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FCA REFRESHER COURSE

Paediatric analgesia: perioperative opioids

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Introduction

Opioids have held a prominent role in the management of moderate to severe perioperative pain in children despite rising concerns over their use and risk of opioid-induced ventilatory impairment (OIVI).[1] As anaesthetists, we must consider multiple pharmacological, social, psychological, legal and environmental factors when prescribing and administering an opioid to paediatric patients.[2]

Despite our best efforts, children around the world are still suffering from significant perioperative pain.[2-4] In 2017, the United States Food and Drug Administration (FDA) issued a new warning recommending against the use of both tramadol and codeine in children under the age of 12 years, and children < 18 years undergoing tonsillectomy and/or adenoidectomy, adolescents (12–18 years) with obesity, obstructive sleep apnoea (OSA) or severe lung disease and breastfeeding mothers.[5]

This warning grouped tramadol and codeine into the same group, further minimising the pool of available analgesics for paediatric patients.[6] Despite this warning, the European,[7] American[1] and Australian[5] Societies have still included tramadol in their respective guidelines.

In 2021 the South African Society of Anaesthesia (SASA) released local guidelines recommending the appropriate and safe prescription of opioids.[8] Unfortunately, tilidine (Valaron®) production was discontinued by Pfizer in 2021 and was the most prescribed oral opioid in South Africa.[4] Alternative oral agents available in South Africa include morphine, tramadol, and oxycodone. The regulatory bodies are currently unable to recommend safe and efficacious alternatives due to a lack of robust data. This review aims to summarise institutional and international paediatric anaesthesia society recommendations.

Age-related pharmacokinetic/pharmacodynamic opioid effects

The efficacy and side effects of opioid analgesia vary with age and the pharmacokinetics of opioids are highly variable.[1,9] The greatest variation is in the neonatal period (0–28 days) which results in a larger free fraction of the opioid. This is due to decreased protein binding and a larger volume of distribution. Immature hepatic and renal systems reduce the clearance of morphine to less than 10% of clearance in older children and is further impaired in conditions such as intra-abdominal hypertension, renal insufficiency, acid-base disturbances and impaired cardiac function. Neonates are particularly vulnerable to OIVI due to increased blood–brain barrier permeability.[9] Neonates (< 10 days of life) should receive a 50–70% lower dose compared to standard recommendations.[1]

At six months of age, the clearance and metabolic pathways reach the levels of older children, and from 2–11 years of age, there is enhanced clearance and a larger volume of distribution, placing them at risk of under-dosing.[2] The pharmacokinetics of opioids in children and adolescents are comparable to that of adults. The oral route of administration is hampered in neonates due to higher stomach pH, delayed gastric emptying, but has little influence on drug absorption.[9]

The clearance of fentanyl and sufentanil increases significantly from the neonatal to < 1 year. Premature and term neonates have considerably lower clearance of alfentanil when compared to infants and children. Conversely, remifentanil clearance is greatest in neonates.[1]

Opioids in acute postoperative pain management

The primary goals for pain management include a tolerable degree of pain and functional recovery (mobilisation; eating and drinking; and normal bowel movements).[10] Opioids should be prescribed for moderate to severe acute pain as part of a multimodal analgesic plan.[2,11]

The European Society of Paediatric Anaesthesia (ESPA) Pain Management Ladder Initiative, published in 2018, aimed to improve pain management by providing guidelines for analgesia for specific procedures. This guideline provides basic, intermediate and advanced options based on local resources and skill levels.[7]

Morphine

Morphine is the most widely used and studied opioid in children, with proven efficacy and safety.[2] Morphine is a pure agonist primarily acting at the mu receptor, with some activity at the

Table I: Morphine dosage summary (morphine-naïve patients)[1,2,12]

Indication	Dosage	Dosage interval
Initial dose	0.2–0.5 mg/ kg PO/PR	4 hours
	50–100 mcg/kg IV	Every 2 hours (maximum 3 mg)
IV infusion	10–40 mcg/kg/hr IV	Continuous
PCA (1 mg/ml)	10–30 mcg/kg IV	Bolus (5–10 minute lockout)
	4–30 mcg/kg/hr IV	Basal infusion
Intrathecal	2–5 mcg/kg	12–24 hours monitoring
Epidural	30–50 mcg/kg (max 3 mg)	12–24 hours monitoring

PO – per os (oral), PR – per rectum

kappa receptor. It may be administered by the intravenous, intramuscular, subcutaneous, oral, rectal, epidural, and intrathecal routes.[9] Table I outlines the recommended dosages for opioid-naïve children.[1,2,12]

Codeine

Codeine is a prodrug converted via the cytochrome P450 2D6 (CYP2D6) enzyme to morphine and morphine-6-phosphate. It is classified as a weak opioid. In 2013 the FDA advised the use of an alternative analgesic to codeine for postoperative pain control in children who are undergoing tonsillectomy and/or adenoidectomy. A similar warning was issued by the European Medicines Agency (EMA) and the World Health Organization (WHO) removed codeine from its analgesic ladder in 2012.[13] In 2017, the FDA issued a further warning for codeine and tramadol to include breastfeeding women, all children under 12 years and adolescents with obesity, OSA and lung disease.[5]

The genetic polymorphism of the CYP2D6 enzyme accounts for the varied clinical response seen in children and adults. The combination of alleles determines the patient's phenotype.[14]

Poor metabolisers

- activity score of 0, and no analgesic effect.
- 5–10% Northern European Caucasian populations.

Intermediate metabolisers

- activity score 0 to 1.25, with mildly reduced activity.
- 20–28% of sub-Saharan Africa and Asian population.

Extensive metabolisers

- activity score of 1.25–2.25, with normal activity.
- 77–92% of Caucasians.

Ultra-rapid metabolisers

- activity score > 2.25, with high morphine concentrations.
- 29% of Ethiopia's population and Saudi Arabia (21%).[14,15]

Tramadol

Tramadol is a weak opioid agonist, and CYP2D6 is also responsible for the metabolism of tramadol to its active metabolite, O-desmethyltramadol. This metabolite has a mu receptor affinity 200 times greater than tramadol.[14] Ultra-rapid metabolisers are at risk of OIVI due to high metabolite concentrations. The ESPA advised limiting its use to acute postoperative pain in a monitored setting.[7,9] Tramadol can lower the seizure threshold and should be used in caution with epileptic patients. Serotonin syndrome is also a concern in patients on selective serotonin reuptake inhibitors. The IV bolus dose is 0.5–1 mg/kg or orally 1 mg/kg (max 100 mg/dose) every 4–6 hours.[2]

Oxycodone

Oxycodone is twice as potent as morphine, and a semisynthetic opioid. Only 10% undergoes metabolism by CYP2D6 to oxymorphone and noroxymorphone, which have been associated with increased OIVI in ultrarapid metabolisers.[15] Further studies are needed to assess whether oxycodone is safer than codeine in children.[14] The recommended oral dose is 0.05–0.1 mg/kg every four hours. If renal impairment is present, an increased dosing interval is recommended.[2]

Tapentadol (Palexia®)

Tapentadol has a chemical structure similar to tramadol. It is a mu receptor agonist and a noradrenaline reuptake inhibitor. Only 15% of tapentadol is metabolised via CYP450 with no metabolites contributing to its analgesic effect.[13]

It was first licensed in 2011 for use in adults and was approved in 2018 by EMA in hospitalised children aged 2–18 years for treatment of moderate to severe acute pain. The recommended dose is 1 mg/kg, six-hourly, maximum doses of 100 mg per administration.[2,16]

Opioid side-effects and management

Opioids are generally well tolerated, but children report nausea, vomiting, sedation and pruritus most commonly and at a similar frequency as adults.[2]

OIVI is more common with comorbidities such as OSA, severe neurodevelopmental conditions, trisomy 21 and severe epilepsy. A reduced dose of 50–75% in these high-risk groups has been recommended.[5,11] Table II outlines these side effects and pharmacological treatment options.

Chest wall rigidity is a combination of glottis closure and chest wall rigidity, affected by dose, speed of delivery and the age of

Table II: Common opioid side-effects and interventions[10,12]

Side effect	Intervention
Pruritis	• Ensure PRN antipruritic are always available (Diphenhydramine) • Additional antipruritic: cetirizine • Decrease opioid dose if pain is very well managed • Naloxone infusion (0.25 mcg/kg/h)
Nausea and vomiting	• Ensure PRN antiemetics are always available opioids • Ondansetron 0.15 mg/ kg IV every 8 hours (max 4 mg) • If this dose is inadequate, consider a second-line antiemetic • Metoclopramide 0.1 mg/kg IV every 6 to 8 hours (max 10 mg/dose) • Decrease opioid dose if pain is very well managed
Sedation	• Decrease opioid dose if pain is very well managed • Switch from intravenous to enteral route • Check for other sedatives concomitantly prescribed • Maximise opioid-sparing analgesics
OIVI	• Apnoea, severe hypopnoea, or severe desaturation events: ◦ Stop opioid, supplemental oxygen or bag-mask ventilation ◦ Consider naloxone and critical care services ◦ Administer full reversal: naloxone 10 mcg/kg IV every 2 minutes until awake and breathing ◦ Observe closely for re-narcotisation over an extended time • Moderate respiratory depression without immediate oxygenation or ventilatory compromise: ◦ Titrate down opioid dose and monitor for respiratory improvement ◦ Partial reversal: naloxone 5 mcg/kg IV every 2 minutes until respiratory rate is age-appropriate and patient is responsive
Urinary retention	• Catheterisation
Constipation	• Decrease opioid dose if pain is very well managed • Promote physical activity • Stool softener/laxatives

PRN – pro re nata (when necessary)

the child. The association is higher with synthetic opioids and younger age. Neuromuscular blocking agents and induction agents may reduce the development of chest wall rigidity.[1]

Pain sensitisation remains a concern when considering opioid adverse effects. Morphine and fentanyl may have long-term neurodevelopment effects, but there is still much debate in this area and alternative analgesic strategies may be prudent.[1,12]

Monitoring of patients on perioperative opioid therapy

The goals of monitoring patients on opioid therapy include pain assessment and assessment of opioid and sedation-related side effects.[1] Serious OIVI is not common with opioid use in children, but the incidence is higher for patients < 1 month of age and in those with comorbidities. This includes neonates, children with neuromuscular diseases, cognitive impairment and OSA. Respiratory rate, ECG and pulse oximetry are recommended if on supplemental oxygen or at risk of OIVI. Pulse oximetry alone if using a PCA or continuous infusion is being used.[1]

Outpatient opioid use

Paediatric outpatient surgeries have become increasingly common. These patients postoperatively still experience moderate to severe pain.[1,3] Reasons include lack of information, inadequate or inappropriate dosing, poor drug understanding and child refusal.[1]

The major concern with opioid use is OIVI in an unmonitored setting. This concern is further compounded by the increasing incidence of obesity and OSA in the paediatric population. Minimising the risk of opioid-related adverse events should not come at the expense of providing adequate postoperative pain control. Inadequate postoperative analgesia often results in these patients receiving escalating doses of opioids, further increasing the risk of an adverse event. The concept of multimodal analgesia is emphasised in the ambulatory setting.[3]

Cravero et al.[1] recommended the use of clear written and verbal discharge instructions and educational information with specific avoidance of codeine in the outpatient setting. The use of opioids at the lowest effective dosage was also recommended.

Addiction issues related to perioperative opioid use

The "opioid crisis" originated in the USA after increased deaths from prescription opioids. In 2017 the USA's Department of Health and Human Services declared a public health emergency.[1] This is now being felt in South Africa, with increasing use of prescription and non-prescription opioids.[17] The 2021 United Nations World Drug Report revealed North, Central and West Africa accounted for 87% of pharmaceutical opioids seized worldwide, due almost entirely to tramadol trafficking. The number of drug users in Africa is projected to rise by 40% by 2030.[18]

It is imperative to decrease opioid use after surgery. Although uncommon, discharge opioid prescribing has been linked with long-term opioid use in adolescents. Risk factors include a history of chronic pain, substance use disorder and mental health issues.[2] Prescriptions should be written only for the amount needed in the immediate postoperative period.[3] When

providing perioperative analgesia for patients with opioid addiction on chronic opioids, it is important to optimise all non-opioid modalities and not withhold opioids if needed. The usual maintenance opioids should be continued perioperatively.[1] The stigmatisation of opioids places paediatric patients at risk of inadequate pain relief. Children are particularly vulnerable to being denied opioids.[2]

Conflict of interest

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Supplementary tables

Supplementary Table I: Morphine dosage summary (morphine naïve patients)[1-3]

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OIVI	**Apnoea, severe hypopnea, or severe desaturation events:** Stop opioid, supplemental oxygen or bag mask ventilation Consider naloxone and critical care services Administer full reversal: Naloxone 10 mcg/kg IV every 2 minutes until awake and breathing Observe closely for re-narcotisation over an extended time **Moderate respiratory depression without immediate oxygenation or ventilatory compromise:** Titrate down opioid dose and monitor for respiratory improvement Partial reversal: Naloxone 5 mcg/kg IV every 2 minutes until respiratory rate is age appropriate and patient is responsive
Urinary retention	Catheterisation
Constipation	Decrease opioid dose if pain is very well managed Promote physical activity Stool softener/ laxatives

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