Ibuprofen compared with indometacin for patent ductus arteriosus

A Cochrane review reports that ibuprofen is as effective as indometacin for closure of patent ductus arteriosus in preterm or low-birthweight babies, and is associated with a lower risk of necrotising enterocolitis, reduced time on assisted ventilation and a lower risk of negative effects on renal function.

Overview: The ductus arteriosus is a normal blood vessel in the fetus that connects the pulmonary artery and the aorta. It allows the fetal blood flow to bypass the lungs, which are not used before birth, and usually closes at or shortly after birth. However, in about one-third of low-birthweight infants, the ductus arteriosus remains open (patent), especially during early days of life, and in preterm neonates it often fails to close. The resulting haemodynamic instability can cause renal or gastrointestinal effects, including spontaneous perforation and necrotising enterocolitis, and chronic lung disease. If not managed, patent ductus arteriosus may lead to death.

Current advice: Drug therapy is preferred to surgical correction of patent ductus arteriosus because of the risks associated with surgery. Prostaglandins play a significant role in keeping the ductus arteriosus patent. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the synthesis of prostaglandins, and, for many years, the NSAID indometacin was used intravenously to treat patent ductus arteriosus. However, indometacin has been associated with adverse effects and is no longer licensed for this indication. An intravenous formulation of a different NSAID, ibuprofen, is licensed for treating haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age.

New evidence: An updated Cochrane review by Ohlsson et al. (2013) assessed the effectiveness and safety of ibuprofen compared with indomethacin or no drug for closing patent ductus arteriosus. All studies in the review included preterm (less than 37 weeks gestational age) or low-birthweight (less than 2500 g) infants with patent ductus arteriosus diagnosed during the neonatal period (less than 28 days after birth).

In a meta-analysis of 20 randomised controlled trials (n=1019), there was no significant difference between ibuprofen and indometacin (both drugs given orally or intravenously) in ductus closure (risk ratio [RR] for failure of ductus closure=0.98, 95% confidence interval [CI] 0.80 to 1.20).

There were also no significant differences between ibuprofen and indometacin in all-cause mortality (8 studies, n=470), or need for retreatment (7 studies, n=241) or surgical closure (13 studies, n=848). However, ibuprofen was associated with a lower risk of necrotising enterocolitis (15 studies, n=865, RR=0.68, 95% CI 0.47 to 0.99, number needed to treat [NNT]=25) and a lower risk of oliguria (6 studies, n=576, RR=0.28, 95% CI 0.14 to 0.54, NNT=11). Duration of ventilator support (6 studies, n=471) was also shorter with ibuprofen (mean difference=2.35 days shorter, 95% CI 0.99 to 3.71 days shorter).
Oral ibuprofen was superior to intravenous ibuprofen in ductus closure (3 studies, n=236, RR for failure of ductus closure=0.37, 95% CI 0.23 to 0.61, NNT=4), with no significant differences in other important outcomes.

**Commentary:** “Ibuprofen has been used in the UK for many years, and it has been the only product used for closure of patent ductus arteriosus in my own large neonatal unit for over 15 years. The move to ibuprofen was trialled because of the very real problems of renal insufficiency and necrotising enterocolitis caused by indometacin. The change proved very positive in terms of reduction in side effects.

“This Cochrane review has helped support the comparable efficacy of the 2 products, while supporting the better safety profile of ibuprofen that we have already seen in our unit. Although indometacin is still available in the UK, there is currently no licensed preparation for patent ductus arteriosus and this evidence review would not support its future use.

“Intravenous ibuprofen is not a cheap option for patent ductus arteriosus, but its cost is generally outweighed by the reduced need for surgical closure of the duct. It is the oral use of ibuprofen for this condition that may substantially reduce the costs. The evidence is starting to look very promising for this change of route, although this approach would be an off-label use of the drug.” – Mr Steve Tomlin, Consultant Pharmacist for Children’s Services, Evelina London Children’s Hospital, Guys and St Thomas’ NHS Foundation Trust, and Honorary Senior Lecturer, University College London School of Pharmacy and King’s College London

**Study sponsorship:** Eunice Kennedy Shriver National Institute of Child Health and Human Development, US National Institutes of Health.

---

**About this article:** This article appeared in the May 2014 issue of the Eyes on Evidence e-bulletin. This free monthly e-bulletin from NICE Evidence outlines interesting new evidence and what it means for current practice. They do not constitute formal NICE guidance. The opinions of contributors do not necessarily reflect the views of NICE.

To receive the Eyes on Evidence e-bulletin, please complete the online registration form.