

## PARACETAMOL (Commentary)

### Use to control pain in young children

**Route of administration:** Systemic reviews show that 1 gram of paracetamol given by mouth prior to surgery can do much to reduce the pain that adults feel during recovery. For reasons that are only poorly understood it seems to relieve the pain associated with orthopaedic and ENT procedures much better than pain of visceral origin. Formulations using codeine (and/or caffeine) do not seem to be more effective than regimens using plain paracetamol (Zhang and Li Wan Po, 1996).

It is less clear what constitutes an effective dose in infancy, and what constitutes an effective dose for rectal administration. Many standard texts still suggest that the correct dose to give is the same whether paracetamol is being given by mouth or into the rectum, even though rectal administration is now known to be erratic and incomplete. Rectal administration also results in slower absorption than oral administration, except in the neonate. Rectal administration still remains a popular peri-operative strategy in some units, but it really should be considered rather 'old fashioned' now an IV preparation has become so widely available and now we know so much more about the drug's pharmacokinetic behaviour in early infancy (see below). A single 20 mg/kg dose *per rectum* does little to provide effective analgesia in the neonate – several studies have now shown that the resultant blood level seldom exceeds 10 mg/l, and that even 6 hourly repetition of such a dose does not improve the blood level achieved in term babies. In addition, peak levels after a single rectal dose are often only reached after 2-3 hours (the speed of absorption depending very much on the formulation used).

Birmingham *et al.*, in a study published in 1997 (in which some of the published  $V_D$  estimates were remarkably low), came to much the same conclusion after studying 28 two to twelve year old children undergoing orthopaedic surgery. Indeed in a further more recent study, they have concluded that such children need an initial 40 mg/kg loading dose and further 20 mg/kg doses every 6 hours to maintain serum concentrations of 10-20 mg/l (Birmingham *et al.*, 2001). However, although this regimen did not produce drug accumulation in these children, it can not be assumed that the same would be true if used in a child younger than this.

Just how effectively such a strategy relieves postoperative pain is also still unclear. There have been relatively few rigorously designed randomised controlled trials. A study by Bremerich *et al.* was unable to find any evidence that high dose rectal paracetamol reduced the amount of opioid analgesia required by 1-2 year old children undergoing cleft palate surgery, but palate surgery does not cause very much pain (especially if the child was also given a local anaesthetic). Similarly, a study by van der Marel *et al.* (2001) was unable to find any evidence that the degree of pain relief correlated with the serum drug level. Anderson *et al.* (2001), on the other hand, were able to show, in the same year, that a 40 mg/kg preoperative dose *did* provide significant pain relief in older children undergoing tonsillectomy – optimal analgesia being provided by a 40 mg/kg preoperative oral dose and a 20 mg/kg rectal dose 2 hours later. However when Anderson and his colleagues in the Netherlands did another study looking at the best way to provide good pain relief to 6–24 month old children undergoing craniofacial surgery they found, yet again, that rectal uptake was unpredictable and that the best way to provide sustained post-operative relief was to give a preoperative loading dose of paracetamol and then 20 mg/kg IV once every 6 hours once the operation was over (Prins *et al.*, 2008).

On the other hand one recent systematic review of four trials looking at the use of paracetamol to control fever, rather than pain, has suggested that the rectal route can be as effective as the oral route (Goldstein *et al.*, 2008), and that doubling the dose when giving the drug rectally only marginally increases the speed with which temperature falls (Tréluyer *et al.*, 2001; Scolnik *et al.*, 2002). Parents are also said to find the rectal route as acceptable as the oral route (Scolnik *et al.*, 2002), although not all children find it equally acceptable, especially when the drug is administered by somebody they do not know. There is, however, increasing evidence (see below) that ibuprofen may be marginally more effective than paracetamol when caring for a feverish child who is clearly miserable and distressed.

The conclusion has to be that paracetamol should only given *per rectum* when no other route is available. The oral route works perfectly well for most feverish children, but peri-operative pain relief presents more of a challenge because of traditional "nil by mouth" rules. Here all the evidence is that conventional low dose rectal treatment is largely ineffective and that, even though high dose treatment can reduce pain and discomfort, absorption and clearance can be frustratingly unpredictable. Now that an IV formulation is becoming very widely available it has become very hard to support the continued use of rectal administration. The one advantage of giving older children a single 40mg/kg rectal dose rather than a 15 mg/kg IV dose during tonsillectomy was that the rectal dose provided relief from pain that only wore off after 10 hours rather than 7 hours (Capici *et al.*, 2008).

**Give it early and give a 'loading dose':** Paracetamol has a large volume of distribution. As a result, irrespective of how the drug is given, it is only possible to achieve an effective therapeutic blood level quickly if the first dose given is a large 'loading dose'. Indeed, an effective, therapeutic, blood level will only

be achieved after three or four doses have been given if a loading dose is not given. This is also, without doubt, why Tréluyer *et al.* (2001) found that the optimum oral dose needed to bring fever under control was 30 mg/kg (more than twice the dose currently recommended in most reference texts). We also know that, in older children at least, paracetamol only starts to have any effect about an hour after the blood level has peaked because we have increasingly come to understand that it takes about an hour for the drug to reach those centres in the brain where it has its analgesic effect (Anderson *et al.* 2001). An antipyretic effect is, however, seen much sooner than this (Gibb and Anderson, 2008).

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### Intravenous paracetamol

Propacetamol hydrochloride is a soluble di-ethylglycidyl-ester of paracetamol. The product's ready solubility in water made it relatively easy to prepare a parenteral formulation, and the drug's rapid hydrolysis by non-specific esterases after injection then results in the rapid release of paracetamol (one gram of the pro-drug propacetamol hydrochloride generating 500 mg of paracetamol). After this IV product was developed in France it quite widely used in Europe for almost 20 years, but it was never actively marketed elsewhere, and it was eventually withdrawn from sale in 2004 after a formulation of paracetamol itself, solubilised in mannitol (Perfalgan<sup>®</sup>), came onto the market. However, because the two products are, for pharmacokinetic purposes, almost identical, a lot is already now known about IV use in children and, even though the manufacturer of the formulation currently available is not yet ready to recommend the use of this product in the preterm baby, IV use is now rapidly becoming the preferred route of administration when oral treatment is not possible, and the advice given in this *Formulary* has now been updated to reflect this new information.

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### Speed of administration when given IV

Clinicians used to giving propacetamol found that this drug caused flushing when given quickly, and this is why the product came with a recommendation that any IV dose ought to be given slowly over 15 minutes. Although this advice got carried over into the advice included in the manufacturer's SPC for Perfalgan there is, in fact, no evidence that the new IV product ever causes flushing. Indeed, many clinicians can testify to the fact that it seems to be perfectly safe for the new product to be given in just the same way as most other IV drugs.

## Optimising blood levels

Optimising analgesia is difficult in the pre-verbal child, and the best we can probably do is to assume that the blood levels that seem to work in older children (and the levels in the central nervous system where the drug seems to have an effect on the endocannabinoid system) are probably a reasonable guide to what is effective in younger children. It is for these reasons that it is now believed that people need to aim for blood levels of between 10 and 20 mg/l in order to offer a child really effective pain relief. That is certainly the thinking behind the advice to aim for a trough level of 10 mg/l. We just do not know whether a similar level is needed to optimise the management of fever. Some have said that a 5 mg/l level is enough to control fever but, given how fluctuant temperature can be in fever, it is going to be very difficult to prove this and, since feverish children are also miserable, there is much to be said for aiming for a similar blood level when managing fever as seems appropriate when managing pain.

It is now widely accepted that the best way to control pain when using morphine is often to give a constant infusion, but those with the most experience say that this does not seem to be the most effective way to give IV paracetamol. Indeed there is a growing impression that optimum control in some children may well require peak levels of more than 20 mg/l. Whether a 'one dose fits all' approach is really adequate also seems doubtful. Clinicians have long realised that different patients need to be given different amounts of morphine to obtain similar relief from pain. What we know about paracetamol's variable pharmacokinetic profile in very young children must lead us to suspect that, if the 'normal' dose does not seem to have contained a child's pain, there has to be a case for checking what trough blood level that dose is currently providing. It is not as though checking this level requires a lot of blood, or requires the local laboratory to provide a service that it does not need by the hospital's accident and emergency department anyway.

## Drug toxicity

For a report on the management of paracetamol toxicity in the neonatal period see a short paper by Isbister (2001), which also comments valuably on the management of women taking a severe overdose while pregnant. The experience summarised in this paper provides further confirmation that slow oxidative metabolism and rapid glutathione synthesis make paracetamol a relatively non toxic drug in early infancy. Early delivery, within 24 hours of ingestion, may be appropriate where serious maternal toxicity has occurred. A review by Heubi in 1998 shows that repeated high dose medication is a much commoner cause of hepatotoxicity in children than exploratory ingestion by a wandering toddler. A paper by Anderson in 1999 has usefully pointed out that with liquid formulations it is not necessary to wait 4 hours before assessing how much has been ingested, as has been traditional in the past. A further valuable paper by Anderson (2000) provides more pharmacokinetic evidence as to the way in which babies handle this drug in infancy, but much remains to be discovered about the oxidative metabolism of this drug in young children (van der Marel, 2003). The plasma drug level above which lethal toxic liver damage becomes possible quoted in the main monograph comes from data on adults. The corresponding level in early childhood remains unclear, although experience suggests that those who act on the threshold used for adults have left themselves with a substantial safety margin. It is not paracetamol that is toxic however but its oxidative metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI), and it can not be assumed that, in a child given the drug many times, the NAPQI level is low merely because the serum paracetamol level is low. The whole topic of paracetamol toxicity in children was reviewed by the Committee on Drugs of the American Academy of Pediatrics in October 2001, and a further paper and commentary appeared in the *Journal of Pediatrics* in May 2002. The key to success certainly remains early intervention.

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### Managing the feverish child.

Fever phobia remains extremely common and, like the illnesses that cause most fever in early childhood, the phobia seems to be highly infectious. If clinicians, by their actions, act as though the prompt and rapid control fever is important it is not surprising that parents then proceed to reach for the Calpol bottle, or for some similar magic remedy, each and every time their child gets hot and bothered after that..

A recent major paper in the *Lancet* (Beasley *et al.*, 2008) has also raised another issue that needs to be taken into account when deciding whether it is really wise to use paracetamol widely in young children, and especially in children less than a year old. This paper has suggested that such use may be associated with an increase in the incidence of asthma, rhinoconjunctivitis and eczema in 6–7 year old children. It is not possible from an observational study of this sort to show that paracetamol actually **causes** an increase in the incidence of later asthma, but it is not going to be easy to dismiss this report because the authors came up with a strikingly consistent set of findings after studying more than 200,000 children from 73 centres in 31 different countries. The Odds Ratio [1.46 (95% CI 1.36 to 1.56)] may only be moderately raised, but the finding was very significant, and asthma has become increasingly common in recent years. Asthma can also be a debilitating, life-long, illness. There also seemed to be a very suggestive dose-dependent trend, with high recent use being associated with a higher prevalence of symptoms at 7 years. Other recent papers (Kanabar *et al.* 2007; Thomsen *et al.* 2008; Rebordosa *et al.*, 2008) have also appeared recently suggesting that the report in the *Lancet* is not a chance finding.

This does not mean that clinicians should necessarily switch to using ibuprofen instead of paracetamol when called on to treat an uncomfortable or feverish young child. Many will conclude that paracetamol still remains the better drug to use, especially in children less than three months old and in children who may also be, or may be becoming, dehydrated. Even more will also conclude that oral or IV paracetamol remains the best drug to use at present when managing serious pain in a young child in a hospital setting, because its use has been so much more thoroughly studied. Frequent indiscriminate home use is a different matter.

For a more detailed discussion of the management of fever see the web commentary on ibuprofen.

Kanabar D, Dale S, Rawat M. A review of ibuprofen and acetaminophen use in febrile children and the occurrence of asthma-related symptoms. *Clin Ther* 2007;**29**:27162–3.

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### Maternal use during pregnancy and lactation

**Pregnancy:** All the evidence is that paracetamol is an extremely safe drug to use during pregnancy. Aspirin (q.v.) has many therapeutic uses in pregnancy but evidence is accumulating that self-medication around the time of conception measurably increases the risk of a miscarriage. Other non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen seem to behave in the same way, but paracetamol use seems to have no such effect, making it probably the best all-purpose analgesic to use on the peri-conceptual period (Li *et al.*, 2003). There is just one paper suggesting that asthma is commoner in children born to women who took paracetamol during pregnancy (see above), but it is far from clear at the moment whether this is a causal association

**Lactation:** There is a single report of a baby developing a maculopapular rash after the mother took 1g of paracetamol two nights in a row. The rash resolved within 24 when the mother stopped taking the drug but reappeared when she took it again two weeks later (Matheson *et al.*, 1985). Apart from this one anecdotal report there is no evidence to suggest that use is inadvisable during lactation, and we know that the baby is only exposed to 5% of the weight-related maternal dose.

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