

INDOMETACIN (Comment)

What is the optimal dosing strategy to achieve ductal closure?

Indometacin has now been in use to treat persistent patency of the ductus arteriosus, when this is causing troublesome symptoms in the preterm baby, for more than thirty years but, to our shame, it is still not clear what the best dosing strategy is. For a long time almost everyone followed the regimen adopted by the very first studies to prove efficacy, and give a first 200 microgram/kg dose and then two further 100 microgram/kg doses 24 and 28 hours later. This proved very effective in babies of more than 28 weeks gestation – the main target population when the drug first came into use – but reports of treatment failure became more and more common as, with advances in neonatal care, a larger fraction of the children requiring treatment became more immature than this. More sustained treatment came into vogue for a time in order to not just “shut the duct, but nail it shut”, and this *Formulary* followed that trend, but formal trials of making extended treatment routine were equivocal as to whether this really offered very much benefit. As ultrasound scanning facilities became more sophisticated and more widely available, and were able to document not just continued patency but the amount of flow through the duct, its timing and its direction, a more logical and selective policy of only providing sustained treatment to children in whom significant left to right flow was still present after three days became more popular.

Recently at least three population-based observational studies have reported the use of higher doses of indometacin to treat infants whose duct failed to close with conventional dosing, and achieved closure in almost 90% of all children, the most persuasive of which was the report by Sperandio *et al.* in 2005. The logic was clear – although indometacin is more widely distributed round the body (i.e. it has a higher V_D), in the very preterm baby, clearance from the blood stream occurs more quickly in babies more than 1–2 weeks old (Shaffer *et al.*, 2002). As a result the blood levels achieved in a moderately preterm baby one week old are significantly higher than those achieved in a very preterm baby almost a month old. The logic of offering these more vulnerable babies not just longer treatment but a higher dose seemed impeccable.

However, a relatively small but elegant, randomised, controlled trial involving 105 of the 118 eligible babies of less than 28 weeks gestation has now shown this approach to be wrong, even if it was logical. This was a trial masterminded by Priya Jegatheesan and Vlad Ianus under Ronald Clyman's leadership, involving babies cared for in four large centres in America between 2003 and 2006. It is just another example of where “more is not better for the preterm infant”, as Alan Jobe says in a brief linked perspective. Half the babies who still had a demonstrably patent duct just before the third conventional dose of indometacin was given were given another three 100 microgram/kg doses at daily intervals (i.e. six doses in all), while the other half were then given a higher dose (100 or 250 micrograms/kg) *twice* a day for the next three days.

Although high dose treatment during the second three days produced a 2.9 fold increase in the final serum indometacin level, it did *nothing* to increase the number of ducts successfully closed (45% v. 52%). High dose treatment did, however, result in a significant rise in the serum creatinine level (suggesting some, at least brief, effect on kidney function) and, more worryingly, an increase in the number of babies with moderate or severe retinopathy of prematurity. What is more, those babies with the highest post-study serum indometacin levels had the worst retinopathy (Odds Ratio 1.75; 95% CI 1.15 to 2.68). That this could well be a true causal effect of high dose treatment is backed by work showing that indometacin can decrease retinal blood flow, increase retinal vascular endothelial growth factor production, and make retinopathy worse in experimental animals. The conclusion has to be that, while a further three days of treatment can close half the ducts that were still patent at three days, such treatment should only be given where it can be shown to be necessary. In addition, we now know that it is not just ineffective but positively dangerous to use an escalating dose. Because this had been an option suggested when the fifth edition of this *Formulary* was first published in October 2006, an update of this monograph, that takes these new findings into account, has now been posted.

Shaffer CL, Gal P, Ransom JL, *et al.* Effect of age and birthweight on indomethacin pharmacodynamics in neonates treated for patent ductus arteriosus. *Crit Care Med* 2002;**30**:343–8.

Sperandio M, Beedgen B, Feneberg R, *et al.* Effectiveness and side effects of an escalating, stepwise approach to indomethacin treatment for symptomatic patent ductus arteriosus in premature infants below 33 weeks of gestation. *Pediatrics* 2005;**116**:1361–6. (See also **117**:1363–4.)

Jegatheesan P, Ianus V, Buchh B, *et al.* Increased indomethacin dosing for persistent patent ductus arteriosus in preterm infants: a multi-center, randomized, controlled trial. *J Pediatr* 2008;**153**:183–9. [RCT]