An update of systemic analgesics in children

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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, whilst 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

Learning objectives

After reading this article, you should be able to:

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

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 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 review 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.

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Paracetamol

Paracetamol (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/litre[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 $T_{1/2}k_{eo}$ 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 metabolized by hepatic glucuronide conjugation (UGT1A6). This enzyme is immature in neonates so sulphate conjugation assumes a greater role. A small portion (1–10%) undergoes hepatic metabolism via 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 then eliminated. However hepatic necrosis can occur with NAPQI accumulation. This is seen in patients on CYP2E1 inducing medications, in paracetamol overdose, and, in those with inadequate glutathione stores such as chronic liver disease and malnutrition. Interestingly, 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] where the maximum effect is a reduction in pain score of approximately 5/10. The $T_{1/2}k_{eo}$ is shorter than paracetamol for ibuprofen, ketorolac and diclofenac; this means less time to achieve maximum effect ($T_{1/2}k_{eo} = 15–30$ 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		4 g/d	4 g/d	

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

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 risk 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),[5] 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 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 a tonsillectomy, with no increase in bleeding rates, and improved analgesia, nausea and vomiting.[6] Aspirin is commonly avoided in children with a viral illness because it may be associated with Reye's syndrome causing hepatic failure, encephalopathy and death.

Animal models have demonstrated delayed bone healing following high-dose NSAIDs, while studies in children given ketorolac for scoliosis surgery did not show an increase in

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	
>3 months	5–10	6–8	PO/PR	30	1.2 g
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