

Use

Indometacin causes effective patent ductus arteriosus (PDA) closure, as does ibuprofen (q.v.).

Pharmacology in pregnancy

Indometacin is an inhibitor of prostaglandin synthesis widely used as an analgesic anti-inflammatory drug in rheumatoid arthritis and gout. It is normally well absorbed by mouth, but neonatal oral absorption is sometimes unpredictable. The neonatal half life averages 16 hours (nearly 7 times the half life in adults). Indometacin crosses the placenta and is excreted in the urine. There is no evidence of teratogenicity. Maternal treatment (25 mg by mouth every 6 hours after a loading dose of 50 mg) can be used to treat polyhydramnios, but the use of double this dose to control premature labour has now declined because there are better alternatives. Some recent studies have also suggested such use may also increase the risk of the baby developing necrotising enterocolitis, and focal gut perforation. A recent meta-analysis did not find any increase in the risk of treatment-resistant PDA, but it did find that periventricular leukomalacia was more common. Breast feeding is quite safe because the baby gets less than 1% of the weight-adjusted maternal dose.

Pharmacology in the neonate

Indometacin was first used experimentally to effect ductal closure in 1976, and some centres still use the dose used in the early studies (three 200 microgram/kg doses 12 hours apart). This dose is of proven value in the **treatment** of symptomatic patent ductus, especially when used within 2 weeks of birth, but more sustained treatment is measurably more effective in the very preterm baby (where the risk of treatment failure is highest), as is the use of a higher dose. A left atrium to aortic root (LA:Ao) ratio of 1.5 or more, a ductal diameter on colour Doppler of over 1.3 mm/kg, and descending aortic flow reversal in diastole on ultrasound after the first two days of life, all suggest the presence of a haemodynamically significant duct. Babies offered early **prophylaxis** (as in the TIPP trial) had less ultrasound evidence of serious intraventricular haemorrhage, but cerebral palsy and other disability was *no* less common. Nor was bronchopulmonary dysplasia (BPD) less common. However for every 20 babies of under 1 kg so treated 5 avoided prolonged duct patency and one avoided duct ligation. Evaluation at school entry has failed to confirm an earlier report that early prophylaxis reduces the number of survivors with speech and language problems. Nor, however, is there any evidence that early low-dose use increases the risk of necrotising enterocolitis or ischaemic brain damage – an issue of real concern since even slow infusion causes a brief drop in cerebral, renal and gut blood flow.

Serious coagulation problems are traditionally considered a contra-indication to neonatal treatment because of the effect of indometacin on platelet function, as is necrotising enterocolitis. Jaundice is not a contra-indication. The decrease in urine flow is transient even with sustained treatment, so indometacin can still be given, even when there are early signs of renal failure, and *no* adjustment needs to be made in the dosage of other renally-excreted drugs. Focal ischaemic gut perforation is the most dangerous, and gastro-intestinal haemorrhage the commonest, complication (even with IV administration). Whether sustained, or high dose, treatment increases the risk of these complications is not yet clear. Ligation is usually undertaken if the duct remains patent, although there are suggestions that this may occasionally make any existing BPD worse.

Drug interactions

Babies given steroids while on indometacin are at increased risk of focal ischemic gut perforation.

Treatment options

Early pre-emptive treatment: Give babies under 28 weeks gestation three 100 microgram/kg doses IV (traditionally over 20 minutes) at daily intervals starting 12 hours after birth (as in the TIPP trial).

Haemodynamically significant ducts: Give 200 microgram/kg IV, and then a 100 microgram/kg dose 24 and 48 hours later. In very preterm babies with residual patency after this a further 3 days treatment can halve the number eventually judged to need surgical ligation. A higher dose is no more effective, and seems to exacerbate any co-existent retinopathy of prematurity.

Supply

1 mg vials of the IV preparation cost £7.50. They should be reconstituted just before use with 2 ml of sterile water for injection to give a solution containing 500 micrograms/ml. The IV formulation can also be given by mouth. A 5 mg/ml oral suspension (containing 1% alcohol) is available in North America.

References

See also the relevant Cochrane reviews ©

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