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.


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., 2002), but it did cause the parallel French trial to close early (Gournay et al., 2002). No such effect was recognised with very early indomethacin use.

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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.

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, and Thomas et al., 2003 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 (Desfriere et al., 2003).

**Supply:** 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. There are also two studies suggesting that oral treatment may be as effective as IV treatment in most children (Hariprasad, et al., 2002; Heyman, et al., 2003).


Patel J, Roberts I Azzopardi D, et al. Randomized double-blind controlled trial comparing the effects of ibuprofen with indomethacin on cerebral hemodynamics in preterm infants with patent ductus arteriosus. Pediatr Res 2000;47:36–42. [RCT] (See also 4–5.)


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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 convolution, 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, but 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 very uncommon. In all other respects head-to-head trials suggest that the two drugs are of equal efficacy. A recent Cochrane Review (Meremikwu, 2003) has shown that the speed with which body temperature falls in response to treatment with one or other of these two drugs can be increased by gentle tepid sponging.


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