An update of systemic analgesics in children

Jennifer A Wright

Abstract

Effective and safe pain management in children can be complex and challenging. It remains an important goal in order to minimize acute distress, behavioural changes, central sensitization and hyperalgesia. Neonates are particularly susceptible to long-term neurodevelopmental changes due to the neuroplasticity of their immature brains, and adequate analgesia may help ameliorate these changes. The focus of this review is to look at systemic analgesic options available for children, infants and neonates. This review includes a brief description of important pharmacokinetic, pharmacodynamic and pharmacogenomic issues that can influence the effectiveness and safety of these medications, while highlighting the impact organ-immaturity in neonates can have on pain processing and analgesic pharmacology.

Keywords Analgesia; clonidine; diclofenac; fentanyl; gabapentin; ibuprofen; ketamine; morphine; NSAID; opioid; oxycodone; paediatrics; paracetamol; tramadol

Royal College of Anaesthetists CPD Matrix: 1AO2, 1DO2 and 2DO5

Introduction

Pain management in children can be complex and challenging, needing staff familiar with age-appropriate pain assessment tools, skilled in interpretation of signs and symptoms, and capable of selecting an effective and safe management plan. The assessment can be particularly challenging in children unable to articulate their symptoms due to age, developmental delay or comorbidities.

A multimodal analgesic strategy is recommended for children with pain. Multimodal analgesia refers to a combination of analgesic techniques, or drugs from different classes that act on the pain pathway at different points, thus minimizing nociceptive transmission and reducing pain perception. This improves analgesic effectiveness while minimizing adverse effects from individual or ancillary drugs (e.g. morphine). Unfortunately the analgesic options available for children are limited in comparison to adults. This is exacerbated by ethical restrictions on research involving children, meaning that treatment is often empirical and not based on sound evidence.

This article provides a summary of systemic analgesic options available for children, including a brief review of pharmacokinetic, pharmacodynamic, pharmacogenomic, adverse effects and contraindications. It also highlights the impact of organ immaturity in neonates on drug clearance and effect.

Jennifer A Wright *MB ChB BMLSc Dip Child Health FANZCA is a Consultant Paediatric Anaesthetist at Starship Children's Hospital, Auckland, New Zealand. Conflicts interests: none declared.*

Learning objectives

After reading this article, you should be able to:

- list a range of analgesic options for consideration when treating children
- describe the benefits of a multimodal analgesic approach
- summarize the risks, contraindications and potential adverse effects of these drugs

Paracetamol

Paracetamol (acetaminophen, N-acetyl-p-aminophenol) is an antipyretic and analgesic drug. It is a mild−moderate analgesic causing a maximum reduction in pain score of 5 when using a 10-point numerical rating scale.[1] It has no anti-inflammatory effects. The recommended dose of paracetamol for children varies widely in literature and institutions, particularly in premature neonates. However, a similar effect-compartment concentration of 10 mg/L[2] should be aimed for in all paediatric age groups (Table 1). Paracetamol is available in oral (elixir/tablet), intravenous and rectal formulations. The oral route is frequently used as it has high bioavailability ($F > 0.9$). In contrast, rectal bioavailability is very variable ($F = 0.25-0.98$). There is a delay between plasma and effect site equilibration with a $T_{1/2}$ keo of 30 −50 minutes.

Paracetamol's mechanism is thought to be by inhibition of prostaglandin synthesis acting through the peroxidase (POX) site of prostaglandin H_2 synthetase enzyme (PGHS), although an active metabolite may also influence cannabinoid receptors.[3]

Paracetamol is predominantly metabolized by hepatic glucuronide conjugation (UGT1A6). This enzyme is immature in neonates so sulphate conjugation assumes a greater role. A small portion (1−10%) is metabolized by cytochrome P450 2E1 (CYP2E1) to produce a hepatotoxic metabolite (N-acetyl-p-benzoquinone-imine, NAPQI). In most patients this metabolite causes no harm as it is rapidly conjugated with glutathione and then eliminated. However, hepatic necrosis can occur with NAPQI accumulation. This is seen in patients taking CYP2E1 inducing medications, in paracetamol overdose, and, in those with inadequate glutathione stores such as chronic liver disease and malnutrition. CYP2E1 activity is reduced in neonates, which may offer some hepatic protection.

Paracetamol can be combined with other analgesic agents (e.g. NSAIDs) to provide multimodal analgesia, resulting in increased analgesic effectiveness and duration[4] while minimizing opioid requirements and possible opioid-related adverse effects.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs provide anti-inflammatory, antipyretic and analgesic effects. They are well absorbed enterally and most undergo hepatic metabolism. Efficacy of NSAIDs such as ibuprofen and diclofenac is similar to that described for paracetamol.[1] The $T_{1/2}$keo is shorter than paracetamol for ibuprofen, ketorolac and diclofenac; this means less time to achieve maximum effect ($T_{1/2}$keo = 15−30 minutes).[1] Typical doses are shown in Table 2.

Paracetamol dose recommendations

Age	Loading dose (mg/kg)		Maintenance dose (mg/kg)			Total daily dose (mg/kg/day)		
Neonate	**PO**	**PR**	**PO**	**PR**	**IV**	**PO**	**PR**	**IV**
28–32 weeks PMA	20	20	10–15	15	–	30	30	–
>32 weeks PMA	20	30	10–15	20	7.5	60	60	25
>37 weeks (term)	20	30	10–15	20	10	60	60	30
Infant								
1–3 months	20–30	30	15–20	15–20	15	90	90	60
3–12 months	20–30	30–40	15–20	15–20	15	90	90	60
Child								
1–6 years	20–30	30–40	15–20	15–20	15 mg/kg if <50 kg	90	90	60 mg/kg/d if < 50 kg
6–12 years	20–30	30–40	15–20	15–20	1 g if > 50 kg	90	90	4 g/d if >50 kg
12–18 years	N/A	N/A	1 g*	1 g*		4g/d*	4g/d*	

From the *British National Formulary (BNF) for Children* 2013–2014. Maximum loading dose 1g. Maximum daily dose 4g. Caution in underweight children.

Table 1

The analgesic effect of NSAIDs is secondary to inhibition of the cyclooxygenase (COX) site on the PGHS enzyme. This enzyme usually metabolizes arachidonic acid to prostaglandins, prostacyclin and thromboxane A2. During tissue injury these mediators cause inflammation, peripheral and central nociceptor sensitization, and thus pain.

NSAIDs inhibit two key isoenzymes: COX 1, 'a constitutional enzyme,' is primarily located in gastric mucosa, renal parenchyma, platelets and osteoblasts. Inhibition of this enzyme is responsible for most of NSAIDs unwanted adverse effects including gastric ulceration, renal dysfunction and bleeding. Most NSAIDs are non-specific, inhibiting both COX 1 and 2, e.g. aspirin, indomethacin, diclofenac, ibuprofen. Aspirin is unique as its enzyme inhibition is irreversible, producing prolonged inhibition of platelet aggregation. This is useful in children with cardiovascular disease.

COX 2, 'an inducible enzyme,' produces large amounts of prostaglandins in response to injury. Selective COX 2 inhibitors have been developed with the hope of reducing adverse effects associated with COX 1 inhibition (e.g. celecoxib, rofecoxib and parecoxib). Unfortunately, the role of COX 2 inhibitors in children remains unclear and advantages of these newer NSAIDs over those still commonly used is not demonstrated.[5]

The most common adverse events in NSAID recipients are nausea, dizziness and headache. They also have the potential to cause gastrointestinal irritation, blood clotting disorders, renal impairment, neutrophil dysfunction and bronchoconstriction. The estimated risks of acute gastrointestinal bleeding in children given short-term ibuprofen is low at 7.2 in 100,000 (95% CI, 2–18 in 100,000),[6] which is not different from children given paracetamol. These effects are thought to be related to COX-1/COX-2 ratios, although this concept may be an oversimplification.

Contraindications to NSAIDs include gastric ulceration, severe cardiac failure, liver and renal dysfunction. Caution is recommended in children with hypotension and hypovolaemia as NSAIDs reduce renoprotective prostaglandin effects. Asthmatic children (2%) with rhinosinusitis, nasal polyps, eczema and allergies also have an increased risk of bronchospasm with NSAIDs. This is not a contraindication, however a thorough history should be taken and NSAIDs avoided if a prior exacerbation has occurred. The risk of bleeding should also be considered in children with thrombocytopenia, coagulopathy or platelet dysfunction. NSAIDs can be safely used in healthy children having tonsillectomy, with no increase in bleeding rates, and improved analgesia, nausea and vomiting.[7] Aspirin is commonly avoided in children with a viral illness because it is associated with Reye's syndrome causing hepatic failure, encephalopathy and death.

Animal models demonstrated delayed bone healing following high dose NSAIDs, while studies in children given ketoralac for

Ibuprofen and diclofenac dosing

NSAID	Dose (mg/kg)	Interval (hours)	Route	Total daily dose (mg/kg/day)	Maximum daily dose
Ibuprofen					
1–3 months	5	6–8	PO/PR	20	1.2 g
>3 months	5–10	6–8	PO/PR	30	
Diclofenac					
>6 months	0.3–1	8	PO/PR/IV	3	150 mg

From the *BNF* 2013–2014. PO (orally). PR (rectal). IV (intravenous). Caution < 3–6 months old due to potential cerebral and renal effects.

Table 2

scoliosis surgery did not show an increase in re-operation due to non-union. Based on this, NSAID use seems reasonable in otherwise healthy children. Where there is a high risk of non-union caution should be exercised and an assessment made on the risk and benefits.[8]

Tramadol

Tramadol is an analgesic agent, useful for moderate visceral and neuropathic pain. It is structurally related to morphine and codeine. Tramadol can be administered via a range of routes including intravenous, intramuscular and oral. Some institutions have liquid formulations available (elixir or droplet) that enables administration to children unable to take tablets. Oral bioavailability is approximately 0.7, however repeat dosing can increase this to 0.9. Tramadol 100 mg PO has an equivalent effect to morphine 10 mg PO.

The analgesic mechanism of tramadol is due to a combination of effects including activation of mu receptors and inhibition of noradrenaline and serotonin re-uptake in the descending inhibitory pathway. Mu receptor activation is enhanced by formation of O-desmethyl-tramadol. This is a potent metabolite formed by hepatic metabolism (CYP2D6) of 10% of the tramadol dose. O-desmethyl-tramadol has more than 200 times affinity for the mu receptors than tramadol. CYP2D6 is the same enzyme responsible for metabolism of codeine. Therefore tramadol can have a variable analgesic effect via opiate receptors due to genetic polymorphism of this enzyme. (See Codeine below).

Tramadol is commonly used in paediatric practice despite age-related licensing restrictions in some countries.[9] It has proven useful as rescue medication after tonsillectomy in children poorly managed with paracetamol and ibuprofen.[10] Dose recommendations are 1−2 mg/kg PO/IV 6 hourly with up to 5−8 mg/kg/24 hours. Slow release tablets can be given at 2−4 mg/kg PO 12-hourly. Adverse effects associated with tramadol are similar to those seen with all opioids, although there is a higher incidence of nausea and vomiting. Slow-release tablets may be associated with reduced nausea because peak concentrations are less. Respiratory depression can also occur with tramadol and it is unlikely to be fully reversed by naloxone. Tramadol should be avoided in children with a history of seizures because it lowers the seizure threshold. The role of tramadol in neonates remains unclear. However, if used the dose should be reduced because of immature clearance.

Codeine

Codeine is used to treat mild-moderate pain. It is available in oral (elixir/tablet), rectal and intramuscular preparations. There is no intravenous preparation due to marked histamine release that can cause hypotension. The terminal elimination half-life is 3−3.5 hours in adults. The neonatal half-life is longer due to immature clearance (e.g. 4.5 hours), while in an infant it is shorter (e.g. 2.6 hours).

Codeine is effectively a prodrug analgesic, with only 5−15% metabolized by CYP2D6 to produce morphine that is responsible for the majority of its analgesic effect. The remainder is metabolized to codeine-6-glucuronide and norcodeine. Metabolism of codeine is highly variable between individuals, secondary to genetic polymorphism, ethnicity, enzyme maturity, organ function and comorbidities. Genetic polymorphism refers to variation in the function of CYP2D6 that metabolizes codeine. Children can be classified as poor, intermediate, extensive and ultra-rapid metabolizers based on this enzymes function. A 'poor metabolizer' gets inadequate analgesia from codeine, while 'rapid' and 'ultra-rapid' metabolizers experience enhanced analgesia and adverse effects.

Recent reporting of mortality in children given codeine after an adenotonsillectomy has raised questions about whether this drug has a role in paediatric anaesthesia. These deaths have been linked to ultrarapid metabolism of codeine, and increased sensitivity to opioids due to sleep apnoea. Updated recommendations for tonsillectomy analgesia now exclude codeine and suggest regular administration of paracetamol and a NSAID. This is supported by multiple regulatory authorities that now warn against codeine use in children (US Food and Drug Administration, UK Medicines, Healthcare Products Regulatory Agency, European Medicines Agency and the Australian Therapeutic Goods Administration). Unfortunately evidence for the most appropriate dose and type of opioid for rescue analgesia is limited.

Morphine

Morphine is a potent analgesic. Its analgesic action is through mu (predominantly), kappa and delta receptors located in central and peripheral sites. Morphine can be administered using oral (elixir/tablets), rectal, intravenous, subcutaneous, epidural and intrathecal formulations. Oral formulations include quick and slow release preparations. Unfortunately oral bioavailability is poor, due to high first pass metabolism ($F = 0.3-0.5$). Therefore, the equivalent oral to intravenous dose is approximately 2−3:1, i.e. 10 mg oral morphine is equivalent to 3−5 mg intravenous morphine. Peak plasma concentrations occur approximately 1 hour after an oral dose, with the maximum analgesic effect seen 30 minutes after this ($T_{1/2}keo = 16$ minutes in adults). A common target concentration is 10 μg/L, with respiratory depression occurring above 20 μg/L.

Morphine undergoes hepatic metabolism. The majority (75%) gets metabolized to inactive morphine-3-glucuronide (M3G). Active metabolites are in a much smaller concentration, including morphine-6-glucuronide (10%), normorphone (5%), and codeine (a 'prodrug'). Morphine-6-glucuronide (M6G) is a potent mu agonist that is more active than the parent drug. In hepatic and renal failure both morphine and its metabolites can accumulate and cause respiratory depression. This can be prevented by avoiding continuous infusions, reducing the frequency and dose administered, or using an alternative opioid, e.g. oxycodone or fentanyl.

Morphine pain pumps are a common technique used to administer opioids to children on wards. PCA (patient-controlled analgesia) requires patient understanding and physical dexterity to press a button to enable administration of a bolus. NCA (nurse-controlled analgesia) is used in infants and children who have developmental, physical or cognitive impairment making a PCA unsuitable. Both regimes can have a background infusion of morphine that is supplemented by the bolus function (10−20 μg/kg/bolus).

Morphine remains remarkably safe when used as an infusion in hospital practice, with the overall incidence of serious harm

only 1:10,000. The use of 4 μg/kg/h morphine infusion as part of a PCA regime has been shown to improve analgesia without a concomitant increase in adverse effects. Safety features associated with pain pumps include a 'lockout' period of 5–15 minutes between boluses and follow up by a pain service. Those predisposed to harm are young infants, those with neurodevelopmental, hepatic, renal, respiratory or cardiac comorbidities.[11] Premature neonates are particularly vulnerable as they have heightened sensitivity to the respiratory depressant effects of opioids, as well as immature hepatic (UGT 2B7) and renal function that can lead to drug and metabolite accumulation.

Common adverse effects associated with morphine include nausea, vomiting, drowsiness, pruritus, constipation and sedation. Interestingly, opioids can also cause paradoxical hyperalgesia, resulting in increased sensitivity to painful stimuli. This is thought to be secondary NMDA receptor activation. Less common but more serious adverse effects include dependence, respiratory depression, coma and death. In opioid narcosis the key management priorities are respiratory support and naloxone (reversal agent).

Adverse effects can be minimized by using a multimodal approach as this introduces a range of analgesic drugs that function via different mechanisms, reducing opioid requirements and thus associated adverse effects. Caution is advised when using sedative agents with opioids, as the combination can result in respiratory depression.

Fentanyl

Fentanyl is a synthetic lipid soluble opioid approximately 100 times more potent than morphine. It has a rapid onset ($T_{1/2}$keo 6.6 minutes in adults) and a relatively short half-life. This is secondary to rapid redistribution from plasma to body tissues, followed by hepatic metabolism to inactive metabolites. The metabolism is predominantly by oxidative N-dealkylation (CYP3A4) into norfentanyl.

Most fentanyl is administered intravenously. This may be as a bolus (e.g. 1–5 μg/kg), infusion (1–10 μg/kg/h) or via a pain pump (PCA, NCA). A plasma concentration of 15–30 μg/L is required to provide total intravenous anaesthesia (TIVA) in adults, whereas the EC_{50} based on EEG evidence is 10 μg/L. The context sensitive half-time (CSHT) after a 1 hours infusion of fentanyl is ~20 minutes, which increases to 270 minutes after an 8 hours infusion in adults.

Intranasal administration of fentanyl is gaining increasing popularity in emergency departments, for children with anxiety or in those requiring rapid but brief analgesia (2 μg/kg). Transdermal patches are also available for palliative care and children with chronic pain. They provide a sustained release of fentanyl over 72 hours. Other routes of administration include intramuscular, buccal, intrathecal and epidural.

Fentanyl has a similar adverse effect profile to morphine, although itch and bronchospasm are less common due to lack of histamine release. Other differences include laryngeal and chest wall rigidity that can occur with high doses, and rapid development of tolerance witnessed in those nursed in intensive care. Fentanyl has no direct myocardial depressive effects, making it ideal for cardiovascularly unstable children. In preterm neonates the clearance of fentanyl is markedly reduced ($T_{1/2}$ β 17.7 hours) contributing to prolonged respiratory depression in this population.

Remifentanil

Remifentanil is a μ selective opioid that has rapid onset ($T_{1/2}$keo 1.16 minutes) and offset (3–10 minutes). It can be administered intravenously as a bolus (e.g. for intubation) or more commonly as an infusion (0.2–1 μg/kg/min). The target concentration may vary depending on the magnitude of desired effect. A remifentanil target of 2–3 μg/L is adequate for laryngoscopy, 6–8 μg/L for laparotomy and 10–12 μg/L might be sought to ablate the stress response associated with cardiac surgery. Analgesic concentrations are 0.2–0.4 μg/L. Clearance decreases with increasing age, with rates of 90 mL/kg/min in infants <2 years of age, 60 mL/kg/min in children 2–12 years of age, and 40 mL/kg/min in adults. Remifentanil is rapidly cleared by non-specific tissue and plasma esterases and this makes it an ideal analgesic for long operations that require immobility, sympathetic suppression and rapid wake up, without being at risk of drug accumulation. This rapid organ independent clearance also makes it safe to use in children with renal and hepatic disease, however it is a poor choice for postoperative analgesia. Adverse effects include bradycardia, hyperalgesia, chest wall rigidity, and respiratory depression.

Oxycodone

Oxycodone is a potent analgesic used to treat neuropathic, acute and chronic pain. It has a minimal effective concentration of 25 μg/L and a target concentration of 45–50 μg/L for postoperative pain relief. Oxycodone is predominantly used in intravenous and oral formulations. Oral options include rapid-release (elixir and tablets), or sustained-release tablets. Oral bioavailability is excellent ($F > 0.85$), with low first pass metabolism. This high oral bioavailability accounts for 5 mg oral oxycodone being equivalent to 10 mg oral morphine. Intravenous formulations enable infusions, patient and nurse-controlled analgesia.

The majority (90%) of oxycodone undergoes hepatic metabolism (CYP450) forming oxymorphone (potent) and noroxycodone (weakly active). Despite the oxymorphone metabolite being potent, it is produced in such a low concentration that it does not usually contribute to the analgesic effect of oxycodone. Metabolites are excreted by the kidney, along with 10% of the un-metabolized parent drug. The elimination half-life is 2–3 hours in children. Adverse effects associated with oxycodone are similar to that seen with other opioids. In addition, doses and drug intervals need to be adjusted in renal and hepatic impairment to prevent drug accumulation.

Methadone

Methadone is a synthetic opioid engineered during World War II. It is an opioid receptor agonist, NMDA receptor antagonist and it prevents reuptake of noradrenaline and serotonin. Methadone is used to treat opioid dependence, hyperalgesia, acute pain (e.g. after scoliosis surgery) and more commonly chronic pain.

Methadone is 2.5–20 times more analgesic than morphine. It is available in intravenous and oral preparations, associated with

high oral bioavailability. Methadone has a long elimination half-life of 15–25 hours, enabling once daily dosing. A minimum effective analgesic concentration of methadone in opioid naïve adults is 0.058 mg/L. Methadone is cleared by the cytochrome P450 mixed oxidase (CYP3A4, CYP2B6 and CYP2D6) enzyme systems; all of which are immature at birth. In neonates CYP3A7 is more dominant, enabling clearance to be similar to adults.[12] Like morphine, methadone can cause respiratory depression, constipation and biliary tract spasm. However, there is less sedation, miosis and euphoria than with morphine. Methadone can also cause QT prolongation.

Ketamine

Ketamine is an anaesthetic, sedative and analgesic agent. These effects are mediated by non-competitive N-methyl-D-aspartate (NMDA) receptor antagonism in the central and peripheral nervous systems. This prevents voltage dependent flow of ions (Na^+/Ca^{2+} influx, K^+ efflux). Inhibition of these receptors halts central sensitization, wind up and formation of a pain memory. As a result, ketamine is used to manage children with acute pain, chronic pain, neuropathic pain, hyperalgesia and allodynia. Ketamine also has a synergistic effect with opioids, reducing opioid requirements and associated adverse effects. This makes it an ideal adjunct for children on high dose opioid infusions as seen in children with cancer, neuropathic pain or severe surgical pain (e.g. after spinal surgery), although its role continues to be debated.[13]

Ketamine undergoes N-demethylation to norketamine; metabolized mainly by CYP3A4, although CYP2C9 and CYP2B6 also have a role. Norketamine is one third the potency of its parent drug.

Ketamine is available as a mixture of two enantiomers; the S (+)-enantiomer has four times the potency of the R (−)-entantiomer. S (+)-ketamine has approximately twice the potency of the racemate. Ketamine has a high hepatic extraction ratio and the relative bioavailability of oral, nasal and rectal formulations is 0.2–0.5. Plasma concentrations associated with anaesthesia are approximately 3 μg/ml, hypnosis and amnesia during surgery are 0.8–4 μg/ml and awakening usually occurs at less than 0.5 μg/ml. Pain thresholds are increased at 0.1 μg/ml.

The role of ketamine in neonates is less clear. It is thought to have a superior effect due to abnormal receptor function, greater distribution and number of receptors at birth. However clearance is reduced, and there is concern it may contribute to neuronal apoptosis in neonates. Other adverse effects associated with ketamine in children include hallucinations, sedation, nausea and vomiting.

α_2 Adrenoceptor agonists

Clonidine and dexmedetomidine are α_2 agonists. They act on supraspinal, spinal and peripheral sites causing membrane hyperpolarization via activation of G1 protein-gated K channels in the neurons, and they reduce calcium conductance into cells via Go protein-coupled voltage gated channels. This prevents neuronal firing and local signal propagation.

Clonidine is commonly used in paediatric anaesthesia as a premedication, an adjunct to anaesthesia and analgesic agents, an antiemetic, for control of postoperative shivering, as a supplement to regional blockade, to reduce emergence delirium, and for reduction of the stress response secondary to tracheal intubation and surgery. It can also facilitate weaning of children from opioids after prolonged use. The target concentration depends on the effect sought. A plasma clonidine concentration range of 0.3–0.8 μg/L has been estimated as satisfactory for preoperative sedation in children 1–11 years. Clonidine may be given orally, intravenously, intranasally, as a transdermal patch, or it can be added to local anaesthetic in regional anaesthesia to prolong block duration. This is a common technique in caudals (1–2 μg/kg) and epidurals. The relative bioavailability of epidural, nasal and rectal clonidine is unity (F = 1). Clonidine clearance is by the liver (CYP2D6) and kidney.

Dexmedetomidine is also an α_2 agonist, but compared to clonidine it has an eightfold greater affinity for α_2 verses α_1 receptors. It may be administered by nasal, buccal, rectal and oral routes. In anaesthesia and intensive care it is used as an IV infusion for procedural sedation and as an anaesthetic adjunct during surgery. A plasma concentration in excess of 0.6 μg/L is estimated to produce satisfactory sedation in adult intensive care patients and similar target concentrations are estimated in children. Dexmedetomidine is metabolized in the liver by UGT1A4 and UGT2B10, aliphatic hydroxylation (CYP 2A6) and N−methylation.

Both clonidine and dexmedetomidine can lead to unwanted sedation, bradycardia and atrioventricular nodal block. Therefore, α_2 agonists may not be desirable during electrophysiological studies and in children at risk of bradycardia or heart block. Alpha 2 agonists can also increase blood pressure at high concentrations (a direct effect on smooth muscle) and decrease blood pressure at lower concentrations (a central effect). Doses of both clonidine and dexmedetomidine should be reduced in neonates due to immature hepatic and renal function.

Gabapentinoids

Gabapentinoids are used to treat chronic neuropathic pain, epilepsy and anxiety. They are also used as adjuncts to perioperative analgesia in children, reducing central sensitization, hyperalgesia and allodynia. When included in a multimodal regime they enhance opioid analgesia, reduce opioid tolerance and opioid related adverse effects. However, they only cause minor reductions in acute pain scores.[14] Sedation is a common adverse effect, particularly on commencement of treatment. Other adverse effects include dizziness, vomiting and visual disturbance.

Gabapentin and pregabalin mainly act on voltage sensitive calcium channels, inhibiting calcium influx. This reduces release of excitatory neurotransmitters such as glutamate, substance P, and calcitonin gene-related peptide from primary afferent nerve fibres, thus suppressing neuronal excitability after nerve or tissue injury.

Gabapentin and pregabalin are well absorbed after oral administration. They are rapidly excreted by the renal system as parent drugs, as they do not undergo hepatic metabolism. As a result, doses should be reduced in renal failure to prevent drug accumulation. The rapid half-life of both gabapentin and pregabalin means that doses should be divided over 24 hours in

order to maintain therapeutic plasma concentrations. Maximum plasma concentrations of gabapentin are obtained after 3–4 hours, and pregabalin after 1 hour. This difference is secondary to gabapentin exhibiting nonlinear (zero order) kinetics. This makes it less predictable, as plasma concentrations do not increase proportionally with dose increases. In contrast, pregabalin undergoes linear kinetics, with plasma concentrations increasing proportionally with the dose. ◆

REFERENCES

1 Anderson BJ, Hannam JA. Considerations when using pharmacokinetic/pharmacodynamic modeling to determine the effectiveness of simple analgesics in children. *Expert Opin Drug Metab Toxicol* 2015; **11:** 1393–408.

2 Allegaert K, Naulaers G, Vanhaesebrouck S, et al. The paracetamol concentration-effect relation in neonates. *Paediatr Anaesth* 2013; **23:** 45–50.

3 Anderson BJ. Paracetamol (Acetaminophen): mechanisms of action. *Paediatr Anaesth* 2008; **18:** 915–21.

4 Hannam JA, Anderson BJ, Mahadevan M, et al. Postoperative analgesia using diclofenac and acetaminophen in children. *Pediatr Anesth* 2014; **24:** 953–61.

5 Tan L, Taylor E, Hannam JA, et al. Pharmacokinetics and analgesic effectiveness of intravenous parecoxib for tonsillectomy +/- adenoidectomy. *Paediatr Anaesth* 2016; **26:** 1126–35.

6 Lesko SM, Mitchell AA. The safety of acetaminophen and ibuprofen among children younger than two years old. *Pediatrics* 1999; **104:** e39.

7 Cardwell M, Siviter G, Smith A. Non-steroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy. *Cochrane Database Syst Rev*, 2005; CD003591.

8 Dodwell ER, Latorre JG, Parisini E, et al. NSAID exposure and risk of nonunion: a meta-analysis of case-control and cohort studies. *Calcif Tissue Int* 2010; **87:** 193–202.

9 Anderson BJ, Thomas J, Ottaway K, et al. Tramadol: keep calm and carry on. *Pediatr Anesth* 2017; **27:** 785–8.

10 Hannam JA, Anderson BJ, Potts A. Acetaminophen, ibuprofen, and tramadol analgesic interactions after adenotonsillectomy. *Pediatr Anesth* 2018; **28:** 841–51.

11 West N, Nilforushan V, Stinson J, et al. Critical incidents related to opioid infusions in children: a five-year review and analysis. *Can J Anaesth* 2014; **61:** 312–21.

12 Ward RM, Drover DR, Hammer GB, et al. The pharmacokinetics of methadone and its metabolites in neonates, infants, and children. *Pediatr Anesth* 2014; **24:** 591–601.

13 Pestieau SR, Finkel JC, Junqueira MM, et al. Prolonged perioperative infusion of low-dose ketamine does not alter opioid use after pediatric scoliosis surgery. *Paediatr Anaesth* 2014; **24:** 582–90.

14 Doleman B, Heinink TP, Read DJ, et al. A systematic review and meta-regression analysis of prophylactic gabapentin for postoperative pain. *Anaesthesia* 2015; **70:** 1186–204.