Paediatric analgesia

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Summary

Three main analgesics are routinely used for treating pain in children – paracetamol, ibuprofen and codeine. Paracetamol and ibuprofen are equally effective when used in recommended doses. Codeine has high inter-individual variation in its effectiveness, particularly in children, which significantly limits its routine use in paediatrics. Paracetamol is associated with fewer adverse effects than ibuprofen and so generally remains the first-line analgesic drug in children. However, paracetamol may not be the most appropriate choice in all patients depending on the type of pain being treated and the presence of comorbid illnesses. Paracetamol has unpredictable absorption with rectal administration so this route is no longer recommended. The combined use of paracetamol with non-steroidal anti-inflammatory drugs may be of benefit for some postoperative and musculoskeletal pain.

Key words: codeine, ibuprofen, NSAIDs, paracetamol.

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Introduction

In Australia, the main analgesic medications used in children in an ambulatory setting are paracetamol, ibuprofen and codeine. There has been significant debate in the literature recently as to which of these is the safest and most effective drug to use in children. In general these drugs are safe and effective when used at their recommended doses (Table 1). There are however a number of situations where one may be more appropriate than the other. Factors that need to be considered include the type of pain being treated, comorbidities and concomitant medication use. There are also situations when non-pharmacological methods may be the most appropriate form of intervention, either in isolation or in combination with drugs. This is often the situation in cases of chronic or recurrent pain.

Paracetamol

Paracetamol was discovered over 100 years ago and came into routine over-the-counter use approximately 40 years ago. Its popularity increased significantly in the 1980s when aspirin went out of favour due to its association with Reye's syndrome. Paracetamol is now the most widely used over-the-counter analgesic in children and is approved for use from one month of age. It is available over the counter in multiple paediatric dosage forms including liquids, chewable tablets and suppositories.

Mechanism of action

Despite being used so extensively, paracetamol's exact mechanism of action is still being debated. It has recently been postulated that it works through the inhibition of an isoenzyme of cyclo-oxygenase (COX)-3 that is only found in the brain and the spinal cord.[1] An alternative theory is that it works through the indirect activation of cannabinoid CB(1) receptors.[2] Regardless of this debate, the primary clinical outcome is that paracetamol increases pain tolerance via an effect in the central nervous system. Paracetamol is not an effective anti-inflammatory drug as it does not inhibit prostaglandin production outside the central nervous system, unlike non-steroidal anti-inflammatory drugs (NSAIDs).

Table 1

Recommended doses of paediatric paracetamol, ibuprofen and codeine [10]

Paracetamol	Ibuprofen	Codeine
Community setting		
15 mg/kg every 4–6 hours Maximum 4 doses (60 mg/kg) per day for up to 48 hours	5–10 mg/kg 3 or 4 times a day	0.5–1 mg/kg every 4–6 hours
Other settings		
Up to 90 mg/kg per day can be used under medical supervision with review after 48 hours Single doses of 30 mg/kg may be used for night-time dosing (do not exceed 60 mg/kg per 24 hours)	For juvenile rheumatoid arthritis 10 mg/kg 3 or 4 times a day	

Pharmacokinetics

Although paracetamol is available for administration via the oral, rectal and intravenous route, the oral route is preferred. The oral availability of paracetamol is approximately 90%. Its onset of action is approximately 30 minutes and duration of action is four hours. The rectal route is not recommended as absorption is highly variable and unpredictable, with the reported bioavailability ranging from 24% to 98%. The intravenous route is only used when the oral and rectal routes are not available, as may be the case in some inpatients postoperatively.

Efficacy

Paracetamol has repeatedly been shown in placebo-controlled clinical trials to be an effective analgesic in children with mild to moderate pain. It is effective for minor musculoskeletal pain, headaches including migraines, pain associated with infections such as otitis media and pharyngitis, and for postoperative pain after minor procedures such as adenotonsillectomies and insertion of ventilation tubes. It is not the most appropriate choice for pain that is associated with a significant inflammatory process, such as juvenile arthritis, when an NSAID is more suitable.

The dose of paracetamol for obese children should be based on lean body mass

Safety

Paracetamol is a safe medication when used in the recommended doses. The main potential harm is liver toxicity (see box), which is caused by the accumulation of a toxic metabolite produced when the liver is depleted of glutathione. Relative to adults, children are less susceptible to acute toxic effects, but may be more susceptible to chronic exposure to paracetamol.

Malnutrition, starvation and intercurrent (febrile) illness increase the risk of liver toxicity. Acute toxicity occurs with paracetamol doses greater than 150 mg/kg. There have been reported cases of children developing liver toxicity who were said to be receiving therapeutic doses. These have tended to be overweight children who had prolonged courses, and were being dosed according to their actual weight, rather than their lean body weight. Children who are more than 20% above their ideal body weight should be dosed according to their lean body weight.[3] A quick conservative estimate of this can be obtained by determining their predicted weight for height (see Case example: Calculating lean body weight in obese children, on pages i and ii at the end of this article).

Drugs that induce cytochrome P450, such as phenobarbitone, phenytoin and rifampicin, increase the risk of liver toxicity.

Risk factors for acute toxicity with paracetamol

- Paracetamol doses greater than 150 mg/kg
- Incorrect dosing in overweight children
- Intercurrent (febrile) illness
- Malnutrition, starvation
- Drugs that induce cytochrome P450 (such as phenobarbitone, phenytoin, rifampicin)

Ibuprofen

Ibuprofen is the most widely used NSAID in Australian children as it has been freely available over the counter since 1998. The approved minimum age has recently been reduced from six to three months of age. NSAIDs work by inhibiting COX and thus limiting the production of numerous prostaglandins involved in the inflammatory response.

Safety

NSAID-related adverse effects that occur in children are the same as those that occur in adults, but they seem to occur less often. These include increased gastrointestinal bleeding, reduced renal blood flow, reduced platelet function and bronchospasm in susceptible individuals. Compared to paracetamol, NSAIDs are associated with more frequent adverse events in children.[4]

The risk of renal toxicity is increased with situations that are associated with decreased renal perfusion, namely dehydration, hypovolaemia and hypotension. Pre-existing renal disease or the concomitant use of other nephrotoxic drugs, such as frusemide, aminoglycosides or ACE inhibitors, will also increase the risk of renal toxicity.

Another special group that is at increased risk of NSAID adverse effects are children with aspirin (or NSAID)-induced asthma. Again this entity is rarer in children than adults, however a recent study estimated the prevalence of ibuprofen sensitivity to be 2% in children with asthma.[5]

Codeine

Codeine has previously been recommended as an analgesic for mild to moderate pain in children.[6] It can be and has been given to children orally, rectally and by intramuscular or subcutaneous injection. In Australia, it is most often given in combination with a simple analgesic as part of an oral fixed-dose combination. Codeine is a weak opioid, with one-tenth the potency of morphine. It has its primary analgesic effects through being metabolised to morphine by the cytochrome P450 enzyme CYP 2D6. The popularity of codeine has been largely related to its perceived lower rate of toxicity compared with other opiates, despite there being relatively few studies of codeine's efficacy in children.

Safety

There is considerable inter-individual variation in the activity of CYP 2D6, with a significant and unpredictable number of individuals being poor metabolisers (7–30% depending on ethnicity) who are unable to benefit from codeine.[7] There is also a proportion of the population who are extensive metabolisers who produce significant amounts of morphine and are thus at increased risk of opioid adverse effects.

The activity of cytochrome P450 enzymes is very low at birth then increases with age. In the very young, CYP 2D6 activity is less than 1% of that in adults and is still less than 25% in children under five years of age.

The wide variation in individual metabolism and the unpredictable influence of age on the effectiveness and safety of codeine means that its routine use in children is not recommended. It can be argued that the use of a small dose of morphine is preferable to codeine as it is more effective and predictable.

Comparative studies

Numerous studies have compared paracetamol and ibuprofen in children. When the current recommended doses of both drugs were used (Table 1), efficacy was essentially the same.[8] A recent study in children with musculoskeletal injuries compared ibuprofen 10 mg/kg, paracetamol 15 mg/kg and codeine 1 mg/kg. Ibuprofen showed a statistically significant benefit over the other two drugs in children with fracture, but not in children with other minor soft tissue injury.[9] However, a significant weakness of the study was that 48% of the children in the paracetamol group received less than the standard dose of 15 mg/kg (as the maximum dose allowed was 650 mg), whereas only 22% of the patients in the ibuprofen group received less than the standard dose of 10 mg/kg (as the maximum dose allowed was 600 mg).

Multimodal analgesia

The evidence for combining paracetamol and NSAIDs in children for analgesia is conflicting. However, it appears that in a significant number of postoperative patients the combination can lead to a decreased need for morphine or other opioid analgesics. The combination of codeine with paracetamol or ibuprofen has not been well studied in children. There is evidence in adults that codeine can add significantly to the analgesic effects of paracetamol, NSAIDs and aspirin.[7] However, given the unpredictable and often poor efficacy of codeine in children, it is unlikely to add to the analgesic effects of paracetamol and NSAIDs.

Conclusion

Paracetamol and ibuprofen are safe and effective forms of analgesia in children. Paracetamol is generally the preferred first-line drug due to fewer adverse effects, however this will not be the case in all individuals, depending on the pain being treated and comorbidities. Codeine has a relatively unpredictable efficacy in children and is thus not routinely recommended. It should also be remembered that in some situations non-pharmacological methods may be the most appropriate treatment.

References

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Conflict of interest: none declared

Note: To calculate lean body weight, see case example and growth charts on pages i and ii at the end of this article.

Self-test questions

The following statements are either true or false (answers on page 83)

1. The dose of paracetamol for obese children should be based on lean body mass.
2. Paracetamol is the most effective analgesia for juvenile arthritis.

Case example: calculating lean body weight in obese children

Lean body weight calculation

Lean body weight (males) = (1.1 x weight) – (0.0128 x BMI x weight)

Lean body weight (females) = (1.017 x weight) – (0.0148 x BMI x weight)

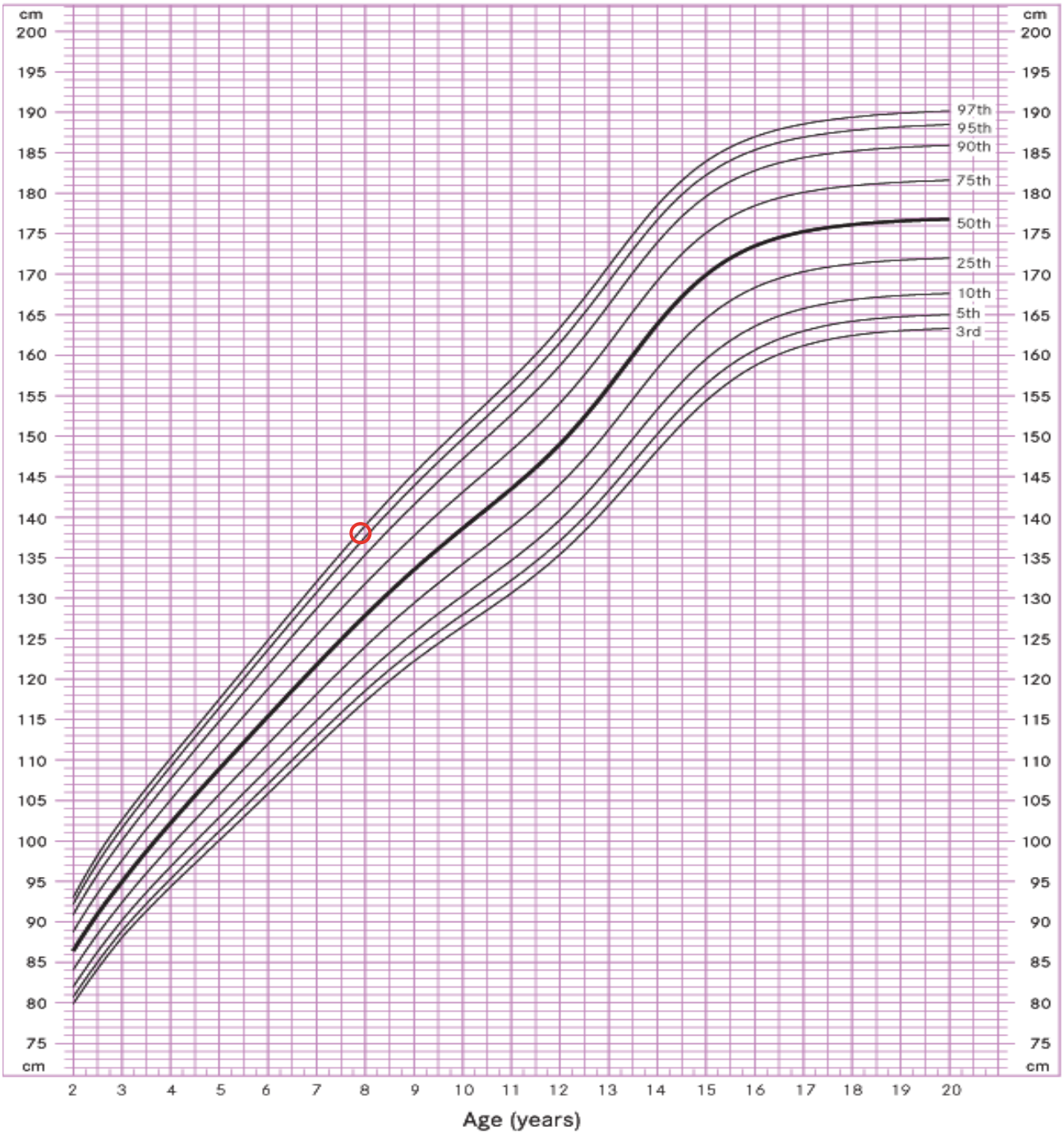
Body mass index (BMI) = weight (kg) / (height (m))^2

Weight for height

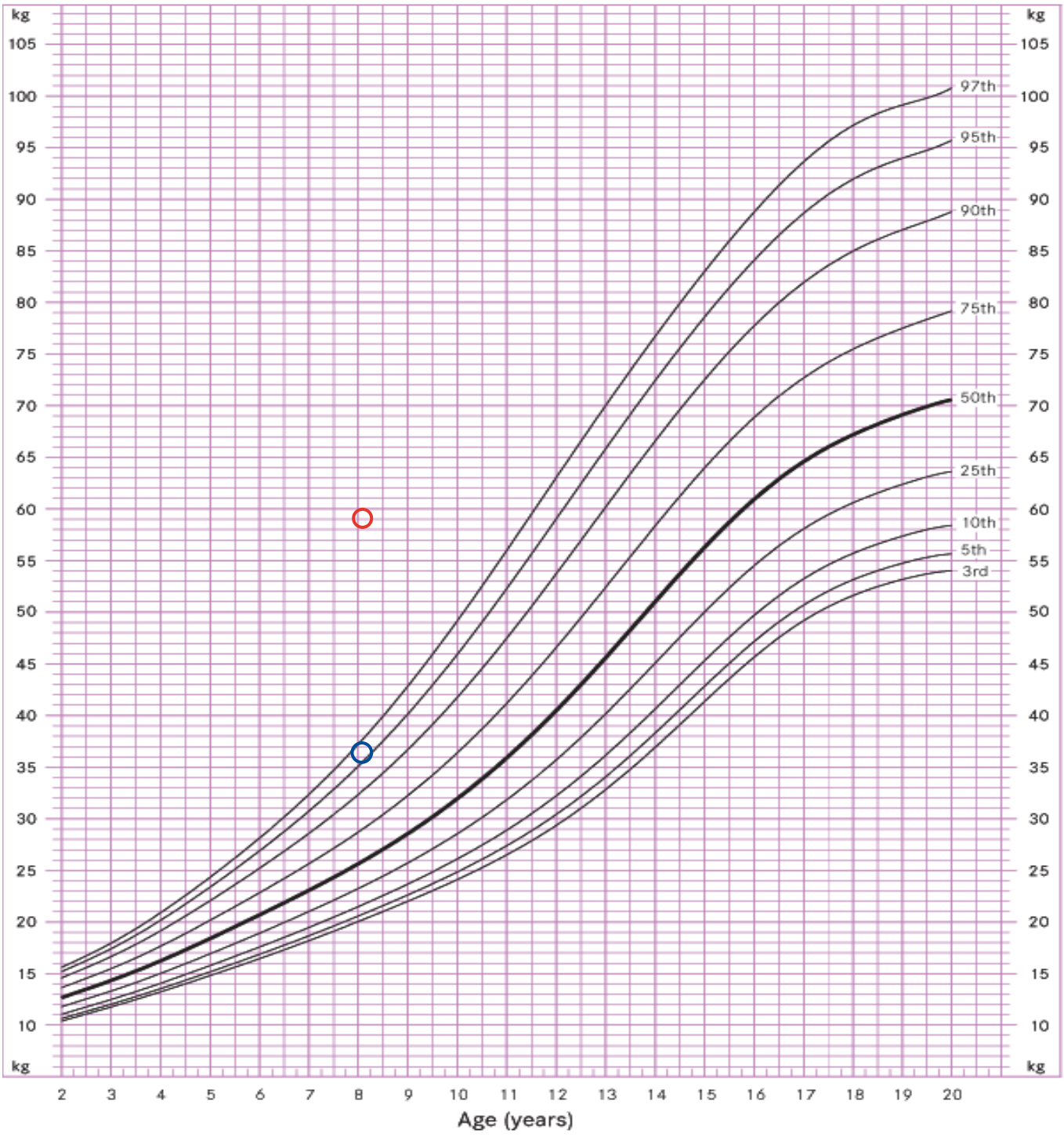
In this example an eight-year-old boy has a weight of 60 kg, and height of 138 cm which is on the 95th percentile for his age, thus his predicted weight for height is obtained by determining what weight corresponds to the 97th percentile for an eight-year-old boy, and here it is 35 kg. Therefore, his doses should be calculated using 35 kg, rather than 60 kg.

○ Actual weight and height ○ Predicted weight for height

Stature-for-age percentiles: Boys, 2 to 20 years



Weight-for-age percentiles: Boys, 2 to 20 years



Growth charts developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). The charts are available at www.health.vic.gov.au/childhealthrecord/growth_details/boys.htm