

IBUPROFEN (Comment)

Managing fever phobia

A high profile research paper published in the *British Medical Journal* in September 2008 (Hay *et al.*, 2008) has recently reignited the debate about the best way to manage fever in early childhood. Everyone agrees that fever is not usually, in itself, something to worry about. Nevertheless although it is nearly always the result of some minor self-limiting viral illness, its appearance always needs to trigger a search to see if there are any other signs of a more serious systemic infection, as the UK guideline published in by NICE (the National Institute for Health and Clinical Excellence) in May 2007 usefully stresses. Unfortunately, the response to a single 15 mg/kg dose of paracetamol does nothing to help separate out children with a bacterial infection from children who were feverish for some other reason as has often been supposed. (Baker *et al.* 1987). However, even if the response to an antipyretic is of no diagnostic value, and fever itself seldom needs to be controlled, parents and nursing staff will always, understandably, want to minimise the child's discomfort and distress. As the monograph on paracetamol (acetaminophen) in *NNF5* says – if we can understand why an adult with a flu-like illness sometimes retires to bed with a couple of aspirins until the worst is over, we should not deny a small child similar relief.

The problem is that nearly all the many trials of the use of paracetamol and ibuprofen in young children have looked at how these drugs lower temperature, and not at how they reduce discomfort. The large study involving 464 children reported by Sarrell *et al.* in 2006 is the most notable exception to this generalisation to date. Most studies have ended up measuring what is easy to measure rather than what matters, and we can not be confident that the relief of fever is a good surrogate for the relief of distress. The most recent study published in the *BMJ* in 2008 only looked at 156 children. It was an extremely well designed and meticulously executed trial and was accompanied by a parallel economic evaluation (Hollinghurst *et al.*, 2008), and it concluded that “Doctors, nurses, pharmacists and parents wanting to use medicine to treat young unwell children with fever should be advised to use ibuprofen first and to consider the relative benefits and risks of using paracetamol plus ibuprofen over a 24 period. There is no evidence from the accompanying cost effectiveness evaluation to contradict these findings.” However it certainly could be argued that the researchers asked the wrong question and, by asking the wrong question, came up with the wrong answer. They have certainly (like Sarrell *et al.*) come up with a conclusion that differs from the advice currently on offer from NICE.

Indeed, as one doctor wrote within eleven days of the electronic version of this paper appearing on the web ahead of its appearance in the print, “Although combining these drugs might seem benign, encouraging poly-pharmacy may lead to confusion and mis-dosing and the overaggressive pursuit of normothermia that many clinicians have worked hard to reduce.” He went on to express concern that “This paper may be used by people who don't really understand the risks and benefits to support an unnecessary treatment for a symptom that does not need treatment, by people who have a comparatively high chance of getting the treatment wrong.” (Purssell, 2008). Perhaps the most worrying aspect of the most recent trial was that 31 of the 156 children received more of the drug than the study staff had intended and, as Harnden comments in a linked editorial, “This suggests that parents may often inadvertently exceed the maximum recommended dose and that a more complicated alternating regimen of paracetamol and ibuprofen may be less safe than using either drug alone.”

There have been very few studies where some children received placebo treatment, and getting parents to take part in such a study is not easy. One of the more clear cut studies was the trial reported by Kramer *et al.* in 1991 in which 123 children 6 months to 6 years old who presented with fever that had not been present for more than 4 days and a rectal temperature of at least 38°C but less than 41°C were given 10 to 15 mg/kg of liquid paracetamol every 4 hours for as long as seemed necessary, while another 102 children received placebo treatment. It took 8 years to complete this study, such was the desire of most parents to see that their child received at least some form of active treatment. There was no significant difference in the length of time parents *thought* fever persisted in the treated as compared to the placebo managed children (34.7 v. 36.1 hours), or the persistence of other symptoms (72.9 v. 71.7 hours), in this trial. The only difference this trial established was that parents rated the children given paracetamol as having become more active and alert slightly sooner using a 5-category Likert scale.

Nevertheless, as is so often the case, while even quite a small study can be enough to establish efficacy, if a simple surrogate measure such as temperature is employed, it can be very much more difficult to establish **safety**. Where treatment is important even serious risks may be acceptable, if they are uncommon. However, the issue of safety is of no little importance in this instance, because the parents of more than a third of all preschool children in the UK currently consult a healthcare professional when their child is feverish every year, and many more give their children one or other of these two drugs on their own initiative. Indeed, parents spent £400 million on buying over-the-counter (i.e. unlicensed) supplies of these two drugs in Europe in 2004. There is much to suggest that parents already focus too simplistically on the use of medication, do too little to minimise discomfort in other ways, and often fail to focus on the need to sustain

fluid intake. ‘Tepid sponging’ has got itself a bad name because over-vigorous sponging can be distressing, but in fact three small controlled trials suggest that, as an adjunct to a modest dose of medicine, it can be quite helpful (Meremikwu and Oyo-Ita, 2003). It should not be pursued if it seems to be causing distress. It should aim to sooth, and offer the reassurance that goes with the parents’ personal presence.

So, is drug treatment safe? Somewhat provocatively, just two weeks after an electronic version of the paper by Hay *et al.* was first posted, a major paper appeared in the *Lancet* suggesting that there may be a link between the use of paracetamol, especially in the first year of life, and the incidence of asthma, rhinoconjunctivitis and eczema in 6–7 year old children (Beasley *et al.*, 2008). 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.

This does not mean that everyone should now switch to ibuprofen. Indeed there have now been several reports that giving ibuprofen to a feverish but dehydrated young child can sometimes cause acute renal failure severe enough to require peritoneal dialysis (Moghal *et al.*, 2004). Others have raised concerns that use may be linked to an increased risk of soft tissue infections – including necrotising fasciitis (Leroy *et al.*, 2007). As the editorial that accompanies Beasley’s paper concludes “Paracetamol has known benefits for paediatric febrile illness as well as known toxicities. The drug might contribute to asthma incidence, and it might be prudent to minimise casual use of this – and all – drugs in otherwise healthy children. However we need to take the guess-work out of recommending and prescribing antipyretic drugs for children. A population-based randomised trial of adequate power and duration to examine childhood asthma incidence, with paracetamol compared with an active control such as ibuprofen and placebo is warranted.”

Mounting such a study is going to present an immense challenge and, in the interim, as the editorial says, it may well be prudent to minimise the use of *any* drug to control fever in an otherwise healthy child. In the trial recently reported by Hay *et al.* research staff contacted over 4,500 families with a feverish child before they managed to recruit 156 children with an axillary temperature of at least 37.8°C when first assessed. Even if we accept the assumption the authors made – that a child will experience less discomfort if temperature can be lowered fast – and the finding that they (and others) claim to have established – that ibuprofen lowers temperature slightly faster than paracetamol – this only validates the utility of drug treatment in a small minority of feverish children. Indeed even the conclusion that ibuprofen works ‘better’ and ‘faster’ than paracetamol may be flawed because, while several of the recent comparative studies have used quite a high dose of ibuprofen (10 mg/kg per dose in the study by Hay *et al.*), few have used a loading dose of paracetamol or the sort of maintenance dose that seems necessary to achieve optimum pain relief.

Asking for a trial to address not just the short term, but the long term merits of using paracetamol or ibuprofen to control the distress that children often suffer during a febrile illness is easy. Getting it done will not be. In the interim ibuprofen is probably the better antipyretic to choose, especially for home use, except in a very young child (because of the long and rather unpredictable half life of ibuprofen in the very young child). The alternate use of the two drugs has become increasingly common in America in the last few years, partly in response to the appearance of seven randomised trials looking at such a strategy (see references below). Unfortunately such a strategy only serves to reinforce the inappropriate message that temperature must be lowered as much as possible and as quickly as possible. It is also very likely to result in over-treatment because the labelling of most non-prescription medicines currently, and understandably, uses age rather than weight to advise parents as to the right dose to give.

Even in a hospital setting it would seem sensible to optimise the dose of one drug rather than use two – and too many studies to date have assumed that the doses recommended by most reference texts are based on more evidence than is really the case. Recent work has done something to clarify the optimum use of paracetamol (Gibb and Anderson 2008) and this drug can now more easily be given IV in a really ill child, but we know little about the optimum dose of ibuprofen. Nevertheless there are now some rational grounds for using ibuprofen rather than paracetamol in children more than 3 months old if it is clear that the child is clearly distressed and everyone can be quite certain that the child is not, and is not going to become, dehydrated.

Click [here](#) for a copy of the 38 page summary of the NICE guideline on the “Assessment and initial management of fever in children less than 5 years old”. A copy of the full 170 page document can be obtained by going to: www.nice.org.uk/CG47

References

- Baker MD, Childhood fever: correlation of diagnosis with temperature response to acetaminophen. *Pediatrics* 1987;**80**:315–8.
- Doran TF, De Angelis C, Baumgardner RA, *et al.* Acetaminophen: more harm than good in chickenpox? *J Pediatr* 1989;**114**:1045–8.
- Brandts CH, Ndjavé M, Graninger W, *et al.* Effect of paracetamol on parasite clearance time in *Plasmodium falciparum* malaria. *Lancet* 1997;**350**:704–9.
- Brown RD, Kearns GL, Wilson JT. Integrated pharmacokinetic-pharmacodynamic model for acetaminophen, ibuprofen and placebo antipyresis in children. *J Pharmacokinetic Biopharm* 1998;**26**:559–79.
- Kramer MS, Naimark LE, Roberts-Bräuer R, *et al.* Risks and benefits of paracetamol antipyresis in young children with fever of presumed viral origin. *Lancet* 1991;**337**:591–4. [RCT] (See also 1045 and 1347–8.)
- Lal A, Gomber S, Talukjdar B. Antipyretic effects of nimesulide, paracetamol and ibuprofen-paracetamol. *Indian Pediatr J* 2000;**67**:865–70. [RCT]
- Crocetti M, Moghbeli N, Serwint J. Fever phobia revisited: have parental misconceptions about fever changed in 20 years? *Pediatrics* 2001;**107**:1241–6.
- Meremikwu M, Oyo-lta A. Physical methods for treating fever in children. *Cochrane Database of Systematic Reviews*, 2003, Issue 4. Art No. CD004264. [See also review CD003676.]
- Perrott DA, Piira T, Goodenough B, *et al.* Efficacy and safety of acetaminophen vs ibuprofen for treating children's pain and fever. *Arch Pediatr Adolesc Med* 2004;**158**:521–6. [SR]
- Moghal NE, Hegde S, Eastham KM. Ibuprofen and acute renal failure in a toddler. *Arch Dis Child* 2004;**89**:276–7.
- Sarell EM, Wielunsky E, Cohen HA. Antipyretic treatment in young children with fever: acetaminophen, ibuprofen, or both alternating in a randomized double-blind study. *Arch Pediatr Adolesc Med* 2006;**160**:197–202. [RCT]
- Erlewyn-Lajeunesse MDS, Coppens K, Hunt LP, *et al.* Randomised controlled trial of combined paracetamol and ibuprofen for fever. *Arch Dis Child* 2006;**91**:414–6. [RCT]
- Nabuisi MM, Tamim H, Mahfoud Z, *et al.* Alternating ibuprofen and acetaminophen in the treatment of febrile children. *BMC Med* 2006;**4**:4. [RCT]
- National Institute for Health and Clinical Excellence. *Feverish illness in children. Assessment and initial management in children younger than 5 years..* 2007.
- Autret-Leca E, Gibb IA, Goulder M. Ibuprofen versus paracetamol in pediatric fever: objective and subjective findings from a randomized blinded study. *Curr Med Res Opin* 2007;**23**:2205–11. [RCT]
- Leroy S, Mosca A, Landre-Peigne C, *et al.* Quel niveau de preuve de l'efficacité et de la sécurité de l'ibuprofène dans ses indications pédiatriques?. *Arch Pediatr* 2007;**14**:477–84.
- Anon. When the child has a fever. [Review] *Drug Ther Bull* 2008;**46**:17–21.
- Kramer LC, Richards PA, Thompson AM, *et al.* Alternating antipyretics: antipyretic efficacy of acetaminophen versus acetaminophen alternating with ibuprofen in children. *Clin Pediatr (Phila)* 2008; (in press) [RCT]
- Gibb IA, Anderson BJ. Paracetamol (acetaminophen) pharmacodynamics: interpreting the plasma concentration. *Arch Dis Child* 2008;**93**:241–7.
- Hay AD, Costelloe C, Redmond NM, *et al.* Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): randomised controlled trial. *BMJ* 2008;**337**:729–33. [BMJ 2008;**337**:a1302.] [RCT]
- Hollingshurst S, Redmond N, Costelloe C, *et al.* Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): economic evaluation of a randomised controlled trial. *BMJ* 2008;**337**:734–7. [BMJ 2008;**337**:a1490.] [RCT]
- Harnden A. Antipyretic treatment for feverish young children in primary care. [Editorial] *BMJ* 2008;**337**:701–2. [BMJ 2008;**337**:a1409.]
- Purssell E. Combining paracetamol and ibuprofen for fever in children. [Letter] *BMJ* 2008;**337**:593. [BMJ 2008;**337**:a1590.]
- Beasley R, Clayton T, Crane J, *et al.* Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years: analysis from Phase Three of the ISAAC programme. *Lancet* 2008;**372**:1039–48. (See also commentary 1011–2.)

Comment posted September 2008 c