

INDOMETACIN (Commentary)**Use to delay preterm labour**

Several reports appeared in the 1990s saying that, while maternal treatment with indometacin has some power to delay preterm labour, it could harm the baby (Moise *et al.*, 1988; Panter, *et al.*, 1999), although more recent reports suggest that the risk may have been exaggerated (Vermillion and Newman, 1999; Parilla *et al.* 2000; Macones *et al.*, 2001; Savage *et al.*, 2007; Cordero *et al.*, 2007). A systematic review by Gyetyai in 1999 summarised the evidence that was available for all the various tocolytics, as did a less systematic review by Huddleston in 2003. One small trial reported by Abramov *et al.* in 2000 has suggested that the vaginal administration of a 100 mg suppository twice 12 hours apart may be more effective than a combination of rectal and oral administration for 24 hours. Increasingly, however, it is becoming clear that treatment with nifedipine or atosiban is a more effective way of stopping, or at least delaying, preterm labour.

Prophylactic use after birth

Interest in prophylactic use after birth was spurred in the early 1990s by trials showing that *early* use seemed to be associated with a reduction in the proportion of very low birth weight babies developing ultrasound evidence of severe intraventricular bleeding. This interest has now largely evaporated with the recognition that ischaemia due to poor blood flow (which can be hard to detect on ultrasound examination in the period immediately after birth) causes much more long term brain damage than bleeding (which is easy to see). Although two large trials (Ment, *et al.*, 1994; Schmidt *et al.*, 2001) showed that early prophylaxis reduced not just the number of babies developing any degree of haemorrhage, but the number developing serious grade III or grade IV bleeding (generally interpreted as a sign bleeding into the substance of the brain), long term follow up has failed to show that this is associated with *any* reduction in long term disability. Clinicians are slowly beginning to realise that it is not safe to judge the efficacy (or the safety) of any new treatment strategy by the immediate short-term outcome. Ultrasound, in particular, can not be used as a “surrogate” marker for the outcome that really matters – the child’s later growth and development. The longer the follow-up study has lasted the smaller the difference between the two treatment groups seems to have become. Even the suggestion that verbal ability might be improved in those offered early prophylactic treatment, raised by an evaluation of a sub-group of the children at four and a half years in first large trial, could not be confirmed when all the survivors (other than the 15% lost to follow-up) were assessed yet again at eight years (Vohr, *et al.*, 2003). The only lasting benefit of early prophylaxis in babies of less than 28 weeks gestation seems to be that for every 20 babies so treated the number requiring surgical duct ligation can be reduced by one (Schmidt, *et al.*, 2001). Clinicians may well hold differing views as to whether that alone makes universal prophylaxis worth while.

Treatment for persisting, symptomatic, patent ductus

Several trials have looked to see whether a week of treatment is more effective than short three-dose treatment in securing sustained ductal closure. Early studies by Hammerman and Aramburo (1990), and by Rennie and Cooke (1991), had suggested that sustained treatment was more effective, but the studies by Rhodes (1988) and by Tammela (1999) found no such difference. A further, more recent, trial in 140 babies (Lee, 2003) found a similar closure rate with the two strategies, but less of a reduction in urine output with sustained low dose treatment. van Overmeire (2001) also found closure rates to be similar, but did not see the same reduction in urine output. However, additional doses *did* increase the number of ducts closing in a further study reported by Quinn (2001). The number coming to surgical ligation in these studies was consistently higher than in the observational study of 148 babies of less than 1.5 kg reported by Kumar and Yu (1997). They only ended up ligating the duct of one baby after using early sustained low dose treatment in the 48 who developed a haemodynamically significant duct.

We have known, for more than 25 years, that the clearance of indometacin is extremely variable in the first few days and weeks of life (Yaffe *et al.* 1980; Thalji *et al.*, 1980; Brash *et al.* 1981), and recent work has reconfirmed this variability (Smyth *et al.* 2004). While the half life is as short as 8 hours in some babies, it is four times as long as this in others, and only a small amount of this variability is caused by the fact that clearance occurs more quickly as postnatal age increases. It has long been known that ductal closure is much less likely to occur if the post-treatment plasma level is low (typically a trough level of < 0.4 mg/l), so it is difficult to know why it has taken clinicians so long to break free from the fixed dosage regimens used in early studies, and **titrate** the dose given against what this can be seen doing to ductal patency. The success sometimes achieved by sustained treatment may well be the result of drug accumulation causing a progressive rise in the drug’s blood level. While there is a clear logic to giving indometacin for long enough to not simply contract, but contract the duct for long enough to cause permanent closure, it now looks as though a high closure rate can be achieved more quickly, and more reliably, by giving a higher dose to those babies whose duct does not close in response to standard dose treatment (Sperandio *et al.* 2005).

Prolonged ductal patency is particularly common in babies of less than 27 weeks gestation. In the cohort study reported by Quinn *et al.* in 2002, involving 313 babies as immature as this, standard treatment with just three doses of indometacin over 3 days only caused echocardiographically confirmed duct closure in 214 (68%) even though treatment was usually started within three days of birth. Surgical closure was then offered to the 30 (~10%) in whom there was no clinical evidence of reduced ductal flow. A further 69 had evidence of partial closure by this time. Giving a further 0.1 mg/kg IV dose once a day for 3 more days halved the number coming to ligation. However, the 'take home' message is that, even with sustained treatment, a fifth of all babies as immature as this are still currently going to come to surgical duct ligation at some stage. Any attempt to 'buy time' in these babies probably merely buys increased trouble.

Treatment with indometacin has long been thought to increase the risk of necrotising enterocolitis, but it is now thought that the main risk is an increased risk of a different but related condition – focal intestinal perforation unassociated with bacterial invasion of the bowel wall or the generation of radiologically visible gas in the bowel wall. Unfortunately the trials done to date have not attempted to distinguish between these two rather different conditions. Two studies (Tammela *et al.*, 1999, and Lee *et al.*, 2003) have suggested that prolonged treatment can put the bowel at risk, but this did not seem to be a problem in the other trials. A revised meta-analysis of all the available data is long overdue. Significant left to right ductal shunting can, of course, compromise gut blood flow, so it is not entirely clear how often damage to the bowel is due to the presence of a haemodynamically significant ductal shunt and how often it is caused by treatment for that shunt.

High dose treatment did not cause any detectable increase in the incidence of focal intestinal perforation or necrotising enterocolitis in the study recently reported by Sperandio *et al.*, 2005, but the randomised controlled trial published by Jegatheesan *et al.* in 2008 found that while sustained treatment can close many ducts that are not closed by a three day course, increasing the dose does *not* make closure more likely and seems to make serious retinopathy more likely. Sperandio did not find any evidence that high dose treatment affected renal function more than standard dose treatment, but Jegatheesan showed that it caused at least a transient rise in the plasma creatinine level and nobody knows if this could have long term consequences.

The recent Cochrane Review by Herrera *et al.* (2004) failed to find any relationship between the duration of indometacin exposure and the incidence of necrotising enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity or death. Neither did the more recent logistic regression analysis of the experience gained while treating 446 babies of less than 28 weeks gestation in the William H Tooley Nursery at the University of California between 1994 and 2005 (Chorne *et al.*, 2007). What is increasingly clear is that the risk of gut damage can be reduced by not giving steroids to any baby being treated with indometacin (see below). Ductal sensitivity to indometacin seems to decline with increasing postnatal age, and the drug's half life is very variable. As a result, optimum medical treatment probably requires early recognition of significant persisting ductal patency especially in the very preterm baby, the administration of a first 0.2 mg/kg dose to establish a reliable high blood level, and then sustained treatment for at least another 2 days to achieve sustained ductal closure with three further doses if the standard dose does not achieve closure. Unnecessary treatment can be avoided by monitoring ductal patency at regular intervals.

How important is complete ductal closure ?

While surgical ligation is a remarkably quick and safe procedure in experienced hands, there is little doubt that it would not be needed as often as it currently is in many units if more steps were taken to optimise medical treatment. Conservative care was remarkable effective in the recent West Australian study (Brooks *et al.*, 2005) and others have reported equally low intervention rates (Vanhaesebrouck *et al.*, 2007). There is also increasing evidence that surgery may exacerbate any existing BPD. In the only trial to ever compare the effects of elective medical and surgical treatment (Gersony *et al.*, 1983) surgically treated babies tended to need continuous positive airway pressure longer than medically treated babies. Clyman, when he reviewed experience in California over a period of eleven years, also found that, after adjustment for all other known influences, babies offered surgical ligation were more likely to develop chronic lung disease (Chorne *et al.*, 2007). Developmental progress is also less good (Madan *et al.*, 2009). Kabra *et al.*, in 2007 also found that chronic lung disease was commoner in the babies in the TIPPP trial that had been cared for in units that most often resorted to surgical ligation. While it would be wrong to assume that this is a causal relationship, it does call into question the current tendency to ligate any duct that remains patent in a ventilator dependent baby, irrespective of whether there is any evidence that flow is significant enough to be really causing symptoms (Laughon *et al.*, 2004; Bose and Laughon, 2006; Clyman and Chorne, 2007). Catheter closure rather than open ligation may be an option worthy of further assessment (Roberts *et al.*, 2007).

Simultaneous steroid exposure

Two studies looking to see whether the early use of hydrocortisone in babies with low cortisol levels immediately after birth reduces the subsequent risk of bronchopulmonary dysplasia were stopped early in 2004 because focal gastrointestinal perforation was found to be commoner in those babies who were also

being given indometacin (Watterberg *et al*, 2004; Peltoniemi *et al*, 2005). An earlier trial (Stark *et al*, 2001) had also identified a similar possible interaction between indometacin and dexamethasone. In the study by Peltoniemi 4 of the 25 babies given hydrocortisone developed a gastrointestinal perforation and none of the 26 control babies; 3 of these 4 babies had received indometacin and the fourth ibuprofen. Interestingly the risk seemed to be highest in those later found to have had an above average cortisol level at the time – suggesting that hydrocortisone was increasing the risk of perforation in those children who did not actually need treatment. It would seem wise to assume that the interaction that has now been established for hydrocortisone is equally true for simultaneous treatment with *any* steroid drug, including dexamethasone. It seems more than possible, though not as yet certain, that steroid use in a child simultaneously taking ibuprofen is equally unwise. There is no risk associated with *antenatal* steroid use (Attridge *et al*, 2006).

Speed of administration

The speed with which blood flows through the cerebral arteries has been reported to fall more with rapid than with slow IV administration. Edwards *et al*. however in 1990, using near infra red spectroscopy, found a similar fall in total oxygen delivery to the brain irrespective of the rapidity of administration, and it must be net oxygen delivery, not the speed with which blood is propelled, that matters. Slow (if not timed) administration has however been standard practice for so long that any unit giving this drug as a rapid bolus might find itself in a situation that was hard to defend if challenged. The best established strategy for giving IV drugs at a slow, but not strictly timed, rate is outlined in some detail on pages 3 and 6 of this *Formulary*.

Co-treatment with furosemide

There has been a tendency for many years in some centres to give furosemide at the same time as IV indometacin, in the belief that it will reduce the impact that indometacin has, at least transiently, on renal function. However a formal study recently published by Andriessen *et al.*, (2009) showed that such treatment (1 mg/kg IV before each of the three IV doses of indometacin given at 12 hourly intervals) actually increased the magnitude of the rise in serum creatinine and a significant fall in serum sodium without actually increasing urine output.

Manufacturer's Summary of Product Characteristics

The advice provided by the manufacturer in the UK, has always been that treatment to effect ductal closure must be suspended if urine output falls below 0.6 ml/kg per hour “until laboratory studies indicate that renal function has returned to normal.” This was the advice given when marketing was first authorised in 1986. It was repeated when the product was re-licensed in 1992, and is the advice still offered by the *British National Formulary for Children*. The advice provided by the manufacturer in the US is equally out of date in that it says that use is only indicated “when, after 48 hours, usual medical management (e.g. fluid restriction, diuretics, digitalis, respiratory support, etc.) is ineffective.” The same advice is also still repeated in the widely used North American reference text *Neofax*[®].

However this fails to take into account the fact that the fall in urine output may itself be due to poor descending aortic blood flow because of massive left-to-right ductal blood flow which itself requires urgent correction. Some clinicians try and compensate for the fall in urine output by giving furosemide, but there is now good evidence that this serves no useful purpose and actually causes a further rise in serum creatinine (Andriessen *et al.*, 2009). Most controlled trial evidence shows, in addition, that the reduction in urine output that occurs after the first dose of indometacin is given is usually transient even if treatment is continued. If the child has a *symptomatic* duct the priority must be to close the duct by one means or another. Delay or suboptimal dosing puts the child at increased risk.

This is just one more example of the way that the advice provided by manufacturers frequently becomes ossified in time because modifying the terms of the license negotiated with the regulatory authorities is a costly business, and companies face no pressure to do this unless their lawyers identify some potential adverse outcome for which it seems wise to post a warning.

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