

PARACETAMOL (Comment)

Intravenous use to alleviate pain

Even though an intravenous formulation of the pro-drug for paracetamol (propacetamol) has been available in much of Europe for over twenty years, many have doubted until very recently whether paracetamol itself was of any real use in relieving the pain of children who were too ill, or too recently anaesthetised, to take medicine by mouth (especially as absorption after rectal administration seemed to be rather variable and unpredictable). However, the increasingly widespread availability of a licensed IV formulation in many countries has led to a resurgence of interest in this drug in the last five years. The sale of such a formulation was first licensed for use in children in the UK in 2005, and approval was also given for use in infancy (and in term babies less than a month old) in June 2007. Given the amount of work that Brian Anderson in Auckland, New Zealand, and Karel Allegaert in Leuven, Belgium, have done to assess this drug's safe and effective use in young children in the last ten years, it can only be a matter of time before the manufacturer is also allowed to recommend use in the preterm baby. An application to be able to sell an IV product in America is also currently under active review by the FDA.

Interest in the IV use of this drug has certainly spread rapidly among paediatric anaesthetists in the UK in the last three years, and there is now a growing consensus (Wilson-Smith and Morton, 2009) that it is quite safe to give significantly more than the dose currently advocated by the manufacturer, as currently replicated by the *British National Formulary for Children (BNFc)*. There is also a growing consensus that a higher dose is also necessary to provide effective pain relief (if blood levels can be used to derive some likely measure of efficacy in pre-verbal children). Many paediatricians and neonatologists are, however, currently less aware of the pharmacokinetic information that has recently become available – in part because only a minority of the more recent papers have been published in paediatric journals. The drug's *NNF5* web site commentary has, therefore, now been updated, and the dosage recommendations in the main one-page monograph have also been updated in line with the findings of the various papers published in the last three years.

Morphine remains an excellent, and well studied, drug for managing severe peri-operative visceral pain, but it is still far from clear how often its use is appropriate merely to sedate a baby that is simply in need of respiratory support during intensive care (Anand *et al.*, 2004; Carbajal *et al.*, 2005; Menon and McIntosh, 2008). The sustained high dose use of morphine can cause respiratory depression, and increase the time it takes to wean a baby from respiratory support, while the effect on gut motility can also delay the introduction of full enteral feeding. Several short-acting benzodiazepines with hypnotic, anxiolytic, muscle-relaxant and anticonvulsant activity have been used quite widely to sedate babies and to generate antegrade amnesia, but such use does not address the more fundamental need to alleviate genuine pain and discomfort. There remains, therefore, a very real need to find an effective analgesic that can be used to reduce pain and discomfort in the neonate without causing the side effects seen with opiate use and it now looks as though we now know enough about the half life of paracetamol not only in the term baby (Palmer *et al.*, 2008) in the very preterm baby (Anderson and Allegaert, 2009) to be able to recommend its more widespread IV use.

Oral use: The UK regulatory authority has adopted a very cautious approach to the IV use of paracetamol at present (where the maximum dose currently specified for any child weighing less than 10 kg is 30mg/kg a day), but much higher oral doses have long been in use in the first year of life. Even so, the recommendation in the manufacturer's Summary of Product Characteristics that **all** babies less than a year old should be given 2.5 ml (60 mg) once every 4 to 6 hours irrespective of weight must lead to the undertreatment of many older children weighing over 5kg. Clearly, if a child's pain or discomfort really does merit treatment, then it must merit effective treatment and this is only possible if the dosage is more closely related to the child's actual weight, and the *BNFc* sensibly recommends a 20 mg/kg dose once every 6 hours for any baby more than 3 months old.

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