

Ibuprofen for treating patent ductus arteriosus in neonates

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The availability of a licensed formulation of intravenous ibuprofen has resulted in it being considered for treating patent ductus arteriosus in neonates. This article, part of an occasional feature of drug reviews, examines the clinical evidence

Patent ductus arteriosus (PDA) remains a common problem in neonates with respiratory distress syndrome. This congenital condition is characterised by a persistent connection between the aorta and the pulmonary artery. The left to right shunting through the ductus increases the risk of intraventricular haemorrhage, necrotising enterocolitis (NEC), bronchopulmonary dysplasia and death.

Until recently, licensed treatment options for the management of PDA have been limited with intravenous indometacin being the only product available in the UK. Concerns remain, however, about the side effect profile of this drug. Indometacin affects renal, gastrointestinal and cerebral perfusion and can lead to complications such as transient or permanent renal dysfunction, NEC, gastrointestinal haemorrhage and reduced cerebral intracellular oxygenation. As a result, the majority of neonatal intensive care units now choose to administer a lower dose in an "off label" manner.

In the event of drug treatment failure after a second course, surgical ligation of the duct is indicated. It is estimated that approximately 1 per cent of neonates treated with pharmacotherapy require this intervention.

The availability of intravenous ibuprofen over the past few years has now provided an opportunity for neonatologists to review their practice in the treatment of PDA and to offer a further treatment choice. A licence for intravenous ibuprofen for PDA in neonates has also recently been granted.

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— Clinical efficacy

A review of four open-label, randomised trials showed that ibuprofen was as effective as indometacin in the closure of ducts in preterm newborn infants with gestational ages less than 34 weeks. Ibuprofen was associated with fewer side effects. These studies are now discussed.

A single-centre, randomised, controlled trial involving 40 preterm infants with gestational ages less than or equal to 33 weeks (postnatal age was between 48 and 72 hours at the start of treatment and all had PDA proven by echo)¹ demonstrated no significant difference in efficacy between the ibuprofen and indometacin treatment groups (the primary end point was the closure of the PDA). A significant reduction in urine output for the indometacin group on day two of treatment ($P=0.001$) continued for up to four days after completion of treatment ($P=0.002$). An increase in serum creatinine with indometacin treatment was also recorded. No difference in respiratory function, bleeding tendency or elevation in liver enzymes was seen.

A multicentre, randomised, controlled trial involved 103 patients with an average gestational age of 29 weeks (range from 27 to 31 weeks). All had proven PDA on the third day of life.² Again, curative rates after three doses were not significantly different between the ibuprofen and indometacin groups. In addition, the indometacin group had a lower urine output and elevated serum creatinine up to five days after treatment when compared with the ibuprofen group. No significant differences in intestinal, cerebral or haematological side effects were noted between the two groups.

A larger, multi-centre, randomised, controlled trial³ of 148 preterm infants showed no significant difference in efficacy between the groups or in the number of patients who required a second course of treatment to ensure a successful closure of the duct. All patients had a gestational ages of less than 32

weeks and postnatal ages between 48 and 72 hours. The incidence of oliguria was raised in the indometacin group ($P=0.03$). NEC occurred in a higher proportion of those patients who developed oliguria than those who did not. Twice as many infants in the indometacin group had NEC. From day three to seven, there was a significant lowering of urine output ($P<0.001$) in the indometacin group and the serum creatinine concentration was higher in this group ($P=0.04$). No significant differences relating to other side effects or complications were apparent from the published data.

Another multi-centre, randomised, controlled trial recruited 232 preterm infants, of whom 175 had a persistent, haemodynamically significant PDA at 48 to 72 hours of age.⁴ Gestational age for this study ranged from 23 to 34 weeks. Efficacy was similar for both groups. Indometacin caused a significant increase in the serum creatinine compared with ibuprofen ($P=0.03$) and 15 per cent of the indometacin cohort developed oliguria compared with just 1 per cent in the ibuprofen group ($P=0.017$).

— Adverse effects

Cerebral perfusion and oxygenation A study of preterm infants ($n=16$) compared single doses of ibuprofen with indometacin.⁵ The indometacin group showed significant reductions in both cerebral blood volume and cerebral blood flow velocity.

A second trial on 33 preterm infants with gestational ages of less than 35 weeks⁶ compared the effects of indometacin and ibuprofen on cerebral haemodynamics. Primary endpoints were the effects of the first dose on cerebral blood flow and cerebral blood volume. There was a statistically significant drop in cerebral blood flow after the first dose of indometacin ($P<0.001$) when compared with baseline results and cerebral oxygen delivery decreased significantly. This was confirmed on administration of the

second dose. These effects were not seen when a saline dose was administered.

Ibuprofen administration caused no change in the cerebral blood flow or volume. The median change in cerebral blood volume was statistically significant for the indometacin group in comparison with ibuprofen ($P < 0.001$).

Other cerebral side effects A randomised, prospective study of indometacin versus ibuprofen on 232 neonates (gestational ages of 23–34 weeks) showed no statistically significant difference in cerebral blood flow. The trial also showed no difference in the incidence of haemorrhagic or ischaemic brain lesions, intracranial haemorrhages or periventricular leukomalacia (death of the white matter of the brain due to softening of the brain tissue).

Eighty preterm infants with gestational ages less than 34 weeks had ibuprofen administered to them either within 24 hours of life or at echocardiographic diagnosis of PDA.⁸ Incidences of intraventricular haemorrhage were not statistically different between the two groups. This was further confirmed by a multicentre trial on 358 patients who were all born at less than 30 weeks' gestation.⁹ This trial also showed that ibuprofen did not increase the incidence of grade 3–4 intraventricular haemorrhage.

Other studies have compared ibuprofen with placebo. Cerebral complications were not statistically significant with ibuprofen ($P = 0.1$), although this may be due to lack of statistical powering.¹⁰

A larger study compared active ibuprofen against placebo in 46 preterm infants.¹¹ During the period of treatment there was no difference between the two groups with respect to intraventricular haemorrhage and periventricular leukomalacia. The same cerebral flow patterns were detected on days one, three and seven.

Renal adverse events Renal function was specifically assessed in most of the trials by measuring the impact of drug therapy on urine output, serum creatinine, and sodium and urea concentrations.

A small study comparing the efficacy of ibuprofen with indometacin failed to ensure that all preterm infants had a full course of treatment. There were eight preterm infants in each group and only one patient in the indometacin group received all three doses. Renal dysfunction occurred in 50 per cent of the patients. Only one patient in the ibuprofen group was affected.⁵

In a further study, no adverse renal effects were noted in the ibuprofen group but two patients developed oliguria and raised serum creatinine in the indometacin group and were thus withdrawn from the trial.⁶

When compared with indometacin, ibuprofen appears to demonstrate a more favourable renal side effect profile.

Gastrointestinal side effects Two studies (one with ibuprofen and one with indometacin) showed a favourable outcome in achieving full enteral feeding when compared with placebo.^{10,12} However, one prophylactic trial showed that those neonates undergoing treatment with ibuprofen had more feeding difficulties during the three-day treatment period.¹¹ The onset of full oral feeds was eventually comparable to that of the control group. This effect has failed to be reproduced in other studies.

Haematological side effects The tendency for non-steroidal anti-inflammatory drugs (NSAIDs) to cause bleeding is well documented and this was evaluated in trials by screening for blood in stools, urine, endotracheal and gastric aspirates as well as bleeding from puncture sites. There was no difference in incidence of haemorrhagic manifestations between ibuprofen and placebo groups in two prophylactic trials.^{7,10}

Neutropenia during the first three days of life was found to be more frequent in the ibuprofen group than in the placebo group.¹³

Summary

The availability of a licensed formulation of intravenous ibuprofen offers a further option for neonatologists in the treatment of PDA in neonates. The side effect profile of ibuprofen appears to be better than that of indometacin and there is no loss of efficacy. Therefore it appears reasonable to advocate this choice of NSAID for first-line pharmacotherapy.

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