Pain Management in the Acute Care Setting: Update and Debates

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Abstract (150) 142

Pain management in the paediatric acute care setting is underutilised and can be improved. An awareness of the analgesic options available and their limitations is an important starting point. This article describes the evolving understanding of relevant pharmacogenomics and safety data of the various analgesic agents with a focus on agents available in Australia and New Zealand. It highlights the concerns with the use of codeine in children and discusses alternative oral opioids. Key features of oral, parenteral, inhaled and intranasal analgesic agents are discussed, as well as evidence supported use of sweet tasting solutions and non-pharmacological interventions. One of the biggest changes in acute care pain management has been the advent of intranasal fentanyl providing reliable potent analgesia without the need for intravenous access. The article will also address the issue of multimodal analgesia where a single agent is insufficient.

3 key messages

1. While alternative nonsteroidal anti-inflammatory analgesic agents and newer formulations have become available, oral and intravenous paracetamol and oral ibuprofen continue to be the mainstay of simple analgesic intervention in acutely ill and injured children. Recent research results have improved the understanding of the limitations of analgesic agents.
2. Codeine's efficacy is limited by an individual's ability to metabolise it to its active metabolite morphine. Concerns about a lack of efficacy in some children (due to the inability to metabolise codeine) and deaths in others (associated with ultrarapid metabolism), have led many paediatric institutions to remove or restrict codeine and replace it with other oral opioids.
3. As a recent key innovation, intranasal fentanyl provides potent rapid onset and safe analgesia in children without the need for intravenous access.

Abbreviations:

Cox-2	cyclooxygenase type 2 enzyme
Coxibs	cyclooxygenase enzyme inhibitors (selective for Cox-2)
IV	Intravenous
nsNSAIDs	non-selective non-steroidal anti-inflammatory drugs
OIVI	opioid-induced ventilatory impairment
OSA	obstructive sleep apnoea
PCA	patient controlled analgesia

Introduction

Upon attending an ED, children are subjected to diagnostic and therapeutic procedures which are associated with varying degrees of pain and distress[1-5]. They are commonly young and pre- or early-verbal and disappointingly, analgesic intervention is used with low frequency[3-5]. This is in spite of the recognition that pain has long term consequences on a child's behaviour and reaction to future painful experiences[2,6]. The importance of minimising pain and distress in children is recognised in several clinical practice guidelines in the paediatric, emergency and pain literature[6,7]. Age and developmentally appropriate pain scoring tools should be used in children for assessment[6] to then assist with determining the choice of analgesic intervention. This should then follow with reassessment to determine the response to analgesia.

This article provides an update to guide these choices for the analgesic management of children in the acute care setting. It presents information on the current debates around the adverse event profiles of the various analgesic agents used both commonly, and off-licence, and provides suggested escalation with multimodal intervention, when a single agent is ineffective. **Simple analgesia: *Paracetamol (acetaminophen)***

Paracetamol is used for mild pain in children, and as an opioid-sparing agent for more severe pain[6,8]. The mechanism of action of paracetamol is debated[9]. Paracetamol is available in tablet, elixir, suppository and intravenous (IV) forms. All routes are efficacious and it is frequently a first-line analgesic intervention[6,10]. Peak plasma concentrations are achieved following oral administration reliably at 30 minutes and from then, closely approximate those following IV administration. With rectal administration, absorption is slow with delayed and erratic peaks in plasma concentrations, but the duration of effect is longer as compared with IV administration[11]. See Table 1 for suggested dosing. The IV route is used most commonly perioperatively and in intensive care, but is a consideration in emergency acute care when patients are vomiting and the avoidance of opioids is imperative.

Paracetamol use for pain and fever is generally safe in therapeutic doses[6,12]. Hepatotoxicity occurs with intentional overdose and is concerning with chronic dosing, prolonged fasting and severe illness. It is reported with both accidental supra-therapeutic and therapeutic dosing[9,13]. It is prudent to dose for lean body weight (as the impact of obesity/fatty liver infiltration is poorly elucidated) and to reduce dosing with long term administration or in liver impairment. There is active debate regarding whether paracetamol is protective or precipitates bronchospasm/asthma[9]. It has been used in patients with aspirin sensitive asthma (an old term now replaced by non-steroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD).

Simple analgesia: Non-selective non-steroidal anti-inflammatory drugs (nsNSAIDs) e.g. ibuprofen

Cyclooxygenase (Cox) enzymes, Cox-1 and Cox-2, are responsible for the formation of prostanoids in the inflammatory pathway. Nonselective (ns)NSAIDs (eg ibuprofen, diclofenac, ketorolac and naproxen) variably inhibit these two enzymes to have combined anti-inflammatory and analgesic effects. Because Cox-1 and Cox-2 enzymes are present in multiple tissue sites, inhibitors have a range of other effects. NsNSAIDs are effective for mild to moderate pain and are equivalent or superior to paracetamol for paediatric postoperative pain management[6,8,10]. The commonly used nsNSAIDs equilibrate with the brain effect site more quickly than paracetamol[6,10]. NsNSAIDs are available in tablet/capsule, elixir, rectal and parenteral forms and are used first- and second-line or

in combination as part of multimodal analgesic management. See Table 2 for suggested dosing of ibuprofen and diclofenac.

Like paracetamol, nsNSAIDs use for pain and fever is generally safe. Paediatric institutions vary in their 'acceptable lower age limit' for nsNSAID use. Some choose 12 months, while the labelling nominates a lower age (eg 3-6 months for ibuprofen) unsupported by safety data. The reason for reluctance is that nephrons are maturing until 2 years of age and single doses in neonates can reduce glomerular filtration rate by 20%, albeit reversibly[6,10]. The risk benefit of nsNSAID use is therefore weighed against an infant's illness severity and comorbidities. The impact of multiple doses is uncertain. As in adults, nsNSAIDs are not to be co-administered with diuretics and angiotensin converting enzyme inhibitors. There is an important precaution in renal impairment, and hypovolaemic or compromised circulatory states, where acute kidney injury has occurred[14,15]. Gastric discomfort, gastritis and peptic ulceration are well-known adverse effects[6,10] and patients receiving long-term dosing or at high risk acutely should be considered for co-treatment with acid suppression.

Anaphylaxis is extremely rare, but for allergic reactions, there is within class cross sensitivity. A concern is the variable impact of nsNSAIDs on asthma of different severity. In patients with mild asthma, nsNSAID use does not precipitate bronchospasm; with the anti-inflammatory effect possibly reducing outpatient attendances for asthma flares[6,10]. However, in a percentage of patients with moderate to severe asthma and coexistent nasal disease (indicated by allergic rhinosinusitis or polyps), NSAID-ERD can be precipitated, precluding their use[6,10].

Debate continues about the adverse effects of nsNSAIDs on bone healing. Osteogenic activity is decreased by a Cox-2 mechanism, with studies varying in their conclusions as to whether fusion is impaired in orthopaedic surgery or long bone fractures in adults or children[16,17]. Short term use (3-14 days) of usual (not high) dose is considered acceptable.

The other issue is inhibition of platelets: reversible with nsNSAIDs but non-reversible with aspirin. This means nsNSAIDs should be avoided in low platelet states or conditions where bleeding is a risk. Postoperative bleeding rates are increased (by 2 to 20 fold: from 0-0.4% to 1.7-2.4%) following single dose use in various adult surgery types[18]. The perioperative use of nsNSAIDs is avoided for surgery with high risk of postoperative bleeding. Use in tonsillectomy is controversial[19]. If a patient presents to the emergency department or general practice in pain where bleeding is of consequence (eg post tonsillectomy or with intracerebral pathology), the take home analgesic recommendation must be carefully considered (see below).

Simple analgesia: Selective NSAIDs -Cyclooxygenase (cox)-2 inhibitors (or coxibs) eg celecoxib

Coxibs are of theoretical consideration in acute care when nsNSAIDs are contraindicated and the clinician wants additional analgesia to paracetamol, while avoiding opioids and opioid induced ventilatory impairment (OIVI) or sedative effects (eg patients with obstructive sleep apnoea (OSA) or head injury). However, coxib use is off licence in Australia and New Zealand and paediatric trial data are limited[6]. Dosing information in children requires assessment and clarification and these agents are relatively expensive. Celecoxib is the oral coxib available most commonly in capsule form which

can be dispersed, while some hospital pharmacies and compounding pharmacies are providing a suspension for paediatric dosing (that is not commercially available).

The main issue in acute care is that coxibs do not inhibit platelet activity. They may be pro-thrombotic in adult coronary and cerebrovascular disease but are an option for the child in pain post-tonsillectomy[20] or post haemophiliac bleed[21]. As the renal effects of NSAIDs occur via a cox-2 mechanism[15], it is essential that renal output is established before use. Epigastric discomfort occurs (similar to placebo rates) but peptic ulceration rates are low. The other indication for coxibs is in NSAID-ERD and allergy to nsNSAIDs where coxib use appears safe[6]. The safety profile in paediatric overdose of celecoxib is very good[22].

Opioids

The term opiate refers to substances derived from the opium poppy, and a narcotic is an agent that induces sleep. The term opioid refers to agents that bind opioid receptors with effect. Therefore it is best to replace the terms "opiate" and "narcotic" with the class label of "opioid", although the past literature uses these terms interchangeably. Opioids are effective analgesics but use is associated with many negative effects including itch, nausea and vomiting (30-40% of patients), constipation (~90% of patients) and dose dependent sedation and OIVI.

Opioids: Codeine

Codeine has been used for decades in children, popular due to over the counter availability including as a combination preparation. For analgesic efficacy, codeine requires conversion to its active metabolite, morphine, by cytochrome P450 (CYP)2D6. Pharmacogenomic investigation reveals ~ 100 genes for this liver enzyme and 4 phenotypes of enzyme activity: poor (PM), intermediate (IM), extensive (EM='normal') and ultra-rapid metabolisers (UM)[6]. The PM/IM phenotype is an explanation for codeine's poor efficacy in some comparative analgesic trials and being falsely attributed as causing less sedation and respiratory depression than morphine. People with the UM phenotype produce high morphine concentrations with parallel increase in side effects. The issue to highlight is recent deaths reported in association with UM and EM phenotype in breastfed neonates whose mothers took codeine[23], and toddlers[24] and older obese children[25], where codeine was used for pain or cough. Consequently, several regulatory bodies have relabelled codeine's product information[26], the World Health Organisation has removed codeine from its analgesic ladder[27] and tertiary paediatric centres are removing it from formulary.

The phenotypic representation varies with different racial origin. Asians mostly have normal phenotype (EM 92%). Approximately 10% of Caucasians and Europeans metabolise poorly or not at all, while 10% are at risk as UMs. Patients of African and Arabic origin are at greatest risk with 26-30% UMs, while 20% are PMs with no analgesic benefit. Thus, in acute care it is best to avoid codeine and use an alternative opioid. If no alternative is available, then codeine is best administered under medical supervision and not for the first time as a night time rescue post discharge.

Opioids: Morphine immediate release and sustained release (MSContin®)

Morphine is the gold standard opioid[6]. Oral tablet or elixir is available in various concentrations, but these are unflavoured and bitter reducing the acceptability by children (see oxycodone below). Extended duration 'sustained' release *MSContin®* is available in various tablet sizes and also granules (20 and 30mg sachets). The latter is useful when tablets are refused or administration by enteral tube is required. Large scale audit supports the safety of IV morphine via nurse controlled bolus with continuous infusion[28], patient controlled analgesic (PCA) device or by nurse or parental proxy[29].

Opioids: Oxycodone immediate and controlled release (OxyContin®, Targin®)

Oxycodone orally has recently become available in IV form, but oral administration has established efficacy in various paediatric settings[6]. It is available as tablet (immediate and extended 'controlled' release) and elixir (butterscotch flavour; 1 mg/mL, 200 mL bottle). The elixir's palatability has increased the use of this agent in children. For safe discharge prescription, pharmacies can dispense limited volumes (eg a few prefilled syringes or small 20 mL containers).

The continuous release *OxyContin®* has active drug in its outer core, with improved pharmacokinetic profile over *MSContin®*. Unfortunately, *OxyContin®* is replacing heroin as a drug of abuse. The inner drug core is accessed for subsequent injection (drug misuse website: www.bluelight.com). Drug manufacturers have consequently developed a tamper resistant matrix (*OxyContin®*-OP) and a naloxone extended release combination *Targin®*. The latter offers therapeutic advantage as the incorporated naloxone binds intestinal opioid receptors reducing constipation incidence without reduced analgesic efficacy (as absorbed naloxone experiences 100% first pass liver metabolism).

Opioids: Fentanyl

Fentanyl is potent and more lipid soluble than morphine and used in children via IV, intranasal (IN), epidural (postoperative), trans-buccal and transdermal routes (the latter in opioid tolerant cancer patients)[6]. After IV administration, fentanyl affords rapid onset and short duration of effect.

Intranasal administration (via syringe or metered aerosolised device: MAD; See Figure 1) is increasingly used including in children[30,31], providing effective analgesia for moderate to severe pain (eg in trauma, fracture, burns) similar to IV and oral morphine. The IN route offers convenience when no IV access is available, with similar onset time to IV (2-5 minutes) and longer duration[32]. High concentration (100-300 mcg /mL) low volume administration was initially studied[33]. 'Usual' concentration (standard IV vial: 50 mcg/mL) is also efficacious[34] and is readily available and used in Australian and New Zealand EDs[35] (reducing confusion with stocking multiple concentrations). See Table 2 for IV and IN dosing and Table 3 for indications. A practical tip is to direct the MAD 45 degrees upwards to spray the turbinates, rather than horizontally along the nasal floor (where drug runs to the pharynx and is swallowed, reducing bioavailability and efficacy).

Other analgesic agents

Tramadol

Tramadol is used off licence in the paediatric perioperative setting[6], via various routes. It is effective for somatic and also neuropathic pain: by noradrenaline and serotonin reuptake inhibition (70% of effect) and mu-opioid effect (30%) via its active metabolite (O-desmethy-tramadol; formed by CYP2D6). See Table 2 for dosing. Adverse effects of nausea and vomiting, dizziness and sedation are similar to opioids, with reduced itch, constipation and respiratory impairment. Naloxone administration will reverse adverse effects only in part. In the acute care setting, tramadol should be used in place of opioids for moderate to severe pain when opioids are contraindicated (eg OSA) or causing side effects, or when opioid resistant pain is present (see below). A precaution is that tramadol precipitates seizures in epileptics or seizure prone patients (usually at high doses). A practical tip for IV administration is to infuse it slowly IV over 15 to 20 minutes to avoid a nausea bolus effect. Tramadol in oral immediate release form is most commonly a capsule the contents of which can be dispersed in water for divided administration to smaller children. A concentrated formulation is available for use in adult palliative care as 100mg per mL. This should not be used in children as there is risk of dosing confusion and overdose[6]. New Zealand has recently launched a commercial 10mg per mL suspension. Tramadol sustained release tablets are not used in the acute setting, but may be used postoperatively in the older child.

Tapentadol (Palexia SR®)

Tapentadol is effective via noradrenaline reuptake inhibition (90%) and opioid effect (10%). It is currently licensed for use in chronic pain and may have reduced abuse potential. It is mentioned here as, once the immediate release form is available, it may be used for patients in acute pain susceptible to opioid induced nausea, vomiting, constipation and OIVI.

Ketamine

In addition to its traditional use for dissociative sedation, ketamine can be used as an analgesic in the ED[35,36] and perioperatively, via oral, intranasal and IV routes[6]. Intramuscular route is less preferable to the other routes, but is a reliable alternative when IV access is challenging for acute pain management and procedural sedation in the ED, for example in chubby infants. Intranasal route has been used for analgesia in the prehospital setting with a wide range in dose[6]. Analgesic IV doses 0.1-0.5 mg per kg are sub-anaesthetic (i.e. the patient is coherent and not dissociated). It is particularly useful adjunct in opioid resistant pain.

Inhaled methoxyflurane

Methoxyflurane is a popular Australian prehospital analgesic intervention in patients with various pains, most commonly resulting from trauma. It is used in children and is 78% effective[37], more so for extremity pain rather than the subsequent fracture manipulation[38].

Sweet tasting solutions (eg sucrose) and physical interventions for infants

Sweet tasting solutions (sucrose, glucose, fructose, supplemental breast milk etc) effectively reduce pain and/or behavioural response to skin breaking procedures (heel-lance, venipuncture, IV and arterial cannulation) in preterm and term neonates[39,40] and older infants (1 to 12 months, including when having immunisation[41]), but not once toddler- or school-aged[42]. The optimum

concentration/dose is still unclear but this safe simple intervention should be routinely offered to infants in the acute care setting. Physical interventions that reduce pain scores or behaviours include non-nutritive sucking[39], facilitated tucking[43], and parental holding[44]. When these physical interventions are added to sucrose or breastfeeding, the combinations are superior.

Non-pharmacological interventions –physical and psychological for older children

Use of cold (Coolsense® or ice or vapocoolant) or vibration and cold (Buzzy®) achieve analgesia in children prior to venipuncture/cannulation[6]. Upright position is associated with reduced crying time over supine[44].

Distraction (all ages: music, play, books, video, breathing, guided imagery and virtual reality) and hypnosis are efficacious for procedural analgesia[45-47]. Distraction requires no child preparation and can be directed by the parent or trained assistant and should be routinely performed for all paediatric emergency department and office procedures.

Multimodal analgesia and interventions for 'opioid resistant' pain

Multimodal analgesia is a term describing the administration of 3 or more analgesic agents. This typically includes paracetamol, an nsNSAID or coxib, an opioid and/or tramadol. For mild pain, administration is via the oral route, usually prn schedule, in a stepwise manner with a lower dose of opioid or tramadol administered of the prescribed range. For moderate to severe pain, simple analgesics are prescribed 'strictly' (ie regularly) with prn dosing of a full dose of opioids or tramadol. Oral route can be used or parenteral administration if more rapid onset is required or vomiting or ileus/bowel obstruction is present. There is a probable optimal dose and timing interaction between paracetamol and nsNSAID[10] and tramadol, with more study required to inform administration practices and whether these medications should be given simultaneously or alternated with a delay.

For severe pain, uncontrolled by oral opioid or intermittent IV tramadol, then the next step is to add parenteral analgesia with opioid infusion (e.g. morphine 10-30mcg per kg per h) with nurse initiated boluses (morphine 10-20mcg per kg) or bolus only via PCA device. If pain is still inadequately controlled, the options are to increase the background opioid infusion, or change the opioid.

'Opioid resistant' pain is commonly of neuropathic origin or following extensive burns or multitrauma. There is evidence that aggressive early treatment can reduce the development of chronic pain and the incidence of post-traumatic stress disorder symptoms and syndrome[6]. When a patient's pain remains uncontrolled despite multimodal intervention and high-end opioid dosing, specialised treatments including ion channel blockers such as: oral gabapentin 5-10 mg per kg, IV lignocaine 1-2 mg per kg, ketamine (IV, IN or subcutaneous: SC) titrated in 0.1-0.2 mg per kg boluses and then IV/SC infusion of 0.1 to 0.2 mg per kg per h. Further options are clonidine (for anxiolysis and opioid sparing effect), benzodiazepines (for anxiolysis and pain from muscle spasm eg diazepam) and local anaesthetic regional block or infusion. Specialist consultation is advisable.

Conclusion

Pharmacological and non-pharmacological interventions are available and achieve effective analgesia for children with pain from various sources and of varying severity. To manage acute pain appropriately and avoid long term consequences of inadequately managed pain, increased use of analgesic agents and techniques is to be encouraged within the confines of known adverse event profiles.

Table 1: Suggested paracetamol dosing according to route and child's age based on lean body weight

Paracetamol Route and age of child	**Loading dose**	**Continued dosing**	**Maximum acute dosing**	**Chronic dosing**
Paracetamol PO in older children (Panadol™, Tylenol™, Dymadon™)	Loading dose routine in some centres; may depend upon whether continued dosing is planned consider 20-30mg/kg (maximum 1000-1500mg)	15mg/kg (maximum 1000mg) 4 to 6 hourly	90mg/kg/day for 2-3 days in children then 60mg/kg/day (maximum 4000mg/day)	45mg/kg/day (maximum 3000mg/day)
Paracetamol PR in infants and older children	40mg/kg (maximum 1000 mg)	20mg/kg (maximum 1000 mg) 6 hourly	80mg/kg/day Safety of multiday duration unknown	Data lacking
Paracetamol PO/IV in infants and IV in older children	15mg/kg (maximum 1000 mg)	15mg/kg (maximum 1000 mg) 6hourly	60mg/kg/day (maximum 1000 mg 6 hourly)	45mg/kg/day (maximum 750mg 6 hourly or 1000 mg 8 hourly)
Paracetamol PO and IV Neonates	10mg/kg	10mg/kg 6 hourly	40-45mg/kg/day	Adjust according to liver function including unconjugated hyperbilirubinaemia
Paracetamol IV Premature	10mg/kg	10mg/kg 12 hourly	20mg/kg/day	Above comment applies Limited data to inform acute or chronic dosing in this age group and nil for oral dosing

IV intravenous PO per os =oral route PR per rectum=rectal route

Table 2 Suggested sucrose, NSAID (nsNSAID and Coxib) and opioid dosing in children

Analgesic	**Loading or dose titration**	**Continued dosing**	**Maximum acute dosing**
Sucrose/Glucose	Optimal dose and concentration unknown	20-50% 0.5mL-2mL 4 times per day	Lower doses eg 0.2mL are suggested in premature. Consider capping at 3 to 4 doses per day; but the safety of repeated dosing is unknown
nsNSAIDs:			
Ibuprofen PO (Nurofen™, Brufen™)	10mg/kg	5-10mg/kg 6 or 8 hourly With meals	600- 800mg 6hourly (note NNTs decrease with increasing dose; note higher than the product information maximum)
Diclofenac PO/PR (Voltaren™, Fenac™)	2mg/kg	1-2mg/kg 6 to 8 hourly	50-75mg 8 hourly (note NNT data not assessed; this is the only nsNSAID which has a proposed ceiling effect)
Coxib or Cox-2 inhibitor:			
Celecoxib PO (Celebrex™, Celexi™)	4-6mg/kg	2-4mg/kg 12 hourly	200-400 mg 12 hourly
Opioid			
Codeine PO		0.5-1 mg/kg 4 hourly	30-60 mg 6 hourly
Oxycodone PO (Oxynorm™, Endone™)		0.1-0.2mg/kg PO 4 hourly	Note more potent than oral morphine in 2:3 ratio Usual maximum 5-10mg 4 hourly; higher and or more frequent doses may be used following step down from PCA and in cancer pain
Oxycodone IV	10-50 mcg/kg IV Titration to a maximum of 10mg	Depends on indication	Equipotent to IV morphine
Morphine PO		0.25-0.5mg/kg 4 hourly	Usual maximum 7.5-15mg 4 hourly; higher and or more frequent doses may be used following step down from PCA and in cancer pain
Morphine IV	10-50 mcg/kg (titration to maximum of 5-10mg)	Depends on indication	0.1mg/kg or 10mg usual maximum; in severe pain higher end dosing may have been used – then consider opioid sparing agents or agents for opioid resistant pain
Fentanyl IN	Load 1.5mcg/kg	0.5 -1.5 mcg/kg 10 minutely	3mcg/kg
Fentanyl IV		0.02-	2mcg/kg usual maximum 100mcg

		2mcg/kg	
Mixed action-reuptake inhibition & opioid			
Tramadol (5HT/NA/ mu) PO/IV (Tramal™ Zydol™; immediate release)		1-2mg/kg 6 hourly	50-100mg 6 hourly

5HT	serotonin	mu	mu-opioid receptor	PO	per os
IN	intranasal	NA	noradrenaline	PR	per rectum
IV	intravenous	NNT	numbers needed to treat		
MAOI	monoamine oxidase inhibitors	PCA	patient controlled analgesia		

Table 3: Analgesic agents, their adverse events, precautions and contraindications and practical tips

Analgesic	Adverse events	Precautions	Contraindications	Practical tip
Paracetamol	Hepatotoxicity	Obesity, liver disease, severe illness, prolonged fasting	Hepatic failure	Watch for ALT rise (>3 times baseline) and or ALT:AST ratio of >3
nsNSAIDs: eg Ibuprofen Diclofenac	Nausea, peptic irritation/ulceration, glomerular filtration decrease, impaired platelet function	Renal impairment, surgery with bleeding risk, NSAID-ERD	Active bleeding; untreated peptic ulcer disease	Withhold if circulatory status compromised
Cox-2 inhibitor: Celecoxib	Some epigastric intolerance	Renal impairment		Withhold if circulatory status compromised Safe in NSAID-ERD and NsNSAID allergy
Opioids:				
Codeine PO	Shared with rest of opioid class below; Phenotypic variation with conversion to active metabolite (morphine) resulting in either analgesic failure or excess adverse events	Patients with OSA/OIVI or having adeno-tonsillectomy Particularly if racial origin has high PM/UM rates	[Some countries have altered product labelling to exclude use under 16-18 years and or for paediatric adeno-tonsillectomy]	Use alternative opioid where available; trial administration under medical supervision in daylight hours
Oxycodone PO/IV Morphine PO Morphine IV Fentanyl IN Fentanyl IV	Nausea, vomiting Constipation Sedation OIVI Itch	OSA/OIVI Head injury Neurosurgery (avoid or use opioid sparing agents preferentially; consider lower doses and observe effects)		Give incremental doses and observe effect (titrate to effect); co-treat nausea and vomiting and constipation Intranasal administration: angle MAD up or tilt head back if using syringe to coat turbinates and not nasal floor
Mixed action: Tramadol (5HT/NA/ mu)	Similar rates of nausea, vomiting and sedation to opioids Less constipation, OIVI and itch	Seizure disorder or predisposition. Modify doses or avoid coadministration with other 5HT reuptake inhibiting		Give slowly as IV bolus (eg over 15-20 minutes)

		agents such as TCADs, SSRIs, MAOIs		

5HT serotonin

IN intranasal

IV intravenous

MAOI monoamine oxidase inhibitors

mu mu-opioid receptor

NA noradrenaline

OSA obstructive sleep apnoea

OIVI opioid induced ventilatory impairment

PM poor metaboliser

PO oral

SSRI selective serotonin reuptake inhibitor

TCAD tricyclic antidepressant

UM ultrametaboliser

Figure 1: Picture of metered aerosol device (MAD®) used for intranasal medication administration

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