Gunasekaran Bharathy (Orcid ID: 0000-0002-9866-204X)

Brief Communications

Title: Assessment of potential opioid toxicity and response to naloxone by rapid response teams at an urban Melbourne hospital

Author Details

1. Dr Bharathy Gunasekaran

Basic Physician Trainee (BPT 3), Department of Medicine, St Vincent's Hospital, Melbourne, Victoria, Australia

2. Dr Jennifer Weil

Palliative Care Physician, Centre for Palliative Care, St Vincent's Hospital, Melbourne, Victoria, Australia

3. Mr Tom Whelan

Nurse practitioner, Centre for Palliative Care, St Vincent's Hospital, Melbourne, Victoria, Australia

4. A/Prof John Santamaria

Director of Intensive Care Unit, St Vincent's Hospital, Melbourne, Victoria, Australia

5. A/Prof Mark Boughey

Director Palliative Medicine, St Vincent's Hospital, Melbourne

Co-Deputy Director, Centre for Palliative Care, St Vincent's Hospital, Melbourne, Victoria, Australia

Correspondence

Dr Bharathy Gunasekaran

Postal address: 6 Gertrude St, Fitzroy, VIC 3065

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/imj.13692

Email address: bharathy.gunasekaran@gmail.com
Telephone number: +614 32739940

Acknowledgements

There are no financial supports or relationships that may pose a conflict of interest.

Word count

Abstract: 76 words

Main text: 1654 words

Abstract

Opioid prescriptions have significantly increased in recent years and are used for a wide variety of indications. Electronic medical records of 45 patients who received naloxone by a rapid response team over an 18-month period were retrospectively reviewed. This study found inconsistencies in the management of possible opioid toxicity with variation in the total naloxone dose and number of doses administered. This highlights the importance of a standardised protocol for recognition and management of opioid overdose.

Key words

Naloxone; opioids; opioid toxicity; rapid response system

Brief Communications

Assessment of potential opioid toxicity and response to naloxone by rapid response teams at an urban Melbourne hospital

B. Gunasekaran[1], J. Weil[2], T. Whelan[2], J. Santamaria[3], M. Boughey[2]

[1] Department of Medicine, St Vincent's Hospital, Melbourne, Victoria, Australia

[2] Centre for Palliative Care, St Vincent's Hospital, Melbourne, Victoria, Australia

[3] Intensive Care Unit, St Vincent's Hospital, Melbourne, Victoria, Australia

Introduction

Although pharmaceutical opioids have been recommended in the treatment of acute pain and cancer pain, the use of opioids have expanded in the last decade to include the treatment of acute and chronic non-cancer pain despite the limited evidence of the long-term benefits of opioid use for any indication.[1-3] In Australia, there was a 15-fold increase in the number of Pharmaceutical Benefit Scheme (PBS) listed opioid dispensing episodes (500,568 to 7,495,648) between 1992-2012.[1]

One of the main concerns about increased opioid prescriptions, coupled with prolonged use in patients with chronic non-cancer pain is the potential for opioid-related harm. Between 2002-2011, the number of accidental deaths due to pharmaceutical opioids and illicit drugs in Australia increased from 151 to 266, representing a 1.7-fold rise.[1] People at higher risk of opioid overdose include those with opioid dependence, those who inject opioids, patients who take more than 100mg morphine (or equivalent) daily or who use opioids with other sedating substances, the elderly, and those with comorbid health conditions.[3-4]

Opioid overdose can be identified by a combination of signs including decreased conscious state, respiratory depression and miosis.[3,5] Naloxone, an antidote to opioid poisoning, completely reverses the effects of opioid overdose if administered in time.[3]

Although opioids are widely prescribed in the acute hospital, specific methods to evaluate opioid toxicity in this setting are lacking. The aim of our study was to describe the assessment of potential opioid toxicity and its management. As naloxone is usually stored in crash carts, its use is not easily audited. Consequently, we assessed naloxone use by rapid response teams as a surrogate for cases of suspected opioid toxicity.

Methods

The study population included patients in an urban hospital in Melbourne, Australia who received naloxone by the rapid response team during a Code Blue or Medical Emergency Team (MET) call between January 2012 and June 2013. Electronic medical records of these patients were retrospectively reviewed. Data analysis was done using STATA version 11.2. Ethics approval was obtained from the institutional ethics committee.

Results

There was a total of 49 codes where naloxone was used involving 45 patients over this 18-month period. Forty (81.6%) of these codes were MET calls, five (11.1%) were Code Blues, and four (8.9%) were MET calls subsequently escalated to Code Blues. The characteristics of these patients are described in Table 1.

Table 1 Characteristics of patients

Characteristic	Number (Percentage)
Gender	
Male	29 (64.4%)
Female	16 (35.6%)
Age (years)	
23-50	9 (20%)
51-70	20 (44.4%)
71-93	16 (35.6%)
Admission unit	
Surgical	27 (60%)
Medical	17 (37.8%)
Emergency short stay	1 (2.2%)
Comorbid conditions (renal, hepatic or central nervous system impairment; mental health issues)	
No	10 (22.2%)
Yes	35 (77.8%)
Known documented malignancy	
No	36 (80%)
Yes	9 (20%)
Documented opioid use prior to admission	
No (Opioid naïve)	22 (48.9%)
Yes	23 (51.1%)

Reduced conscious state was the main reason or one of the reasons for the code in 44 episodes (89.8%). Other documented reasons included hypoxia, hypotension and reduced respiratory rate. The respiratory rate prior to naloxone administration was clearly documented in 34 episodes and of these, only four (11.8%) episodes had patients with a consistently documented respiratory rate of less than 12, 18 patients (52.9%) had a consistently normal respiratory rate (12-20) and 9 patients (26.5%) had a consistently increased respiratory rate greater than 20. Pupil size was commented on in 37 episodes and of these, 17 (45.9%) episodes made a note of pupils being constricted.

Opioids taken in the 24 hours prior to the emergency code were also reviewed. Opioid consumption was not clearly documented in three episodes and in one episode, the patient had not received any opioids in the preceding 24 hours. Of the remaining episodes, we were able to convert the opioids consumed to an oral morphine equivalent in 33 episodes. Of these, patients in 16 episodes (48.5%) had more than 100mg of oral morphine equivalent. Overall, patients in 24 of the episodes (49.0%) had also received another sedating substance such as an antipsychotic, antidepressant or benzodiazepine.

There was a wide range of naloxone doses administered. Nine episodes were excluded, as the naloxone dose administered was unclear either because it was not charted in the medication chart or there was a discrepancy between the medication chart and the patient's notes. Of the remaining 40 episodes, the total naloxone dose given during the code itself ranged from 40-2000 micrograms with a mean dose of

367 micrograms. The number of doses given during the code was clearly documented in 23 episodes and ranged from 1-6 doses. One dose of naloxone was given in 16 episodes (69.6%). Two, three and four doses were given in two episodes each and six doses of naloxone were given in one episode.

The route of naloxone administration was clearly documented in 34 episodes. In 30 episodes (88.2%), naloxone was given intravenously only. Naloxone was given through both intramuscular and intravenous routes in three episodes (8.8%) and subcutaneously in one episode (2.9%). Only one episode included a stat dose followed by an infusion of naloxone.

The effectiveness of naloxone was documented in 46 episodes. Table 2 shows a comparison between the perceived effectiveness of naloxone for example, if the rapid response team thought there was an improvement in the patient's conscious state, and whether the team believed opioids were implicated as a cause for the patient's deterioration.

Table 2 Comparison between documented effectiveness of naloxone and documented implication of opioids as a cause for the code by the rapid response team

Effectiveness of naloxone	Opioids not implicated	Opioids implicated	Not documented
No	4	1	2
Yes	4	33	2
Not documented	1	0	2

There was no significant correlation between the perceived effectiveness of naloxone and gender, presence of comorbidities, opioid naïve status prior to admission, concurrent use of another sedative, respiratory depression, or the dose and route of naloxone administration.

The adverse effects of naloxone were difficult to ascertain. Agitation was reported in 7 episodes, one patient had severe rebound pain and one patient experienced vomiting post naloxone. Pain scores post-code were not documented in 29 episodes.

With regards to the outcomes of these 45 admissions, 21 (46.7%) patients were discharged home including to a supported residential service, 14 (31.1%) patients were transferred to another hospital or facility, and 10 (22.2%) patients died with three of these patients transferred to the palliative care unit prior to their deaths. The duration from the code to time of death in these ten patients varied between 0-25 days with a mean of 7.5 days.

There were no discharge summaries available for 4 patients. One patient was not formally admitted and therefore did not have a discharge summary. In the 32 patients where opioids were implicated as one of the causes for the deterioration, opioid toxicity was documented as a complication in ten patients (31.2%), altered conscious state was noted in five patients (15.6%) and naloxone was mentioned in two patients (6.3%).

Discussion

The assessment of potential opioid toxicity in hospital is challenging as there are no systems in place that accurately track opioid prescribing or administration errors. Our study demonstrates a need for improved education and practice guidelines around the recognition and management of opioid overdose. The opioid overdose symptoms of reduced consciousness, miosis and respiratory depression may not always be present. Respiratory depression is the sine qua non of opioid intoxication with a respiratory rate of 12 breaths per minute or less strongly suggestive of acute opioid overdose.[5] Miosis alone is insufficient to infer the diagnosis of opioid overdose particularly as it may be present in chronic opioid use, and polysubstance use may produce normally reactive or mydriatic pupils.[5] Interestingly, a consistently reduced respiratory rate was documented in only four patients in this study. However, naloxone was noted to be effective in 39 episodes and opioids were implicated in 34 episodes. This raises concern regarding the diagnostic assessment of opioid toxicity and the appropriateness of naloxone administered. The deterioration of these patients could potentially be attributed to other factors such as disease progression or sepsis. It is important to note that patients on opioids will become more alert post naloxone but this does not necessarily imply opioid toxicity.

The inconsistencies in the management of possible opioid overdose found in this study with wide variations in the total naloxone dose and number of naloxone doses administered are likely because of the lack of consensus regarding the definition of opioid overdose and its management. This study highlights the importance of having a standardised medical protocol in place to identify the clinical criteria for naloxone administration as well as the recommended route and administration dose.

Choosing the effective dose of naloxone to be administered can be challenging as it depends on multiple factors including the amount of opioids received, the patient's weight, and degree of penetrance of the opioid analgesic into the central nervous system.[5] Boyer *et al* recommends an initial naloxone dose of 0.04mg for adults.[5] If there is no response, the dose should be slowly increased every 2 minutes to a maximum of 15mg.[5] Naloxone has a shorter half-life than that of many opioids and some patients may require repeated doses to achieve satisfactory clinical outcomes.[5] If multiple doses of naloxone are required, a naloxone infusion should be considered. Opioid toxicity is an unlikely cause if respiratory depression continues.

Naloxone may precipitate a short period of acute withdrawal symptoms which include hypertension, tachycardia, tremor, convulsion, confusion, headache and vomiting.[4] Consequently, patients who have received naloxone should be monitored closely for side effects and pain scores post administration of naloxone should be appropriately documented.

Although MET calls and Code Blues are significant events during a patient's hospital admission, there was inadequate documentation during and after these events particularly with regards to the adverse effects of naloxone. The poor documentation of these events and potential opioid toxicity as a complication in discharge summaries were also concerning. It is vital that complications during the admission are communicated to the local doctor as it may reduce irrational or inappropriate opioid prescribing in the community. Along with the relatively small dataset, the lack of adequate documentation in some episodes were potential limitations; and the latter an important finding highlighting the need for education about the importance of

adequate, accurate and structured documentation during rapid response systems as well as in discharge summaries.

In conclusion, true and significant opioid toxicity in acute hospitals are relatively infrequent, however education and guidelines about diagnosis, management and documentation of opioid overdose need improvement. This study presents a useful approach to assessing the use of naloxone in the acute hospital setting during rapid response systems as a surrogate for suspected opioid toxicity, and will allow comparisons and change to be assessed over time.

References

1. Blanch B, Pearson S-A, Haber PS. An overview of the patterns of prescription opioid use, costs and related harms in Australia.. Br J Clin Pharmacol 2014;78:1159-66.

2. Roxburgh A, Bruno R, Larance B, Burns L. Prescription of opioid analgesics and related harms in Australia. Med J Aust 2011;195(5):280-4.

3. World Health Organisation. Information sheet on opioid overdose. November 2014. Available at http://www.who.int/substance_abuse/information-sheet/en/

4. Wermeling DP. Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access. Ther Adv Drug Saf 2015;6(1):20-31.

5. Boyer EW. Management of opioid analgesic overdose. N Engl J Med 2012;367(2):146-55.

Table 1 Characteristics of patients

Characteristic	Number (Percentage)
Gender	
Male	29 (64.4%)
Female	16 (35.6%)
Age (years)	
23-50	9 (20%)
51-70	20 (44.4%)
71-93	16 (35.6%)
Admission unit	
Surgical	27 (60%)
Medical	17 (37.8%)
Emergency short stay	1 (2.2%)
Comorbid conditions (renal, hepatic or central nervous system impairment; mental health issues)	
No	10 (22.2%)
Yes	35 (77.8%)
Known documented malignancy	
No	36 (80%)
Yes	9 (20%)
Documented opioid use prior to admission	
No (Opioid naïve)	22 (48.9%)
Yes	23 (51.1%)

Table 2 Comparison between documented effectiveness of naloxone and documented implication of opioids as a cause for the code by the rapid response team

Effectiveness of naloxone	Opioids not implicated	Opioids implicated	Not documented
No	4	1	2
Yes	4	33	2
Not documented	1	0	2