

## IBUPROFEN (Commentary)

### Use during pregnancy and lactation

Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are among the most widely used drugs in the developed world, and often used by pregnant women. It is known, however, that they inhibit prostaglandin biosynthesis, and that prostaglandins play an important role in human ovulation and implantation as well as having direct effects on the fetus in later pregnancy. NSAIDs seem to inhibit prostaglandin biosynthesis in most organ systems while paracetamol only affects biosynthesis in the central nervous system. It may be this difference that makes paracetamol a much safer routine analgesic to take at any time during pregnancy.

**Pregnancy:** There is no evidence that any NSAID is teratogenic, but the use of ibuprofen around the time of conception seems to double the risk of early miscarriage (Nielsen, *et al.*, 2001; Li *et al.*, 2003), and this is also probably true of other NSAIDs. Indeed the newer drugs that selectively inhibit cyclo-oxygenase-2 (COX-2 inhibitors) have always come with a specific warning from the manufacturer against use around the time of conception. Paracetamol, on the other hand, does not seem to pose any such risk. The deliberate use of indometacin in the third trimester, frequently in the misplaced belief that this is an effective tocolytic, has revealed that use in late pregnancy can have untoward cardiovascular consequences for the fetus. There is also a suggestion that use can increase the risk of the baby developing necrotising enterocolitis. It is more than likely that other NSAID drugs could have similar effects. Ibuprofen, like indometacin, certainly has an effect on the fetal kidney, greatly reducing liquor volume.

**Lactation:** Use of ibuprofen during lactation seems entirely safe because drug exposure is minute – less than 0.1% of the dose taken by the mother on a weight-for-weight basis (Walter and Dilger, 1997). Other NSAIDs are probably equally safe although, with many products, drug exposure will be rather higher than with ibuprofen. Information on the more commonly used NSAIDs for which specific information is available is given in the section of the *Formulary* devoted to maternal medication and its effect on the baby. Nothing is yet known about the safety of using COX-2 drugs during lactation.

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### Early prophylactic ductal closure

**Choice of drug:** A research letter in the *Lancet* in April 2002 reported evidence to suggest that the early prophylactic use of **ibuprofen** may occasionally cause marked hypoxaemia by increasing pulmonary artery pressure and causing reversed ductal and/or intra-atrial shunting. No such risk was identified during two small trials where prophylaxis was initiated more than 6 hours after birth, or in a recently completed Belgian trial (Van Overmeire *et al.*, 2004), but it did cause the parallel French trial to close early (Gournay *et al.*, 2004). No such effect was recognised with very early **indometacin** use during the large TIPP trial, but a

retrospective review has now shown that universal early prophylaxis with this drug also had a small but sustained adverse impact on the need for sustained supplemental oxygenation, suggesting that this drug, too, has a lesser, but long lasting effect on pulmonary vascular tone (Schmidt *et al.*, 2002). Both drugs clearly affect not just ductal musculature, but also the tone of the arteries supplying many organs of the body in a complex, and still only part-documented, way. Although deliberate early ductal closure with ibuprofen has been shown to improve lung function for at least the next two weeks and to decrease the extent to which early delivery causes an arrest of alveolar delivery in the preterm baboon (McCurnin *et al.*, 2008), the implication of this experimental work for neonatal care are not yet clear.

Most will conclude that there are few grounds for offering routine early prophylaxis with either ibuprofen or indometacin to any baby before first establishing that there is a problem with persisting duct patency, and that no duct-dependent cardiac defect is present. There are, however, many good reasons to go for early duct closure in small ventilator dependant babies with echocardiographic evidence of significant ductal shunting two or more days after birth. The meta-analyses by Ohlsson *et al.*, 2003, Swartz, 2003, and Thomas *et al.*, 2005 show that indometacin and ibuprofen are of comparable efficacy. Some will conclude that, because ibuprofen has less affect on vascular tone elsewhere in the body, there is some marginal advantage in choosing ibuprofen in units with ready access to an IV formulation.

**Dose used:** A study in Belgium (Van Overmeire *et al.*, 2001) confirmed earlier work in Canada (Aranda *et al.*, 1997) validating the neonatal ibuprofen dose regimen recommended in this *Formulary*. A recent dose-finding study has come to similar conclusions (Desfrere *et al.*, 2003).

**IV treatment:** No product has yet been licensed for IV use, and most centres in Europe currently giving this drug IV to induce duct closure are using the strategy and product described in the main *Formulary*. This is also the product that has been used in all the clinical trials published to date (a preparation originally developed and licensed for IM use by Merckle) other than the recent French trial which closed early (Roze, *et al.*, 2003) after adverse effects were reported. A larger trial using Ibuprofen L-Lyceine intravenously was completed by the NICHD-PPRU Network in the US in 2005 and, on the strength of that study, the FDA have now approved the marketing of a commercial product (NeoProfen®) in America. The current price of this product is however, ten times what it is in Europe.

**Oral treatment:** This may turn out to be almost as effective as IV treatment in most children. In one small formal trial (Supapannachart *et al.*, 2002) oral ibuprofen seemed to be as good as oral indometacin while in one small pilot trial (Lotfy *et al.*, 2005) oral ibuprofen seemed as good as IV indometacin. Three observational studies (Hariprasad, *et al.*, 2002; Heyman, *et al.*, 2003; Cherif *et al.*, 2007).and one small trial (Cherif *et al.*, 2008) have also suggested that oral ibuprofen may be as effective as IV ibuprofen for most babies.

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## Management of fever in infancy

Both ibuprofen and paracetamol (q.v.) are widely used to control fever in children. While there is no good evidence that such treatment reduces the risk of a febrile convulsion, many doctors and most parents feel the need to do *something* for a child who is fretful and unwell. Many also harbour a belief that all fever is harmful, even though a number of studies have suggested that fever can actually enhance the body's response to infection. The only good reason for turning to drug treatment is to alleviate the discomfort that often accompanies fever, and to reduce the risk of potentially damaging hyperthermia (a rectal temperature somewhere in excess of 40.5°C). While overtreatment is a potential hazard (particularly with paracetamol), serious toxicity is actually very uncommon. Parents do, however, need to be made aware that repeated use of ibuprofen in a fluid depleted child can cause acute renal failure by inhibiting prostaglandin synthesis (Moghal, *et al.*, 2004; Ulinski *et al.*, 2004), and it looks as though other non-steroidal anti-inflammatory drugs can also cause renal failure in the dehydrated child. (John *et al.*, 2007). In all other respects most head-to-head trials suggest that the two drugs are almost equally effective. A recent Cochrane Review (Meremikwu, 2003) has also shown that the speed with which body temperature falls in response to treatment with either of these two drugs can be increased by gentle tepid sponging.

**Anticipatory treatment:** Many children become feverish for at least a short while after immunisation and, because of concern that treatment may not be very effective if it is only started after body temperature has risen, an anticipatory prophylactic strategy has started to become popular in some countries. A recent trial in 370 4–6 year old children given three doses of either ibuprofen or paracetamol when they came back for their fifth dose of the trivalent DPT vaccine (Jackson *et al.*, 2006) found no evidence to support such a policy, but that does not, of itself, mean that such a strategy might not be of some value in younger children.

**Treatment using two antipyretic drugs:** In one recent study (Sarrell, *et al.*, 2006) in which 460 children presenting with fever (a rectal temperature of 38.4°F or more) when 6–36 months old had a loading dose of either 25 mg/kg of paracetamol or 10 mg/kg of ibuprofen, fever settled more quickly in those who were then given alternating maintenance doses of *both* paracetamol (12.5 mg/kg every 6 hours *and* ibuprofen 5 mg/kg every 4 hours, than in those who were then only given one or other drug in order to sustain the antipyretic effect of the initial loading dose treatment given. While this finding does

provide some support for what has recently become a very popular management policy in North America, it does not necessarily mean that a strategy of using alternating doses of these two drugs necessarily provides better fever control than could have been achieved by using a rather higher maintenance dose of just one agent. (Indeed it is worth noting that, although the maintenance doses used in these studies reflect the dosing that manufacturers currently recommend in their package inserts and their promotional literature, there is now quite a lot of pharmacokinetic evidence to suggest that these doses are probably too low and too conservative to deliver a sustained therapeutic blood level of either product).

Erlewyn-Lajeunesse *et al.* reported a smaller study from Bristol in 2006 in which 40 young children were given both 15 mg/kg of paracetamol and 5 mg/kg of ibuprofen simultaneously, and found that this only increased the extent of the fall of ear temperature by 0.3°C after one hour, and this was followed with a more extensive and very fully described three-arm study of a further 156 young children published in 2008 (Hay *et al.*, 2008; Hollinghurst *et al.*, 2008). This showed that 10 mg/kg of ibuprofen lowered axillary temperature marginally faster than 15 mg/kg of paracetamol (in 42 rather than 71 minutes), but no faster than combined treatment with both drugs (45 minutes). Parents were allowed to give further doses of paracetamol every 4–6 hours (but no more than four doses in any one 24 hour period), and further doses of ibuprofen every 6–8 hours (but no more than three doses in any one 24 hour period). Fifty two families were allowed to give their child both drugs. Children given paracetamol seemed to have a temperature of more than 37.2°C (as measured continuously in the axilla) for an average of 8.3 hours in the first 24 hours after treatment started. Those given ibuprofen had a temperature this high for 6.4 hours, and those given both drugs a temperature this high for 3.7 hours.

Hay and his colleagues concluded from this that “Parents, nurses, pharmacists, and doctors wanting to use medicines to supplement physical measures to maximize the time that time children spend without fever should use ibuprofen and consider the relative benefits and risks of using paracetamol plus ibuprofen over 24 hours”, but it should be noted that the different strategies did not seem to influence the time it took for symptoms of discomfort to resolve or the time it took for child’s appetite to return to normal. Many would not support the conclusion that these minor differences make treatment with two drugs appropriate (Harnden, 2008) if the main aim of treatment is to relieve distress rather than simply minimize fever. Just because it is easier to measure fever than discomfort that does not necessarily mean that the one can safely be used as a surrogate for the other. Nor would the results necessarily have been the same had rather different maintenance doses been used.

**Conclusion:** For a more extensive discussion of these issues see the web comment on ibuprofen use first posted in September 2008.

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