponding blocks in the Abbott-first category. For block 2, the 12-24 hour interval, the difference reached statistical significance at the $p \leq 0.05$ level.

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The trend in both categories was from initially higher to lower scores with a more pronounced decrease from block 1 to 2 in the adaptive-first category. A similar decrease was not apparent in the Abbott-first category for the same time period. Subsequent analysis of other data will point out an overall trend in the effects of starting with the adaptive PCA first.

![Nurse Charts: Verbal hourly pain scores](image)

**Figure 7.5** Pooled pain scores for 0-24 and 24-48 hours.

Comparing the 0-24 hour pain scores obtained by averaging block 1 and 2 of each category, yields significant differences at the \( p \leq 0.05 \) level (figure 7.5). By averaging blocks 3 and 4 of each category a similarly significant difference is found when comparing the 24-48 hour intervals. In each case the pain scores for the adaptive-first category are significantly lower.

Similarly the overall pain score for all 4 blocks (48h) of the adaptive-first category is 2.2 which is significantly different \( (p \leq 0.01) \) from that of 3.9 for the Abbott-first category \( (p = 0.0005) \). One possible reason may be that the adaptive PCA is able to achieve good early analgesia which affects the entire trial period.
7.8.4.1 Pain Scores from the 12 Hourly Questionnaires

Pain scores from question 2 of the 12 hourly questionnaire are shown below. At the conclusion of a 12 hour block, whenever the active system was changed a questionnaire was completed which asked the question:

2) Please rate the amount of pain you have now by placing an “X” on the appropriate part of the line.

{no pain} 0-----------------10 {worst pain}

Although the original intention was for the patient to place a mark on the visual analogue scale on the questionnaire, in practice this rarely occurred. The research nursing staff would usually take a verbal pain score from the patient and write this numerical value above the visual analogue scale (VAS) as well as placing a mark on the VAS corresponding in their opinion most closely to the verbal score. The actual procedure used cannot be ascertained for each individual case, however the verbal score would probably be more accurate and was preferred in this analysis whenever it was available and where it was clear that the patient had not placed the mark on the page herself.

Pain scores from Questionnaires

PCA system in active use

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**Figure 7.6** Pain scores from the 12 hourly questionnaires. 12 hour averages for each active system are shown.

The Abbott-first average for block 1 (5.0) is higher than that of block 1 (2.5) of the adaptive-first category ($p = 0.074$, figure 7.6). All averages in figure 7.6 are lower for the adaptive-first category than for corresponding blocks in the Abbott-first category.

A statistically significant difference exists ($p = 0.012$) when the 12 hour averages for which the Abbott system was active in the adaptive-first category (blocks 2 & 4) is compared to the Abbott active averages in the Abbott-first category (blocks 1 & 3). The average 12h pain scores in the adaptive system category when the Abbott system was active for blocks 2 and 4 was 2.0 as compared to 4.5 for blocks 1 and 3 when the Abbott system was active in the Abbott first category.

The relative change in averages between active systems is larger in the Abbott-first than in the adaptive-first category.

### 7.8.4.2 “Pain Scores” from the Handset

The following graph (7.7) shows the average 12 hourly pain scores for the patient handset. The most striking feature of this graph is that the mean scores are all very similar except for the first and second blocks in the adaptive-first category ($p = 0.184$).

A possible account for the relatively uniform averages may be the hypothesis that patients on average request pain relief at approximately similar pain thresholds. Both the verbal pain and the questionnaire pain scores show a clearly declining trend over 48 hours. The handset pain scores show no such decline over 48 hours. On the contrary in the adaptive-first category the lower scores occur in the first two 12 hour blocks with an eventual rise to the level of the Abbott-first range by block 4. Whether the initial decline in averages from block 1 to block 2 in the adaptive-first category was part of a trend that was perturbed by the alternating active systems cannot not be established.
It is also interesting to note that the total average pain score of 2.7 for the questionnaires and 3.0 for the verbal pain scores are both less than half of the total average pain score of 6.6 from the handset. This would indicate that the handset pain scores are scored differently to traditional pain scores and may represent a different aspect of the pain cycle such as a more or less common threshold.

Patients used the handset to request analgesia and thus the pain at that time would be expected to be different from that of other times. One could say that in these trials it seems that patients requested a bolus when the pain was on average twice that of the average resting level. It should be pointed out that the handset pain scores use the same scale as the verbal and visual analogue scales.

The values from the handset have here been called pain scores but it should be kept in mind that patients may not only have been expressing the level of pain at the time of requesting a bolus but were also aware that the choice made on the handset was in some way related to the amount of analgesic that would be dispensed by the system. In this case there is a linear relationship between pain and analgesic amounts. The question of whether patients primarily requested analgesic or rated their pain has here been assumed to be so intimately linked as to be indistinguishable. From observation,
it seemed that patients had quickly learnt to establish a framework of the analgesic effect of different pain scores. This question may be fertile ground for further investigation into the psychology of pain relief.

It was repeatedly observed that patients would make decisions regarding the bolus size based on the perceived pain and the dosage they felt they would expect to receive. In this process it seemed that patients would use earlier doses as a reference point on which the new selection was based.

Pain scores are one of 2 degrees of freedom in handset use. The other being the time intervals between bolus requests. This was a variable which will be illustrated in figures 7.11 and 7.12. At this stage it may be sufficient to point out that patients made use of both degrees of freedom.

7.8.5 Complications: Respiration and Sedation Scores

The common complications of excessive morphine are lowered respiration rates and increasing sedation. This section examines the data collected on these parameters.

![Graph showing respiration rates in breaths per minute (bpm) recorded in nurse charts](image)

**Figure 7.8** Respiration rates in breaths per minute (bpm) recorded in nurse charts (Acute Pain Medication Infusion Chart) on an approximately hourly basis.

The respiration rates for the two trial categories in figure 7.8 above do not show any significant differences. There is no evidence of impaired respiration function as a
result of excessive morphine administration as judged by the respiration averages at this level.

The following graph (figure 7.9) shows the sedation scores from the acute pain medication infusion charts. The scores were recorded approximately hourly on the same chart as the verbal pain scores and respiration rate. The scale for sedation scores as used in the Royal Melbourne Hospital is given as follows: 0 = none; 2 = mild, easy to rouse; 4 = moderate, frequently drowsy, difficult to rouse; 6 = severe, somnolent, difficult to rouse; SX = asleep not assessed.

![Sedation: 12 hour averages](image)

**Figure 7.9** Sedation scores recorded in nurse charts (Acute Pain Medication Infusion Chart) on an approximately hourly basis.

The sedation scores are semi-quantitative in nature and in practice have often been scored as continuous variables. As the respiration rate and pain scores were recorded as continuous variables on the same vertical axis a case for looking at the sedation scores as continuous variables for purposes of analysis is here suggested. It can be seen from the graph in figure 7.9 above above that the average sedation scores were all below 0.8 which is well below the next highest rating of: “2 = mild, easy to rouse”. At no time in the trials did a patient reach a sedation score $\geq 4$.

There is no indication from the data above that the adaptive PCA was responsible for higher sedation scores than the control system.
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7.8.6 Comparison of Analgesic Use

Morphine consumption for both trials and all trials pooled is shown below in figure 7.10. Morphine consumption when the adaptive system was active was considerably higher than for the Abbott system in every block. Statistically significantly ($p \leq 0.05$) more morphine was dispensed in the adaptive-first category in blocks 1 and 3 when the adaptive system was active than in corresponding blocks in the Abbott-first category. The difference for blocks 2 and 4 between categories was high but did not reach statistical significance.

Within the adaptive-first category morphine consumption for block 1 was significantly higher from that of block 2. Likewise consumption for block 3 was significantly higher than for block 4. In the Abbott-first category the differences between active systems was also large but did not reach statistical significance.

There is a slight trend towards decreasing morphine consumption when data for all trials is pooled.

**Figure 7.10** Average morphine consumption per 12 hour block in terms of background infusion component and bolus component. No background infusion was ever prescribed for the Abbott PCA. Trials 4 & 5 for which the background infusion was not operational, are included.
In the adaptive-first category it was initially thought that the large decrease in consumption from block 1 to 2 may have been compensatory, however this seems not to have been the case when examining the Abbott-first category in which the consumption for block 1 is similar to that of block 2 in the adaptive-first category.

It is interesting to note that despite higher morphine consumption for the adaptive active system, the respiration and sedation scores show no significant difference between the systems. It may also be recalled that the pain scores for the adaptive active system were consistently lower than those for the Abbott active system. This data seems to suggest that there may be a range of analgesic consumption, a window of optimal pain relief, which patients are better able to access using the adaptive system. Conventional fixed size bolus PCA would be able to provide higher analgesic amounts alone but would not be able to provide the range of dosages of the adaptive system. Not surprisingly the variances of 12 hourly averages for the adaptive system were usually 1 or 2 orders of magnitude higher than for the conventional system.

The background infusion component supplied 37% of the total morphine requirements in the adaptive-first category, or 45% for block 1 and 42% for block 3, while no background infusion was prescribed for the Abbott PCA at any time for any of the trials.

In the Abbott-first category the background infusion of the adaptive system was not operational for trials 4 and 5 as pointed out in section 7.4.1 point ‘1)’. Excluding trials 4 and 5 the background infusion component was 19% (16% inc. 4 & 5) for all trials or 23% (20% inc. 4 & 5) and 27% (24% inc. 4 & 5) in blocks 2 and 4 respectively. The background component of 19% in this category is almost half that of 37% for the adaptive-first category. The single most relevant factor to account for this difference would at first appear to be that of trial categories, ie: the start of the adaptive system in block 1 as opposed to block 2. This does however not account for the fact that the infusion component remained fairly constant in each category (45-42% and 21-24%) rather than approaching a common endpoint in blocks 3 and 4.

It is clear that the background infusion constituted a major contribution to the total morphine received from the adaptive system and that this component will have to be considered in the evaluation of the adaptive system.
7.8.7 Bolus Requests

The average number of requests for each active block, both fulfilled and unfulfilled, are shown in the graph below (figure 7.11). The trend in the adaptive-first category decreases linearly towards block 4 whereas in the Abbott-first category the number of requests for all blocks other than block 3 is between 15-17. Block 3 has an average of 10.9 requests per 12 hours. Blocks 1 and 4 of the adaptive-first category almost achieve a statistically significant difference at $p = 0.0507$. There is no statistically significant difference between any of the blocks of the two trial categories.

![Average requests per 12 hour block graph](image.png)

Figure 7.11 Bolus and lockout request averages for active (approximately 12h) blocks.

Assuming other factors to be equal then it would seem that the fact that the adaptive PCA commenced in block 1 is the major source of influence for the differing request patterns between categories. The precise mechanism for these differences are beyond the scope of the trial series at this stage. However it may be speculated that patients were initially able to gain a higher degree of control with the adaptive active system in block 1 which subsequently resulted in better control for the remainder of the trials.
The trials were originally structured to detect any 12 hourly differences in button pressing frequency depending on which system was active. Such a 12 hourly difference is not apparent at this stage. It appears that the type of active system in block 1 may have more far reaching effects on patient button pressing behaviour than the kind of active system. Thus at this stage the number of trials may be too low to show any 12 hourly variations and in addition the influence of day and night time variation could in part obscure any underlying trends which might become apparent with a larger number of trials.

The variation in verbal pain scores discussed above would however indicate that patients were able to detect a difference in active systems to some extent but that this particular difference seems to either not have been detected thus far or was not primarily expressed through a change in button pressing frequency.

The percentage of unfulfilled bolus requests (lockout requests) in each 12 hour interval is shown below.

![Percentage of unfulfilled requests](image)

**Figure 7.12** The percentage of unfulfilled (lockout) requests per 12 hour block.

There is no statistically significant difference in the percentages of lockout requests shown in the graph above (figure 7.12). It is perhaps worth noting that 71% (12
requests) of the lockout requests in block 1 of the adaptive-first category are from patient 6B, who was pre-operatively placed on adaptive PCA as patient 6A when the conventional PCA was found to be inadequate. This patient had been placed on the reduced range for over 60 year old patients as his button pressing frequency on the conventional PCA was of such frequency that medical staff were concerned for his safety if the same frequency persisted with the adaptive system. The highest single component of lockout requests in block 1 for the Abbott-first category was 37% (7 requests).

The ratio of bolus to unfulfilled bolus requests has been proposed as a measure of the comfort of patients. From these trials there seems to be no indication that this ratio could be used as a primary endpoint of a measure of comfort. On the contrary the ratio was fairly constant or again rose slightly as the verbal pain scores fell towards the end of the trial period. If the ratio of unfulfilled bolus requests were to be used as an effective control parameter and endpoint, it would perhaps be necessary to review patient education as to the presence of a lockout interval.

### 7.8.8 Discussion

An underlying assumption to the idea that switching active PCA systems would be detectable by patients is the assumption that patients are frequently reassessing the chosen pain scores with the relief experienced and that patients would be able to distinguish any longer term difference between desired and actual relief from other factors such as day and night variations in pain, effect of wound healing and general changes taking place in the usually stressful post-operative period. The impression from the data thus far is that while changing active systems did affect 12 hourly painscores somewhat, patients were unable to clearly perceive the 12 hourly changes in active systems. This could be due to the small patient numbers. One major difference between active systems however was the total morphine consumption which was significantly higher for the adaptive system. It may be that patients received more analgesic because of the background infusion and larger bolus doses. The fact that a background infusion did not necessarily result in fewer demands was also found in a relatively large study by Dawson [Dawson et al. 1995].

A more pronounced effect however was observable depending on which system commenced block 1. In the adaptive-first trials, verbal pain scores, questionnaire and handset pain scores were all generally lower in almost all blocks.
when compared to corresponding blocks in the Abbott-first category. It may be possible that the initial impression formed in the first 12 hours is relatively firmly fixed in patients’ minds and not constantly reviewed as was originally assumed. Patients might require a certain time and pain threshold to induce a change in initially formed modes of pain relief behaviour. Certainly the effects of initial impressions in this regard have been well known in the area of psychology, but how many of these factors are relevant in this case is not clear.

The kind of surgical procedure and the concomitant analgesic agents have not been specifically taken into account in this analysis section but are recorded in abbreviated form in appendix G on the “Medical History Record” page for each patient.

If the adaptive-first PCA system is indeed in some significant way responsible for the observed lower pain scores then this could be a related phenomenon akin to the longer term beneficial effects ascribed to good early analgesia [APMGP 1992]. The high adaptation range was especially added to the adaptive PCA in order to ensure good early analgesia with its concomitant benefits in terms of a more complication-free and ‘smoother’ recovery. In the adaptive-first category only 3 patients commenced adaptive PCA less than 12 hours post-surgically.

The high adaptation range was not effectively tested in these trials. It appeared however that most of the high analgesic needs of patients were met adequately within the normal range.

The findings of other researchers that chronic pain patients generally do not use large amounts of analgesic seem to be echoed in these trials [Ferrante et al. 1988]. Patients in trials 15 and 19 suffered from chronic pain and only required the system for 36 hours by which time only 25mg of morphine had been requested.

Although there is no clear evidence from the sedation and respiration scores it was the subjective impression of some of the research nurses and the author that the amount of analgesia some patients had requested from the adaptive active system was close to the upper acceptable range. For any purely adaptive only trials, unmoderated by the intervening Abbott system, a lower maximum bolus and infusion limit of for example 3 mg of morphine may be more advisable. Alternatively or in addition a maximum limit of analgesic for the preceding 120 minutes might be added. This suggestion is made in view of the fact that the button pressing frequency of patients did not show a clear change between active systems and that the morphine intake on the adaptive active system likewise remained higher than that of the Abbott active blocks. It is presumed that this increase in morphine intake for the adaptive active system is in
part compensating for the lower values of the Abbott active system. In a purely adaptive system the overall consumption of morphine may presumably distribute itself more evenly. The two trials of the adaptive only system (#3 & #6A Table 7.10) which were carried out showed no signs of an excessive amount of morphine being used.

Regarding the safety of PCA, it should also be pointed out that PCA generally does not stand alone but is part of a number of safety protocols consisting of 1) regular monitoring by clinical staff, 2) electronic monitoring as required and available, 3) patient education. It is here suggested that conventional PCA prescriptions have leaned towards conservative PCA prescriptions in an effort to impose a further measure of safety into PCA use. Since the bolus dose is fixed in conventional PCA this is a reasonable course of action given the widely varying patient population and the difficulty of estimating a particular patient’s individual requirement range. In the adaptive PCA device described here the range of analgesic dosages is greater than that usually available for conventional PCA. Nevertheless the usual safety protocols apply and are assumed to be in force as for any PCA device. In particular regular manual observation of patients is assumed. Patient education both pre- and post-surgically is important for safety reasons as well as to optimize the effectiveness of PCA.

7.9 Conclusion

It is a major tenet of the design of the adaptive PCA system that patients would be able to control and chose the range of analgesic that is most appropriate in each particular case. The principle of PCA has here been carried a step further in allowing patients to not only control the timing of their analgesia but the range of increments as well.

Although conventional PCA is usually able to provide the required dosages of analgesic, the standard prescription (1-1.5 mg bolus) must be tailored to the more sensitive range of the population and has been found insufficient in some cases. As it is usually very difficult to predict which patients would require above (or below) standard prescriptions those patients who do require higher bolus dosages will be underprescribed. Trial patients 6A and 9 were originally placed on conventional PCA.
with a 1mg bolus. With these patients the pain relief was so poor that the adaptive PCA system was specifically called for and proved to be satisfactory.

The system presented here effectively incorporates a broader range of PCA prescriptions in that the patient is able to select increments of a full bolus depending on the perceived equilibrium point between analgesia and side-effects.

The adaptive system has only been trialed using morphine and clinical trial data is primarily relevant for morphine only. Other analgesic agents could also be used in the adaptive system but some system modifications would be required depending on the particular agent used.

The number of patients in these trials was relatively small, however some meaningful qualitative and statistical analysis could still be made. There were no instances in which the adaptive PCA was not at least as good in providing pain relief as the conventional control PCA system. In the balance of efficacy versus safety conventional PCA has usually favoured the side of safety in its prescription regimens. There seems to be evidence that the adaptive PCA system is able to expand the safe analgesic dosage range by allowing patients room to tailor their dosages within broader limits without compromising safety.

Whatever the actual technology employed, it must be borne in mind that the technology of PCA alone does not guarantee superior pain relief. It is the responsiveness of the pain service and nursing staff in conjunction with appropriate technology which provide effective pain relief. The adaptive PCA system here is presented as a suitable tool in the total pain management plan.
Chapter 8 Conclusion

8.0 Introduction

The overall aim of this PCA system is to provide improved patient-controlled pain relief when compared with currently available systems. To achieve this aim, a number of propositions and objectives were formulated and outlined in chapter 4. The degree to which these objectives have been met can be assessed from the clinical trial data and will be discussed in this chapter.

8.1 The Complete System and the Expert System

The overall concept of adaptive PCA was to aim for a total system that represented the best approximation to patient-controlled pain relief according to current medical expertise. It was the objective of the author and the medical team to propose a complete system that would imitate as closely as possible best clinical practice. For this reason the various components of the adaptive system were not trialled separately but the proposed system was designed and tested as an integrated whole.

An alternative approach might have been the separate testing of the handset, the variable background infusion and the high adaptation range, each incorporating a relevant aspect of expert knowledge. Whether such an approach would have led to the current proposed system may be debated. However the proposed system grew out of the combined knowledge of the clinical staff as a unit and was seen as a ‘best’ technological implementation of medical expert opinion in pain relief at the Royal Melbourne Hospital.

Thus the proposed system incorporates expert knowledge in its various components of handset, high adaptation range and background infusion algorithms and also in its totality as a system comprising these various elements. There seems to be evidence from verbal pain scores and patient response that the proposed adaptive system does provide better pain relief than the conventional PCA system used as a control (7.8.4).
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The expert knowledge aspect of the various components will be discussed below.

8.2 The Variable Background Infusion

The objective of the proposed background infusion algorithm was to make the background infusion more adaptive to patients’ varying needs. The background infusion implemented in this system was a function of the bolus amounts delivered and the time since the last bolus was given. This scheme was proposed as a practical way of reconciling the arguments for and against the use of a fixed rate background infusion in PCA.

The expert algorithm for the background infusion was designed in consultation with the medical team, such that it would form a substantial part, but less than 50% of the total analgesic administered by the adaptive system. Conceptually the background infusion was designed to be able to reach its maximum level (from zero) in a series of 10 bolus requests for which the pain scores were greater than 5 and each separated by less than 60 minutes, or in half that number should all requests be of pain score 10. It was furthermore intended to decrease the infusion level in a number of steps in the absence of any requests of pain score greater than 5 and to reach zero after a maximum of 3 hours of no bolus requests regardless of the actual infusion level. In effect the expert algorithm, formulated in terms of medical protocol, forms a kind of weighted moving average of the bolus amounts of the preceding 2 to 4 hours. This has been encoded in the expert algorithm as a series of ‘If ... Then ...Else...’ rules.

The original intention of the background infusion algorithm has been met within a broad context in as much as two of the ways of failing were 1) for the background infusion to form an insignificant (approx. <10%) component of the total analgesic administered and 2) for the background infusion to administer more than approximately 50% of the total analgesic from the adaptive system.

In the trials the background infusion has been found to form a large part (20-45%) of the total analgesic administered over the 12 hour periods during which the adaptive system was active. It remains unclear as to why the average background infusion component of the adaptive system was approximately 44 % in the adaptive-first category and 25% in the Abbott-first category (Figure 7.10). The most likely factor seems to be the difference in trial categories of adaptive or Abbott PCA.
systems first and the fact that the number of trials in each category was relatively small.

It is the opinion of the medical team that a background infusion would be appropriate in times of high need and for some time after the cessation of any bolus requests. From the trials it is thought that the proposed background infusion algorithm met its objectives in the sense of adapting itself to what appear to be varying needs in background infusion in patients. Thus from the point of view of providing expert care the background infusion component of the proposed system was thought to approach best clinical care. It is however understood that a human operator continually supervising a patient on PCA would be able to take into account a number of factors such as the actual respiration rate and the general subjective impression gained of the patient, to make more specific and finer adjustments to a background infusion than is possible with a generic algorithm.

A recent double-blind study by Dawson et al has found that a 1ml/h fixed background infusion was beneficial (lower pain scores) in the first 24 hours but showed a higher complication rate thereafter in abdominal surgery patients [Dawson et al. 1995]. It is interesting to note that the background infusion was of some benefit but only for a limited time and not as a fixed constant component. It is in this context that the variable background infusion of the adaptive system would best be considered.

The infusion rate in the adaptive PCA trials varied considerably over time for each patient and this variation almost always included a number of hours when the infusion rate was zero. In section 7.7.2 it has already been suggested that the risk of respiratory depression may vary over time within the same patient and that a period of no analgesic infusion of any kind may be beneficial in reducing this risk. There is no evidence at present to support or refute this speculative hypothesis but it may be worth considering in future trials.

It may also be worth speculating that the action of morphine when interspersed with longer periods of no morphine administration may be different from that of even low level continuously administered morphine [Milne et al. 1993]. Again, it should be noted that the trials carried out thus far have not sought to investigate this matter.

8.3 The High Adaptation Range
It was postulated that the provision of a high range capable of administering elevated doses of analgesic would aid recovery by ensuring that especially in the initial period, as well as for the entire period of PCA therapy, the patient was adequately catered for with respect to analgesic. The initial post-operative period is thought to be especially crucial in setting the tone for the entire recovery period. The expert algorithm incorporated in this PCA system was designed to detect situations of high demand and to supervise the safe administration of especially large boluses and background infusions.

Initially for the high adaptation range to be available both a capnograph and an oximeter were required to furnish a steady uninterrupted stream of data on SpO2, end-tidal CO2 and respiration rate. This configuration was tested in full after trial 13 and a number of problems were discovered in the practical implementation (refer to section 7.4.2 for full details). The oximeter probe and the capnograph probe frequently suffered from movement artifacts. As a result the adaptive system was modified in the course of the trials, the capnograph was deleted, and the data filtering software was modified such that the system now only requires the oximeter for high adaptation (refer 7.4.3).

It was anticipated that the high adaptation range would only be required by a limited number of patients. Of the 18 patients who actually participated in a trial for more than 12 hours, approximately 5 were potential candidates for the high adaptation range (trials: 6A & 6B, 9, 18, 7). However the high adaptation range was not accessible to most of these patients as the full complement of both safety monitors was not available or did not furnish an uninterrupted data stream that permitted high adaptation. Thus the effect of a fully operational high adaptation range cannot be ascertained from the data.

One patient (trial 18) was able to exceed the upper limit of the normal range (5mg) by 0.5mg/h and enter the low end of the high adaptation range for a number of hours while the Abbott system was active. It may be that the fixed bolus amount of 1mg and no background infusion from the Abbott system was felt to be insufficient by the patient at that stage.

The high adaptation range was originally formulated in recognition of the fact that the immediate post-operative period has been found crucial in laying the foundations of good analgesia and that the effects of good analgesia have longer term physiological and psychological effects. It is interesting to note that in the adaptive-first category there seem to be some indications of longer term effects of the kind which might be expected from initial good analgesia. These effects appear most clearly when
comparing the data from the adaptive-first category with that of the Abbott-first category. Pain scores from questionnaires, hourly observations and the average bolus request rate show differences between trial categories that are thought likely to originate from the fact that the adaptive PCA commenced the first 12 hour time period (Figures 7.4, 7.6, 7.11). These differences usually consist of lower scores, less variation and a more pronounced trend over 48 hours for the adaptive first category.

It would also appear that the normal range was able to fulfil at least to some extent the role of the high range in ensuring adequate analgesia. How much more pronounced the effect of the initial 12 hours would have been on the course of the trials if the high range had been fully operational remains unclear.

Regardless of the exact interpretation of the longer term effects of starting trials with the adaptive PCA first, it appears that the trials confirm the importance of the starting period in pain relief as being important [APMGP 1992]. It was part of the original proposition on which the high adaptation range for the adaptive system was founded that the early postoperative period has properties which have longer term effects and which to some degree set the tone of subsequent pain relief and recovery.

Although difficult to quantify it should not be overlooked that there appear to be psychological components to the early analgesic period such as the setting of patient expectations (refer 4.2.1.1).

**8.3.1 Alternative High Adaptation Algorithm**

In view of the difficulties experienced with practical clinical monitoring the high adaptation range was not evaluated in the trials. The problem was mainly one of data acquisition, however since the kind of data the current algorithm requires is not likely to available in practice, it seems that the high adaptation algorithm would need revision in such as way as to still maintain the basic intention of enabling patients to gain additional amounts of analgesic whilst fully monitored for any possible adverse reactions.

Thus apart from a deving a more robust algorithm, the main difficulty to be addressed is the problem of obtaining a reliable and meaningful stream of data regarding patients’ SpO2 levels and possibly respiration rate. The use of sensors on patients who, whilst bed-bound, are still relatively mobile presents a special challenge for data acquisition. Some suggestions which might be taken up in the future have been made by Jones and Visram [Jones et al. 1996, Jones et al. 1992, Visram et al. 1994]. In this project data pre-processing was carried out to deal with short-term
problems caused by patients moving in bed, moving the sensor or in any way modifying the data by their actions. It may be possible to improve on the current situation using intelligent data pre-processing to adapt to the behaviour of particular patients. This could involve some learning ability on the part of the intelligent pre-processing algorithm. It should be noted that any advances in this area would also benefit similar sensing applications in clinical data acquisition in other circumstances.

Some efforts using a moving average filtering algorithm were made in the clinical trials (refer 7.4.2). Further refinement in this direction would be recommended. Fuzzy logic might be considered for future PCA systems, not only in data filtering but also in interpretation of the handset scores.

Whatever success is achieved in obtaining more uninterrupted data from patients, a totally artifact-free data stream for PCA patients seems highly unlikely and the actual high adaptation algorithm should be able to accommodate this fact. The algorithm currently employed suffers from the fact that once invalid data is received for any length of time the algorithm for safety reasons resets itself to the start of the high adaptation range i.e: dropping back to the normal range. The requirement for a steady uninterrupted stream of data for a number of hours has been found to be completely impractical in the trials.

Alternative algorithms should be able to continue in the high range without resetting to the lowest level if short-term error artifacts are received. A possible alternative algorithm could consist of expanding the normal bolus range by a certain percentage (up to a maximum) once a patient was judged to be in need of the high adaptation range.

8.4 The Patient Handset

Current fixed bolus PCA systems require the PCA prescription to take account of the more opioid sensitive section of the patient population and thus generally aim for bolus sizes which are considered safe for all the most likely circumstances.

The objective of the adaptive PCA was to produce a system better able to respond to individual variations in pain intensity. The method proposed to meet this objective was via a handset which allowed patients to register pain intensity in increments. These increments were then translated into varying analgesic bolus amounts by the expert algorithm.
In evaluating the handset there are a number of aspects ranging from physiological elements to the psychological components thought to derive mainly from an increased sense of control in patients.

Data relating to the handset pain scores and thus to the amount of analgesic requested indicate that patients made use of the full range of the handset. To what extent the range of actual amounts requested reflected the physiological need at the time would be extremely difficult to determine, especially bearing in mind the subjective element of pain. It is here suggested that the range of analgesic amounts chosen via the handset reflected a need consisting of both physiological and psychological components in patients. It is however difficult to countermand this suggestion except insofar as complications are concerned. There was no statistical evidence that the adaptive PCA system was responsible for an increase in complications as measured by sedation, respiration scores or antiemetics administered. No reversal agents for respiratory depression were administered at any time. The patient in trial 9 was twice recorded as having a respiration rate of below 8 breaths per minute (7.5 and 7 bpm) while asleep when the adaptive PCA was active. However no action was deemed necessary in the opinion of medical staff (refer to section 7.8 for full details).

Patients generally found the handset easy and simple to use and the two step algorithm involved in a bolus request did not present difficulties for patients. Patients from all backgrounds were able to use the handset successfully.

Benefits derived from the element of choice offered by the handset are difficult to quantify. Questionnaires have been used to elicit patient responses to the handset. From these it can be said that the choice of buttons was generally appreciated by patients, with some patients actively recognizing the choice as a special feature and others accepting it without special mention (refer to section 7.5.4). Only one patient (trial 15) suggested that a single button system might be easier to use. This patient made very little use of the PCA system and was a chronic pain sufferer.

The question of how well patients would be able to judge pain levels and request an appropriate bolus was considered before the clinical trials took place. Trial patients were found to be responsible in their use of the handset and the choice of analgesic amounts indirectly offered through the handset. It is the impression of researchers that patients generally had a clear understanding of the balance between analgesia and the common unpleasant analgesic side-effects.
It was observed that patients would generally remember the effects of past bolus requests and use this as a guideline in requesting future boluses. Patients were observed to reduce their bolus demands if nausea had set in. Patients generally saw a connection between nausea and the number of bolus requests made. It was also found that patients would anticipate pain from physiotherapy or other activities and choose a pain level that in their opinion was appropriate. Thus it seems that patients had some conceptual framework within which to judge pain intensity and which was used as a basis for rating their pain on the handset.

The question of how much patients saw the handset in terms of requesting bolus amounts and how much the handset was seen only as a way of rating pain is perhaps best answered by noting that all patients in the trials seemed to be aware of the connection between pain intensity as rated on the handset and the amount of analgesic dispensed. It seemed that this connection was indeed fundamental to the understanding of the handset and appeared to form the basis and rationale for grading their pain. In this sense it is the opinion of researchers that the handset was seen both as a way of rating pain and a way of determining the bolus dose appropriate to the pain. Regarding what was considered ‘appropriate’, it was observed that patients seemed to use past experience as a guideline in forming a conceptual model in deciding which pain intensity level was appropriate for currently experienced pain. Exactly what type of conceptual models patients had constructed in their minds was not investigated in this trial series and could form the basis of further research.

It is noteworthy that patients very rarely asked the nursing staff for guidance in selecting an appropriate dose on the handset. From this is would seem that patients themselves took control and responsibility for the use of the handset. This in turn would indicate that patients did not see adaptive PCA as an outside technology which “did something to them”, but as a means of expressing themselves and taking control of their pain to some extent. This would be referred to as an internal locus of control in psychology. It would also further confirm the impression that the handset was integrated into whatever conceptual framework of the way the PCA system operated patients had constructed in their minds.

8.5 The User Interface

An objective of the adaptive system was to address the issue of user interfacing. This objective was in part motivated by the issue of safety in that a system which is easy to use and has user friendly interfaces is also generally thought to be safer as far as
human operator error is concerned. The computer screen, the handset and the operational procedures have all been designed for ease of use and to avoid ambiguity. The patient interface through the handset has already been discussed in section 8.4 above and will not be covered here.

Medical and nursing staff found the computer interface easy to use although the presence of a personal computer on the wards was occasionally intimidating for some of the nursing staff unfamiliar with computers. The number of separate items, infusion pump, computer, handset, oximeter and computer monitor as well as the Abbott PCA made the experimental trial system a little bulky and perhaps intimidating.

The concept of grouping the data relevant for nursing charts in one corner of the status screen was appreciated and found useful by the nursing staff. Research nursing staff were more familiar with the system and found the interface logical and coherent.

Small modifications were carried out during the course of the trials but no major redesign was required. One such small modification was to indicate a normally working system by a flashing red status light as opposed to a steady red status light. This enabled staff to check from a distance that the system was indeed operational.

Staff generally were able to read and use the graphical data on the number of boluses, background infusion and safety monitors. Graphical data was used informally to review PCA use by patients. The operational procedures were clear and staff found the system easy to use.

8.6 The Clinical Trials

There are a number of ways of interpreting the trial data of the preceding chapter. It could be argued that patients did not show any awareness of the difference in algorithms (PCA systems) as the active systems were interchanged at 12 hourly intervals because there is no clear and consistent change in button pressing behaviour at 12 hourly intervals.

This line of reasoning would however ignore certain other differences in trial data such as the average 12 hour verbal pain scores which were lower for all corresponding 12 hour blocks in the adaptive-first trial category when compared with the Abbott-first category (Figure 7.4). More importantly the influence of the first 12 hour block seems to have extended across the whole trial period and to have had a
more decisive impact on the overall pain scores than later 12 hourly changes of active systems. It seems that the initial experience of PCA has had a lasting effect on the subsequent periods. This trend is also found in the average number of requests. In the adaptive-first category the average number of requests is lower and declines uniformly, whereas in the Abbott-first category the average number of requests is higher and the decline is halted by an increase in the average number of requests in the last 12 hour block (Figure 7.11). The pain scores obtained from the 12 hourly questionnaires likewise show a trial-wide trend of lower pain scores and less variation in 12 hour averages which seems likely to have had its origin in the first 12 hour period (Figure 7.6).

The 12 hour changeover interval between active systems was chosen as a practical compromise between the time required for patients to notice a change in the underlying algorithm and the time by which healing had significantly changed the pain profile. In addition the underlying assumption made in the trial design was that patients would be able to respond to changes at 12 hourly intervals in some way that was easily detectable as a reflection of the 12 hourly changeovers. It was furthermore assumed that perceived pain would vary in some way with the 12 hourly changeover in active systems and it was hoped that patients would express this perception of pain as an increase in the number of bolus requests. No such clear variation in 12 hourly changes were detectable as this stage.

It is suggested here that the influence of the initial 12 hour block was such that patients established a pattern of expectations and behaviour that was not easily changed. For a clear 12 hourly pattern to be recognisable in the data, it is assumed that patients are frequently monitoring their perceptions of the system. There is evidence in the psychology literature that the initial conceptual model of expectations formed can often be quite firmly lodged and may only be subject to revision as a last resort (Section 4.2.1.1). In other words there is a phenomenon in which there is considerable resistance towards revision of the initially formed impression, even in the face of clear evidence to the contrary. It is also suggested that the effect of initial impressions may have been such that revision of these expectations was not immediate and either too slow or such that its period was longer than 12 hours. In the case of the latter, by the time a change in algorithms had been noticed a changeover back to the original system would have taken place. Variations in day and night rhythms, as well as irregular sleeping patterns following surgery, have not been specifically accounted for and are further factors which might obscure any underlying 12 hourly trends in the trial data. It is further suggested that the pattern of expectations established in the first 12 hours may have been responsible for the difference seen in the verbal and questionnaire pain scores and the bolus requests.
when comparing the trial categories of adaptive versus Abbott system-first (Figures 7.4, 7.6, 7.11).

It is also reasonable to argue that the active system changeover seems to have caused perturbations in the data but did not allow a clear pattern within either trial category to establish itself. One can only speculate as to whether this was the case in for example the painscores for the handset (figure 7.7) and whether a more definite trend in diminishing pain scores would have emerged from a series of trials of only the adaptive system.

The morphine consumption for the adaptive active system is the only parameter which follows a clear 12 hourly cycle in synchrony with the changeover period between active systems. When the adaptive system was active, patients received considerably more analgesic than for the conventional control system (figure 7.10).

It should however be noted that the average morphine consumption for the adaptive active system fell from 55mg in block 1 to 35mg in block 3 in the adaptive-first trial category ($p =0.24$) and instead rose from 46mg to 49mg for the Abbott-first category in blocks 2 and 4 respectively. A similar pattern may be discerned for the average number of bolus requests for the adaptive active system. The average number of requests fell from 15.0 in block 1 to 9.0 in block 4 in the adaptive-first category ($p = 0.0507$) whereas it remained essentially constant in the Abbott-first category with an average of 15.5 and 15.4 requests for the blocks 2 and 4 respectively.

Thus although the morphine consumption for the adaptive system active is considerably higher than for the active Abbott system there seems to be an indication of a trend towards decreasing consumption in the adaptive-first category. This trend is mirrored in some way in the average number of bolus requests per 12 hour block. If this trend is assumed to be valid then it would indicate patient awareness of the different systems. It would also be a further instance of the trial-long effects of starting a trial with the adaptive as opposed to the Abbott PCA first.

If the above trend can indeed be substantiated it could be argued that the range of analgesic which was delivered by the adaptive PCA was at the higher end of a range of acceptable analgesic PCA prescriptions and that the Abbott PCA prescription was on the more conservative side of an acceptable range. Since the bolus size is fixed in conventional PCA it is necessary to ensure that the more opioid sensitive segment of the patient population is taken into account by keeping the bolus size at a level which is appropriate for this more sensitive group. Adaptive PCA gives patients control of a range of bolus sizes and this would then allow less opioid
sensitive patients to request higher doses of analgesic. Thus a higher analgesic consumption of adaptive PCA would seem reasonable to expect.

To summarize, the clinical trials have demonstrated a difference in a number of variables between the adaptive and the conventional PCA systems (Figures 7.4, 7.5, 7.6, 7.7 and 7.11). These differences are generally most marked between trial categories, that is between trials starting with either the adaptive system in the first 12 hours or the conventional Abbott control system. The differences point towards improved analgesia from the adaptive system and would indicate further development of the adaptive system is desirable.

At this stage it is recommended that future trials test the adaptive PCA system by itself in order to give some of the possibly latent trends an opportunity to clearly establish themselves.

8.7 Possible Future Directions of the Adaptive PCA System

There are a number of areas which may warrant further refinement of the current adaptive PCA system. The following is a suggested list of aspects which are more or less speculative and are offered as starting points.

The background infusion algorithm has thus far been translated from expert knowledge. Having observed the algorithm in the trials it could now be attempted to derive a formula based algorithm. Such an approach could yield benefits in terms of tighter control and would permit ready modifications through known mathematical techniques.

Alternative control algorithms for the handset and the method by which bolus increments are decided may be worth investigating. For example, it may be worthwhile testing a handset using a more sophisticated intelligent interpretative algorithm and only 3 pain levels such as Low, Medium, High [Owen et al. 1995].

The safety monitoring equipment would probably benefit from further refinement in terms of removal of noise artifact and dealing with motion artifact from the patient. Intelligent processing of data may be useful in separating spurious oximetry alarms from the genuine acute condition [Jones et al. 1992, Visram et al. 1994].

The PCA system described here uses a 5 minute lockout period. It would also be possible to dispense with the lockout period altogether and instead limit the
amount of analgesic given to a certain level per hour. This strategy has been used in the Prodac (Department of Engineering Science Oxford) devices and in trials by Jadad [Jacobs et al. 1985, Jadad et al. 1992]. A modification of the present system using this alternative to the lockout period could warrant further investigation.

Having implemented the system to its current level, fuzzy control may be considered for future PCA systems. The understanding and insights gained from implementing a simple expert system would lend themselves very well to a fuzzy model approach. This is best illustrated using a simple example. In the rule-based expert system, rules of the form: IF X AND Y THEN Z are used. In a fuzzy system such a rule could be changed to: IF (X to degree A) AND (Y to degree B) THEN (Z to degree C). A crisp output value for C could be obtained by defuzzifying the output using such methods as taking the first moment of area [Dingli et al. 1992]. Fuzzy logic might even be more robust in artifact rejection of monitoring data.

A speculative idea regarding PCA is the possible use of predictive models to create a composite human-machine system. The requested bolus size could be compared with the predicted bolus size and a difference error generated. This error could then be used in, for example, a self-modifying neural network to screen for unreasonable bolus requests based on a patient’s past bolus request behaviour pattern.

A button pressing profile in terms of statistical estimators as used in signature analysis may be able to characterize patients in ways that would permit the identification of groups and trends in patients which correlate with other aspects of pain relief.

The system described thus far and used for clinical trialling has been primarily designed for morphine. A more generic system using volume rather than dosage infusion parameters would be a logical further step once the system had been validated in larger trials. Technically this would be a relatively simple task.

The above list offers only suggested starting points for future modifications and enhancements of adaptive PCA. Any such changes would best be based on further trials of the current system.

8.7.1 Psychological Aspects of Adaptive PCA Use
In evaluating the trials it has become apparent in a number of instances that a better knowledge of the psychological aspects of PCA and the handset in particular would be beneficial to better understanding PCA use. Some suggested directions which could be used as starting points for future research might be the following.

The impression gained from the trials is that patients generally benefited psychologically from the element of choice incorporated in the handset and that this aspect of PCA could yield useful results. In particular an investigation of the conceptual models in the minds of patients regarding pain relief and the process of quantifying pain could provide further material for improving future PCA technology.

The clinical trials of chapter 7 are seen as a starting point but further trials of the adaptive system would be highly recommended.

The question of how much patients consider pain intensity as distinct from the anticipated analgesic amount when making a choice on the adaptive handset may deserve further attention. Thus far the inter-relationships between these two aspects have been assumed to be so close as to be virtually indistinguishable. The role of patient education in handset use is considered especially important in this respect.

It was observed in the trials that some patients seemed to feel no compunction about using the whole range of the handset to express their varying pain levels, whereas others seemed to restrict themselves to the lower end of the scale and yet others would not utilize the range of choices very much. Trials with a larger population may be able to delve into this aspect more. In the clinical trials thus far observation alone seemed to indicate a group of patients who were unconcerned about any adverse effects and who would choose whatever level they felt appropriate and another group who had frequently experienced adverse effects such as nausea and who were much more reticent in their use of PCA. It was speculated whether some patients felt the need to test limits by going some way into a zone of discomfort in order to obtain what was perceived as optimal analgesia and whether other patients were satisfied by a simple diminution of pain as such.

A further consideration would be the process which patients used to select a particular pain score and to what degree past association was a factor. The adaptive PCA expert system could be modified to take into account whatever conceptual model patients generally use. It may be asked whether patients attach most importance to the most recent bolus requests and less importance to more temporally distant ones Thus one such suggested model would be the analogue of a weighted moving average filter in determining the current pain score.

The issue of a self-imposed upper button pressing limit has been mentioned in the literature and would also be a candidate for further investigation.
Chapter 8 Conclusion

The above are only offered as starting points for future research.

8.8 Conclusion

PCA constitutes an effective closed loop system, if one considers the patient as part of the control loop. PCA rests on the fundamental tenet that patients are best qualified to judge their level of pain and that the technology of PCA allows patients to assume control of their own pain relief. The proposed adaptive PCA system described here is a further step in this technology.

The system presented here is distinguished from those available at present by providing a number of additional features. These include a patient handset on which pain intensity levels can be registered, a monitoring device for enhanced safety, expert adaptation to a patient's analgesic need even if high doses of analgesic are required, and a self-adjusting background infusion. Clinical trials have indicated that the system provides effective pain control and is well accepted by both patients and clinical staff.
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