

Newsletter



DECEMBER 2004

Paediatric use of ibuprofen

The Government's strategy on medicines for children¹ emphasises the importance of properly evaluating paediatric indications for drugs developed originally for adults. As the Medicines and Healthcare Products Regulatory Agency observes, children are not miniature versions of adults - they are a diverse group of individuals ranging from premature infants to toddlers to adolescents².

Ibuprofen is widely used in children as an analgesic and antipyretic and to treat patent ductus arteriosus in premature infants, and recent studies have significantly improved our knowledge of its efficacy and safety in these age groups.

Ibuprofen for patent ductus arteriosus in premature infants

Indomethacin has long been the standard treatment for patent ductus arteriosus (PDA) in premature infants but there is concern that it may impair renal function and cerebral perfusion. Evidence is now accumulating that ibuprofen could offer an equally effective and safe option.

Investigators from Belgium and the USA have reported a meta-analysis of randomised trials comparing treatment with ibuprofen and indomethacin in premature infants with PDA³. Eight trials involving a total of 503 infants were included. Overall, the two drugs were similarly effective in closing PDA and there were no significant differences in re-opening rates or mortality. Ibuprofen, however, had

substantially less impact on renal function, with a significantly smaller rise in serum creatinine (weighted mean difference*, WMD, 0.56; CI_{95%} 0.37-0.76) and a smaller reduction in urine output (WMD 0.50, CI_{95%} 0.29-0.71). In the two trials reporting effects on cerebral blood flow, ibuprofen was associated with significantly less reduction than indomethacin (WMD 1.72, CI_{95%} 1.03-2.42). There was a higher risk of intravascular haemorrhage with indomethacin but no significant differences in the need for additional treatment, surgical ligation, ventilation or use of surfactant.

This study has recently been updated to include another randomised trial, increasing the number of infants involved to 566, and the new analysis has confirmed the original findings⁴.

Recent clinical trials have compared early prophylaxis with ibuprofen with placebo in premature infants (<28 - 30 weeks). Ibuprofen increased the proportion of premature infants with closure of PDA after 3 days (84% vs. 60% with placebo; relative risk 1.40, CI_{95%} 1.23 - 1.59)⁵; and reduced the need for surgical ligation (9% vs. 0%, p=0.03)⁶. It did not significantly affect the risk of intraventricular haemorrhage or death, and adverse events included pulmonary hypertension (3/65 vs. 0/65 with placebo⁶) and transient renal effects.

Pharmacokinetics of ibuprofen in premature infants

As reassuring evidence of clinical outcomes emerges it is important to improve our understanding of the disposition of ibuprofen in premature infants.

Two recent studies have explored the pharmacokinetics of oral and intravenous ibuprofen in premature (gestational age 30 weeks)⁷ and very premature (24 - 28 weeks)⁸ infants. Both reported wide interindividual variation in plasma levels and clearance of ibuprofen. Overall, clearance increased with gestational age and birth weight, though the correlation was weak. Neither study identified factors that might lead to more predictable blood levels.

Despite the variation in blood levels, the likelihood of adverse renal effects seems low, according to investigators in Israel⁹. In 15 low-birth weight infants (mean 1.05 kg, mean gestational age 27.5 weeks) with PDA, they found no changes in renal function or urine output at 24 or 48 hours during treatment with the usual doses of ibuprofen.

An important concern about the use of ibuprofen in neonates is the risk of kernicterus due to displacement of bilirubin from its binding sites on albumin. An *in vitro* study has shown that ibuprofen competes with bilirubin for these binding sites, and that the displacement of bilirubin could be greater than that of the sulfonamide sulfasoxazole¹⁰. Fortunately, this does not appear to be clinically significant: a study in 15 preterm infants showed no change in the concentration of unbound bilirubin in plasma after the administration of ibuprofen at the doses used to treat PDA¹¹.

Another concern is the risk of drug interactions. Although no clinical effects were reported in infants treated with ibuprofen plus vitamin K, phenobarbitone, or the antibiotics netilmicin, amikacin, or cefotaxime⁷, more careful analysis of the pharmacokinetics of amikacin during

prophylaxis of PDA with ibuprofen-lysine suggests that clearance of the antibiotic is significantly reduced and pre-dose blood levels of amikacin were raised¹². The authors note that levels of both amikacin and ibuprofen were too high in these infants and suggested increasing the dose intervals for both drugs.

Ibuprofen to treat migraine in children

Although migraine is quite common in children - around 3% - 5% of school-age children experience periodic attacks - there has been little research into appropriate treatments. Intermittent use of analgesics is the mainstay of treatment for acute attacks and ibuprofen, at a prescribed dose of 10 mg/kg, has been shown to be more effective than paracetamol in aborting attacks¹³.

A double-blind placebo-controlled study has evaluated ibuprofen in the treatment of migraine at the lower dose in which OTC ibuprofen is normally taken (7.5mg/kg)¹⁴. In 84 children aged 6 - 12, the response rate (% children in whom moderate/severe headache was reduced to mild or no pain at 2 hours) was significantly higher with ibuprofen (76% vs. 53%) and significantly more children were pain-free (44% vs. 25%). Ibuprofen also increased the proportion of children with no nausea (60% vs. 40%). Only one of 45 children taking ibuprofen needed rescue analgesia compared with 15 of 39 given placebo. Among girls, the placebo response rate was comparable with that associated with ibuprofen (67% vs. 65%) but the response to ibuprofen was much greater among boys (84% vs. 43%) and headache recurrence less frequent (0 vs. 8 with placebo compared with 5 cases each with ibuprofen and placebo among girls). The authors were unable to account for this finding: although a sex-related difference in migraine pathogenesis cannot be excluded, the small size of the study is the most likely explanation.

Ibuprofen has been shown to be as effective as the 5-HT₁ agonist zolmitriptan 2.5 mg in a new placebo-controlled

crossover study in 32 children aged 7 - 17¹⁵. The dose of ibuprofen was 200 mg in the under-12s and 400 mg in older children. The 2-hour response rate (defined as above) was 78% with ibuprofen, 69% with zolmitriptan and 32% with placebo. Half of children were pain-free at 2 hours after taking ibuprofen or zolmitriptan (8% with placebo) and pain-free without recurrence in 24 hours in 41%, 39% and 8% respectively. There were no significant differences between ibuprofen and zolmitriptan and they were equally well tolerated.

** weighted mean difference is a measure of effect size for use with continuous outcomes; it is the mean difference in outcomes between the treatment arms, adjusted for sample size and differing precision between studies*

References

1. Medicines and Healthcare Products Regulatory Agency and Department of Health. Strategy on medicines for children. July 2004 (<http://medicines.mhra.gov.uk/ourwork/licensing/gmeds/children/paediatricstrategydoc.pdf>)
2. Medicines and Healthcare Products Regulatory Agency. Medicines for children. October 2004 (<http://medicines.mhra.gov.uk/ourwork/licensing/gmeds/children/children.htm>)
3. Thomas RL, Aranda JV, Van Overmeire B, Hamre M. A meta-analysis comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. *Pediatr Res* 2003;53:419A
4. Thomas RL et al. A comparison of the use of ibuprofen and indomethacin for the closure of patent ductus arteriosus by meta-analysis of efficacy and adverse effects. 33rd Annual Meeting of the American Academy of Clinical Pharmacology. Phoenix, Arizona. October 2004-11-16
5. Van Overmeire B, Allegaert K, Casaer A et al. Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2004;364:1945-9
6. Gournay V, Roze JC, Kuster A et al. Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial. *Lancet* 2004;364:1939-44
7. Sharma PK, Garg SK, Narang A. Pharmacokinetics of oral ibuprofen in premature infants. *J Clin Pharmacol* 2003;43:968-73
8. Gregoire N, Gualano V, Geneteau A et al. Population pharmacokinetics of ibuprofen enantiomers in very premature infants. *J Clin Pharmacol* 2004;44:1114-24
9. Hammerman C, Schimmel MS, Bromiker R et al. Does ibuprofen affect renal function in the LBW infant? *Pediatr Res* 2004;55:565A
10. Ahlfors CE. Effect of ibuprofen on bilirubin-albumin binding. *J Pediatr* 2004;144:386-8
11. Van Overmeire B, Vanhagendoren S, Schepens PJ, Ahlfors CE. The influence of ibuprofen-lysine on unbound bilirubin plasma levels in preterm neonates. *Pediatr Res* 2004;55:474A
12. Allegaert K, Cossey V, Langhendries JP et al. Effects of co-administration of ibuprofen-lysine on the pharmacokinetics of amikacin in preterm infants during the first days of life. *Biol Neonate* 2004;86:207-11
13. Hamalainen ML, Hoppu K, Valkeila E, Santavuori P. Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind crossover study. *Neurology* 1997;48:103-7
14. Lewis DW, Kellstein D, Dahl G et al. Children's ibuprofen suspension for the acute treatment of pediatric migraine. *Headache* 2002;42:780-6
15. Kraemer C, Evers S. A randomized, double-blind, placebo-controlled crossover study to test the efficacy of ibuprofen and zolmitriptan in the treatment of acute migraine attacks in children. *Der Schmerz* 2004; suppl 1:abstr P8.6

Further information from:
Secretariat
International Ibuprofen Foundation
PO Box 2566, Marlborough, SN8 4YY, UK
Tel: +44(0)1672 810836 Fax: +44(0)1672 810865
Email: ibuprofen@healthcom.eu.com
Website: www.ibuprofen-foundation.com