Recent developments in the pharmacological management of pain in children

Brian J. Anderson[a] and Greta M. Palmer[b]

Purpose of review

This review explores progress in developmental pharmacokinetics, pharmacogenomics and formulations of analgesic agents, and discusses potential implications for pain therapy.

Recent findings

Characterization of the developmental pharmacokinetics of morphine, tramadol, paracetamol and nonsteroidal anti-inflammatory drugs has improved dosing in children. Oral sugar solutions have replaced the brandy/sugar pacifier and are effective for single painful events in neonates. Intravenous paracetamol offers increased dosing accuracy, and avoids absorption and bioavailability variability. New nitric-oxide-releasing versions of paracetamol and nonsteroidal anti-inflammatory drugs offer safer alternatives to their parent drugs with enhanced potency. Ketamine has come under a cloud for its possible effects on the neonatal developing brain, but it is being used increasingly in children to supplement opioids for pain after major surgery. Hopes that morphine analgesia may improve neurological outcome in premature babies have not materialized. Reports concerning chronic pain are generally case series and controlled trials are rare and nearly nonexistent in children.

Summary

Unlicensed drug use in the very young will increase as familiarity increases. Pharmacogenomic studies have the potential to tailor drug therapy to the individual and decrease between-patient variability. Unfortunately, the pharmacodynamic knowledge in children of analgesic agents remains neglected and is usually extrapolated from adult data.

Keywords

analgesia, neonates, pain, pediatrics, pharmacokinetics

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[a]Department of Anaesthesiology, University of Auckland, Auckland, New Zealand and [b]Department of Anaesthesia and Pain Management, Royal Children's Hospital, Victoria, Australia

Correspondence to Brian J. Anderson PhD, FANZCA, FJFICM, Associate Professor of Anaesthesiology, University of Auckland, Private Bag 92019, Auckland, New Zealand
Tel: +64 9 3074903; fax: +64 9 3078986; e-mail: briana@adhb.govt.nz

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Abbreviations

CBT	cognitive behavioral therapy
CRPS	Complex Regional Pain Syndrome
ECMO	extracorporeal membrane oxygenation
NSAID	nonsteroidal anti-inflammatory drug
PCA	postconception age

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Introduction

Pharmacological approaches to pain management in children remain centered around nonopioids, opioids and adjuvant medications. Pain recognition and assessment remain neglected [1] and cause stumbling blocks to care improvement [2••]. An increased understanding is developing of analgesic pharmacokinetics in children and the influence of genomics on the variability of response. New formulations of old drugs improve efficacy, speed of effect onset and dose precision. Despite the therapeutic orphan label, use of medications not licensed for use in children who might otherwise be denied effective treatments continues, with opportunity to improve care through better knowledge. This review summarizes the recent findings in developmental pharmacokinetics and pharmacogenomics.

Acute pain

Pharmacological advances in acute pain management have been with standard medications rather than new drugs.

Sugar

Opioid peptides within the cerebral ventral striatum are thought to play a key role in regulating the affective response to highly palatable, energy-dense foods such as those containing fat and sugar [3•,4•]. It appears that the converse is also true, and that glucose or sucrose solutions administered orally provide analgesia for procedural pain in neonates. Sugar nipples, usually soaked in whisky, were widely used in the past to settle neonates having operative procedures with or without local infiltration. More recent examples include repeat drops of a 24% sucrose solution to improve the effectiveness of local anesthetic eye drops during examinations for retinopathy of prematurity [5]. A Cochrane Review has confirmed that sucrose is safe and effective for reducing procedural pain from single painful events (heel lance, venepuncture). There is inconsistency in the effective

dose (dose range of 0.012–0.12 g), and the optimal dose is not yet established. The use of sucrose in combination with other behavioral (e.g., facilitated tucking, kangaroo care) and pharmacologic (e.g., morphine, fentanyl) interventions requires further investigation [6].

Intravenous paracetamol (acetaminophen)

Propacetamol is a water-soluble prodrug of paracetamol. It is rapidly hydroxylated into paracetamol. Clearance increases with postconception age (PCA) [7] from 27 weeks PCA (1.87 L/h per 70 kg) to reach 84% of the mature value (16.3 L/h per 70 kg, between subject variation 40.4%) by 1 year of age [8••,9•]. A mean paracetamol serum concentration of 10 mg/L is achieved in children of age 2–15 years given propacetamol 30 mg/kg for 6 h. This concentration in the effect compartment is associated with a pain reduction of 2.6/10 after tonsillectomy and provides satisfactory analgesia for mild to moderate pain [10]. Clearance is reduced in children less than 1 year of age and a reduced maintenance dose of 9, 14, 18, 23 and 27 mg/kg propacetamol in infants aged 28, 34, 40 weeks PCA, 3 months and 6 months, respectively, will achieve similar concentrations [8••]. Effect-site concentrations associated with analgesia for the pains experienced as a neonate are unknown.

The use of an intravenous paracetamol formulation allows greater dosing accuracy, less pharmacokinetic variability attributable to absorption and more rapid speed of effect onset [11]. Propacetamol use is complicated, however, by dose interpretation (1 g propacetamol = 0.5 g paracetamol), pain on injection and occasional reports of contact dermatitis in healthcare workers. A new intravenous paracetamol preparation, with mannitol, cysteine and sodium phosphate as carriers, has circumvented some of these problems. Less injection-site pain and similar analgesia occurred with single infusions over 15 min of intravenous paracetamol 15 mg/kg compared with propacetamol 30 mg/kg following inguinal hernia repair in children. There was a steep reduction in pain relief between 15 and 30 min [12••], consistent with a delay achieving effect-site concentrations in the brain [13,14]. Intravenous paracetamol certainly has a place in children who are not allowed or unable to be given enteral formulations. Pharmacokinetics and pharmacodynamic variability still exists, however, and the benefit of intravenous over oral formulation for many children given routine anesthesia remains to be proven.

Nitroxyparacetamol (nitroacetaminophen) is a new nitric-oxide-releasing version of paracetamol with analgesic and anti-inflammatory properties, although the precise molecular mechanism underlying these actions is not clear [15]. Potency is enhanced and data from rats show that fentanyl antinociception can be strongly potentiated with subanalgesic doses of nitroxyparacetamol [16•]. Animal models suggest reduced liver damage in overdose situations and nitroxyparacetamol may be a safer alternative to paracetamol [17]. It has been suggested that the drug may be useful therapy for paracetamol-induced hepatic damage because it suppresses synthesis of several proinflammatory cytokines [18,19].

Non-steroidal anti-inflammatory drugs

An understanding of pharmacokinetics and side-effect profiles of the nonsteroidal anti-inflammatory drugs (NSAIDs) is improving therapeutic use.

Pharmacokinetics

The NSAIDs are a heterogeneous group of compounds that share common antipyretic, analgesic and anti-inflammatory effects. The NSAIDs, indomethacin and ibuprofen, are also used to close persistent patent ductus arteriosus in premature infants. There are no linked pharmacokinetics–pharmacodynamic studies investigating NSAID analgesia in neonates or children. Our understanding of the NSAIDs in neonates, however, is being improved through examination of their use for patent ductus arteriosus closure.

Neonatal clearance of NSAIDs increases with age, and dosing should take into account the weight and age of the infant. It remains uncertain which age we should be using (postnatal or postconception age), and not much is known about 'temporal switches' that may speed up enzyme pathways responsible for clearance after birth. Ibuprofen clearance increases from 2.06 mL/h/kg at 22–31 weeks PCA [20], 9.49 mL/h/kg at 28 weeks PCA [21] to 140 mL/h/kg at 5 years [22]. Similar maturation is now reported for indometacin [23]. The volume of distribution is increased in neonates compared with older children and adults.

Pharmacokinetic parameter estimate variability is large, due in part to covariate effects of age, size and pharmacogenomics. Ibuprofen, for example, is metabolized by the cytochrome P450 (CYP) 2C9 and 2C8 subfamily. It is known that considerable variation exists in the expression of CYP2C activities among individuals, and functional polymorphism of the gene coding for CYP2C9 has been described [24,25]. CYP2C9 activity is low immediately after birth, and subsequently increases progressively to peak activity at a young age.

NSAIDs exhibit stereoselectivity. Ibuprofen stereoselectivity has been reported in premature neonates (<28 weeks' gestation). R-ibuprofen and S-ibuprofen

half-lives were about 10 h, and 25.5 h, respectively. The mean clearance of R-ibuprofen (12.7 mL/h) was about 2.5-fold higher than for S-ibuprofen (5.0 mL/h) [26]. The lower clearance and longer half-life of S-ibuprofen suggests that pharmacokinetic predictions based on racemic assays may underestimate the duration of pharmacologic effect. Single-isomer NSAIDs are appearing for the treatment of acute pain and may have fewer adverse effects than traditional NSAIDs [27,28].

Side effects

Aspirin or NSAID exacerbated respiratory disease (ERD) is more a disorder of adults but exacerbations in children and teenagers have been reported [29••]. These cases are countered by reports of beneficial reduction of asthma symptoms where ibuprofen was administered for antipyresis [30]. Palmer [29••] concluded that benefit is likely to be seen in younger children with mild episodic asthma and that aspirin ERD is a concern in one in three teenagers with severe asthma and coexistent nasal disease.

Ibuprofen reduced the glomerular filtration rate by 20% in premature neonates, affecting aminoglycoside clearance, and this effect appears independent of gestational age [31,32,33•]. The commonly used NSAIDs have reversible antiplatelet effects, which are attributable to the inhibition of thromboxane synthesis. Bleeding time is usually slightly increased, but it remains within normal limits in children with normal coagulation systems. Ketorolac can be used to treat pain after congenital heart surgery without an increased risk of bleeding complications [34]. Neonates given prophylactic ibuprofen to induce patent ductus arteriosus closure did not have an increased frequency of intraventricular hemorrhage [35]. A Cochrane Review [36••] has established that, even after tonsillectomy, NSAIDs did not cause any increase in bleeding that required a return to theatre in children. There was significantly less nausea and vomiting with NSAIDs compared with alternative analgesics, suggesting that their benefits outweigh their negative aspects.

There are also concerns that NSAIDs may alter cerebral perfusion in the immature brain but no significant difference in the change in cerebral blood volume, change in cerebral blood flow or tissue oxygenation index was found between administration of ibuprofen or placebo in neonates [37•]. Despite the known effectiveness and use by neonatologists of common NSAIDs, anesthesiologists remain reluctant to prescribe these drugs in neonates. NSAIDs are an alternative for neonates with pain known to respond to this class of drug (e.g. bladder extrophy repair) who are unable to be given morphine because of poor nursing care ratios or where alternative medications (tramadol, ketamine) have limited pharmacokinetic and safety studies available.

Reports of the use of COX-2 selective inhibitors in children are appearing in the literature [38,39], but their future use is uncertain following reports of atherothrombosis in adults [40,41•]. COX-2 inhibitors are reported as safe in NSAID ERD [29••]. Future benefits may be derived from nitric-oxide-releasing NSAIDs that have increased potency and reduced side effects [42].

Ketamine

NMDA (*N*-methyl-D-aspartic acid) antagonists (e.g. ketamine) are postulated to cause significant neuronal apoptosis during the periods of synaptogenesis in mammals. Neonatal rats exposed to ketamine have suffered widespread neuronal apoptosis and long-term memory deficits [43,44•]. The applicability of extrapolating rodent data to the care of human neonates continues to be debated [45•,46].

Ketamine remains a popular drug for pediatric anaesthesia and analgesia despite this debate [47,48••,49•]. The S(+)-enantiomer has four times the potency of the R(-)-entantiomer. S(+)-ketamine has approximately twice the potency of the racemate and faster offset, but with similar psychomimetic side effects. The metabolite norketamine has one-third its parent's potency. Plasma concentrations associated with hypnosis and amnesia during surgery are 0.8–4 μg/mL; awakening usually occurs at concentrations lower than 0.5 mcg/mL. Pain thresholds are elevated at 0.1 μg/mL. Ketamine is finding an increasing role as a co-analgesic infusion for intraoperative and postoperative pain control [50]. The adult dose of 0.05 1 mg/h/kg has not been fully tested in children [51,52]. Many clinicians are currently using 0.1–0.2 mg/h/kg as sole therapy or to supplement opioid therapy, and this dose is not associated with hallucinations and dysphoria. A protocol that allows nurses to administer a ketamine bolus (0.1 μg/kg) if the patient has failed to achieve analgesia with two morphine doses (2 × 20 μg/kg) has been successfully introduced in the Royal Children's Hospital, Melbourne.

Tramadol

Tramadol is used increasingly for perioperative analgesia in children [53,54] as a consequence of its familiarity in adult medicine and recent improved pharmacokinetics knowledge in children [55,56••]. The low incidence of respiratory depression and constipation, fewer controls on use and similar frequency of nausea and vomiting (10–40% [57,58]) compared with opioids make tramadol an attractive alternative [59•]. Children suffering respiratory compromise owing to obstructive

sleep apnea or neuromuscular disorders undergoing major surgery gain benefit.

Systemic tramadol use in neonates and infants is limited because disposition data in young infants are not available. It is primarily metabolized into O-desmethyl tramadol (M1) by CYP2D6. The active M1 metabolite has a mu-opioid affinity approximately 200 times greater than tramadol. Tramadol clearance increased from 25 weeks PCA (5.52 L/h per 70 kg) to reach 84% of the mature value by 44 weeks PCA. Formation clearance to M1 contributed to 43% of tramadol clearance, but had no relationship with PCA. A target concentration of 300 μg/L is achieved after a bolus of tramadol hydrochloride 1 mg/kg, and can be maintained by infusion of tramadol hydrochloride 0.09 mg/h/kg at 25 weeks, 0.14 mg/h/kg at 30 weeks and 0.18 mg/h/kg at 40 weeks PCA. CYP2D6 activity was observed as early as 25 weeks PCA, but the impact of CYP2D6 polymorphism on the variability in pharmacokinetics, metabolism and pharmacodynamics of tramadol remains to be established [56••].

Of interest, codeine has been removed from some hospital's formularies because a large proportion (47%) of children under 12 years lack CYP2D6 maturity and cannot convert codeine to its active metabolite, morphine. These patients still experience codeine binding of mu-receptor related side effects such as nausea and vomiting, constipation and itch without analgesia.

Morphine

Morphine remains a cornerstone of pharmacologic analgesia in children. An early pilot study [60] suggested improved neurological outcomes in premature ventilated neonates given morphine infusion. A later multicenter study [61] refuted these claims. Poor neurological outcome, however, appears to correlate with pre-existing hypotension and not morphine therapy. Morphine infusions, although they can cause hypotension, can be used safely for most preterm neonates but should be used cautiously for 23–26-week neonates and those with pre-existing hypotension [62••].

Morphine is mainly metabolized by the hepatic enzyme uridine 5′-diphosphate glucuronosyl transferase-2B7 (UGT2B7) into morphine 3-glucuronide (M3G) and morphine 6-glucuronide (M6G). M3G is the predominant metabolite of morphine in young children and total body morphine clearance increases from approximately 12 L/h per 70 kg at birth at a maturation rate similar to that described for paracetamol. A mean steady-state serum concentration of 15 ng/mL can be achieved in children after noncardiac surgery in an intensive care unit with a morphine hydrochloride infusion of 7.5 μg/h/kg at birth (term neonates), 12.5 μg/h/kg at 1 month, 20 μg/h/kg at 3 months, 28 μg/h/kg at 1 year and 25 μg/h/kg for 1–3 years [63]. Rates in older children are reduced because of the nonlinear relationship between weight and clearance [64]. Age is an important covariate for dosing and care must be taken to reduce dose in very young children, particularly in premature neonates with hypotension.

Morphine clearance is reduced in infants requiring extracorporeal membrane oxygenation (ECMO), possibly reflecting severity of illness. Clearance maturation on ECMO is rapid and normalizes within 2 weeks. Initial morphine dosing may be guided by age and weight, but clearance and distribution volume changes (and their variability) during prolonged ECMO and morphine therapy should be subsequently guided by clinical monitoring [65••].

Aspects of genetic differences influencing efficacy, side effects and adverse outcome of pharmacotherapy will be of importance for future pain management [66•]. The single nucleotide polymorphism A118G of the mu-opioid receptor gene has been associated with decreased potency of morphine and M6G, and with decreased analgesic effects and higher alfentanil dose demands in carriers of the mutated G118 allele. These genetic differences may explain why some patients need higher opioid doses and the adverse effects profile may be modified by these mutations [67,68•].

Imadazoline alpha$_2$-adrenergic receptor agonists

Clonidine is an imadazoline alpha$_2$-adrenergic receptor agonist (potency $\alpha_2 : \alpha_1$ of 200 : 1) that inhibits adenylate cyclase and consequent formation of cyclic adenosine monophosphate (AMP). Analgesic effect appears more pronounced when administered neuraxially than systemically. Rectal premedication with clonidine (5 μg/kg) was associated with a significant reduction in pain in the early postoperative period after tonsillectomy compared with midazolam, and was also associated with moderately increased sedation during the first 24 postoperative hours. The sedative effect of clonidine is in agreement with parental preference for a calm and sedated child during the first 24 postoperative hours [69]. Pharmacokinetics–pharmacodynamic data from children, however, are few and nonspecific. Plasma concentrations within the range 0.2–2.0 ng/mL are believed to have clinical effect [70]. Sedation is dose-dependent and does not usually occur below 0.3 ng/mL [71]. Oral and parenteral use in opioid withdrawal syndrome prevention and treatment in neonatal and pediatric intensive care units is increasing but studies are required.

Epidural use as an adjunct to local anesthetic agents was reported in the 1980s [72]. Use of clonidine in continuous epidural infusions has resurfaced and may be associated with less vomiting. Patients with cerebral palsy having major lower limb surgery appear to have improved pain control and beneficial reduction in muscle spasms. Patients having urological procedures also have reduction in bladder spasms.

Dexmedetomidine is a new agonist with sedative, sympatholytic and analgesic properties that lacks respiratory depression. Recent studies have explored dexmedetomidine sedation for procedures [73•,74–76], for intensive care [77] and to facilitate acute discontinuation of opioids after cardiac transplantation in children [78–80].

Chronic pain

Reports on chronic pain are generally case series and controlled trials in children are few [81•]. All chronic pain interventions have been adapted from adult use [82]. Nonpharmacological interventions of cognitive behavioral therapy (CBT) and hypnosis have greater impact in children because they are highly suggestible, and concepts such as 'favorite places' or 'magic glove' effectively distract paediatric patients from their pain [83•].

Neuropathic pain

There is a lay and medical hesitancy to use opioids in children for all pain types, and pediatric neuropathic pain is often under-recognized. Neuropathic pain is managed with regularly timed simple analgesics, for example opioids to facilitate mobilization and compliance with physiotherapy, and a tricyclic antidepressant drug (TCAD) at night. TCADs are preferred for their convenient single daily dosing and sleep benefit. The antileptic, gabapentin, has improved side-effect profile over the older antileptics. Gabapentin compares well with placebo [84] in adults, but gabapentin lacks a child-friendly formulation, requires frequent dosing and is unlicensed for pain use in children.

Complex Regional Pain Syndrome (CRPS) presents later in children (3–12 months), with female and lower limb preponderance [81•,85]. Transcutaneous nerve stimulation, CBT and relaxation training complement pharmacologic therapy. Pain requiring further intervention recurred in half the children given physical therapy and CBT [86]. Sympathetic blocks are used less frequently (35–40%) in children [85,86] than in adults. Use of an intravenous regional technique followed by peripheral sciatic nerve continuous blockade has been reported [87••].

Cancer pain

Pain associated with cancer is related to four sources: the tumor, its spread, the procedures required and its treatment. A Cochrane Report [88] of morphine use stresses that all therapies are effective, but acknowledges the small size and underpowering of these studies. Long-acting morphine [89] and opioid rotations [90] are successful in children. Rotation resulted in reduced side effects without loss of analgesic control or the need to increase mean morphine equivalents.

Conclusion

It is anticipated that this decade may see further scientific work in the molecular and genomic fields that may enhance our ability to target and better treat acute and neuropathic pain. Population pharmacokinetics and pharmacodynamic studies are required to characterize maturation, variability factors, effect and age-appropriate dosing.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 349–350).

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