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**Search details**

Patent ductus arteriosus in premature infants using ibuprofen for successful closure

**Resources searched**

NHS Evidence; TRIP Database; Cochrane Library; BNI; EMBASE; MEDLINE; Google Scholar

*Database search terms*: patent ductus arteriosus, ductus arteriosus patent, PDA, prematur*, infant*, newborn, neonate*, ibuprofen, indomethacin

Limited to case reports, clinical trial, randomised controlled trial

*Google search string(s)*: patent ductus arteriosus, newborn or premature, ibuprofen

**Summary**

Range of information from 2002 to 2012.

**Guidelines**

None found

**Evidence-based reviews**


A meta-analysis of ibuprofen versus indomethacin for closure of patent ductus arteriosus (Structured abstract)


Published research

1. Oral versus intravenous ibuprofen for patent ductus arteriosus closure: a randomised controlled trial in extremely low birthweight infants.

Author(s) Erdeve O, Yurttutan S, Altug N, Ozdemir R, Gokmen T, Dilmen U, Oguz SS, Uras N

Citation: Archives of Disease in Childhood Fetal & Neonatal Edition, July 2012, vol./is. 97/4(F279-83), 1359-2998;1468-2052 (2012 Jul)

Publication Date: July 2012

Abstract: OBJECTIVE: To compare the efficacy and safety of oral versus intravenous ibuprofen for the pharmacological closure of patent ductus arteriosus (PDA) in less mature preterm infants.DESIGN: Prospective, randomised controlled study.SETTING: Tertiary neonatal intensive care unit.PATIENTS AND INTERVENTIONS: The study enrolled 80 preterm infants with gestational age <=28 weeks, birth weight <1000 g, postnatal age 48 to 96 h, and had echocardiographically confirmed significant PDA. Seventy extremely low birthweight (ELBW) preterm infants received either intravenous or oral ibuprofen randomly as an initial dose of 10 mg/kg, followed by 5 mg/kg at 24 and 48 h.MAIN OUTCOME MEASURES: The success rate and the safety of the drugs in ELBW preterm infants were the major outcomes.RESULTS: PDA closure rate was significantly higher with oral ibuprofen (83.3% vs 61.7%) after the first course of the treatment (p=0.04). Although the primary closure rate was marginally higher in the oral ibuprofen group, the need for a second course of ibuprofen during the whole hospitalisation was similar between groups: 11 of 36 in oral versus 15 of 34 in intravenous groups (p=0.24) because of a higher reopening rate in the oral group. In addition to no increase in side effects with oral ibuprofen use, the need for postnatal steroid use for chronic lung disease was significantly lower in oral ibuprofen group (p=0.001).CONCLUSIONS: Oral ibuprofen is as effective as intravenous ibuprofen for PDA closure even in ELBW infants.

Source: Medline

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Notes: ULHT journal article requests. Complete the online form to obtain articles.

2. Timing of patent ductus arteriosus treatment and respiratory outcome in premature infants: a double-blind randomized controlled trial.
Objective: To determine whether "early" ibuprofen treatment, at the onset of subtle patent ductus arteriosus (PDA) symptoms, would improve respiratory outcome in premature infants compared with "expectant" management, with ibuprofen treatment only when the PDA becomes hemodynamically significant (HS).

Study Design: We conducted a randomized double-blind controlled trial of infants with gestational ages 23 to 32 weeks and birth weights 500 to 1250 g who had echocardiography for subtle PDA symptoms (metabolic acidosis, murmur, bounding pulses). Infants were then randomized to "early" treatment (blinded ibuprofen; n = 54) or "expectant management" (blinded placebo, n = 51). If the PDA became HS (pulmonary hemorrhage, hypotension, respiratory deterioration), infants received open label ibuprofen. Infants with HS PDA at enrollment were excluded from the study. Respiratory outcomes and mortality and major morbidities were determined.

Results: "Early" treatment infants received ibuprofen at median age of 3 days; infants in the "expectant group" in whom HS symptoms developed (20%) received ibuprofen at median of 11 days. A total of 49% of "expectant" infants never required ibuprofen or ligation. No significant differences were found in the primary outcome (days on oxygen [O(2)] during the first 28 days), death, O(2) at 36 weeks, death or O(2) at 36 weeks, intestinal perforation, surgical necrotizing enterocolitis, grades III and IV intracranial hemorrhage, periventricular leukomalacia, sepsis or retinopathy of prematurity.

Conclusion: Infants with mild signs of PDA do not benefit from early PDA treatment compared with delayed treatment.

Author(s) Hammerman, Cathy, Bin-Nun, Alona, Kaplan, Michael

Citation: Seminars in Perinatology, 01 April 2012, vol./is. 36/2(130-138), 01460005

Publication Date: 01 April 2012

Abstract: Over recent years, the clinical approach to patency of the ductus arteriosus in the premature neonate has been the subject of intensive reevaluation. What had once been considered inherently obvious is no longer to be taken for granted. In this review we will focus on some of the controversies surrounding various aspects of the pharmacologic treatment regimens for patent ductus arteriosus closure. The pros and cons of prophylactic vs therapeutic indomethacin, of early vs late therapy, of high- vs low-dose indomethacin, of single vs multiple courses of treatment, and of ibuprofen vs indomethacin will be considered. In addition, the possibility that patency of the ductus arteriosus is merely a physiological manifestation of extreme prematurity, and thus does not necessarily need to be therapeutically closed, has become a viable approach in some cases. As such, we will examine echocardiographic and biochemical criteria aimed at determining the clinical and hemodynamic significance of ductal shunting, and thereby of the need to treat. Finally, we speculate on potential therapeutic directions for the future, including individualized treatment regimens and multidrug treatment cocktails for those who fail initial monodrug therapy.

Source: CINAHL

Available in print from Seminars in perinatology; Notes: ULHT journal article requests. Complete the online form to obtain articles.

5. Evidence-based use of indomethacin and Ibuprofen in the neonatal intensive care unit.

Author(s) Johnston PG, Gillam-Krakauer M, Fuller MP, Reese J

Citation: Clinics in Perinatology, 01 March 2012, vol./is. 39/1(111-136), 00955108

Publication Date: 01 March 2012

Abstract: Indomethacin and ibuprofen are potent inhibitors of prostaglandin synthesis. Neonates have been exposed to these compounds for more than 3 decades. Indomethacin is commonly used to prevent intraventricular hemorrhage (IVH), and both drugs are prescribed for the treatment or prevention of patent ductus arteriosus (PDA). This review examines the basis for indomethacin and ibuprofen use in the neonatal intensive care population. Despite the call for restrained use of each drug, the most immature infants are likely to need pharmacologic approaches to reduce high-grade IVH, avoid the need for PDA ligation, and preserve the opportunity for an optimal outcome.

Source: CINAHL

Available in print from Clinics in perinatology; Notes: ULHT journal article requests. Complete the online form to obtain articles.

6. Pharmacokinetics of oral ibuprofen for patent ductus arteriosus closure in preterm infants.

Author(s) Barzilay B, Youngster I, Batash D, Keidar R, Baram S, Goldman M, Berkovitch M, Heyman E

Citation: Archives of Disease in Childhood Fetal & Neonatal Edition, March 2012, vol./is. 97/2(F116-9), 1359-2998;1468-2052 (2012 Mar)
Publication Date: March 2012

**Abstract:** BACKGROUND: Oral ibuprofen has been shown to be associated with excellent patent ductus arteriosus (PDA) closure rates and a favourable safety profile, but limited data exist regarding its pharmacokinetics in preterm infants.OBJECTIVE: To evaluate pharmacokinetic parameters of oral ibuprofen in preterm infants.METHODS: Plasma ibuprofen levels were determined at various time points, and pharmacokinetic profiles were calculated after a single dose of 10 mg/kg of oral ibuprofen. The rate of ductal closure, adverse effects and patients' clinical course were recorded.RESULTS: The authors studied 13 preterm infants (mean gestational age+/-SD 27.8+/-2.4 weeks, mean birth weight 1052+/-443 g). PDA closure was obtained in all patients after a single dose. Ibuprofen levels were detectable 1 h after administration, peaked after 8 h and remained in a relative plateau until 24 h postadministration. Area under the curve (AUC)>24 was higher than levels reported with intravenous treatment. No adverse effects were observed.CONCLUSION: Oral administration of ibuprofen in very preterm infants is associated with excellent absorption and a high AUC>24, and may be an alternative to intravenous administration.

Source: Medline

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7. Unbound bilirubin does not increase during ibuprofen treatment of patent ductus arteriosus in preterm infants.

**Author(s)** Desfrere L, Thibaut C, Kibleur Y, Barbier A, Bordarier C, Morigie G

**Citation:** Journal of Pediatrics, February 2012, vol./is. 160/2(258-264.e1), 0022-3476;1097-6833 (2012 Feb)

**Publication Date:** February 2012

**Abstract:** OBJECTIVE: To determine whether ibuprofen displaces bilirubin from albumin in preterm infants.STUDY DESIGN: A total of 34 preterm neonates (<32 weeks gestation) treated by ibuprofen (10-5-5 mg/kg) were included in this prospective open-label study. Total bilirubin (TB), unbound bilirubin (UB), and ibuprofen concentrations were measured before, 1 hour, and 6 hours after the first dose; before and 1 hour after the second dose; and 72 hours after the beginning of treatment. The infants were screened by auditory brainstem responses and by neurologic examination at term.RESULTS: At baseline, TB, UB, apparent binding affinity of albumin (Ka), and albumin concentrations were 6.0+/-1.6 mg/dL, 1.9+/-2.2 mug/dL, 14.1+/-5.8 L.mumol(-1), and 28.7+/-2.3 g/L, respectively. Ibuprofen treatment had no effect on TB, UB, or Ka values. No correlation between UB or Ka and ibuprofen concentrations was found. No neurologic symptoms or significant modifications of auditory brainstem responses were observed at term.CONCLUSION: Ibuprofen (10-5-5 mg/kg) did not displace bilirubin in preterm infants with a baseline TB concentration <8.8 mg/dL.. Copyright Copyright 2012 Mosby, Inc. All rights reserved.

Source: Medline

Available in print from Journal of Pediatrics; Notes: ULHT journal article requests. Complete the online form to obtain articles.

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**Author(s)** Dani, Carlo

**Citation:** Journal of Maternal-Fetal & Neonatal Medicine, 02 November 2011, vol./is. 24/(5-
9. Doppler manifestations of ductal steal: role in decision making.

**Author(s)** Sehgal A, Tran H, Carse E

**Citation:** European Journal of Pediatrics, June 2011, vol./is. 170/6(795-8), 0340-6199;1432-1076 (2011 Jun)

**Publication Date:** June 2011

**Abstract:** Patent ductus arteriosus in extremely premature babies is associated with major neonatal morbidities such as necrotizing enterocolitis and intraventricular haemorrhage. Altered systemic blood flow and end-organ hypoperfusion are known associates of a haemodynamically significant ductus arteriosus where descending aorta blood flow profiles may reveal abnormal diastolic retrograde flow. A preterm neonate was noted to have a large symptomatic patent ductus arteriosus with reversal of diastolic flow in the superior mesenteric vessels. Treatment with indomethacin led to ductal closure and concomitant restoration of diastolic flow and resolution of symptoms. Doppler studies of systemic vessels may help improve our understanding of the systemic impact of a haemodynamically significant ductus arteriosus.

**Source:** Medline

Available in print from European journal of pediatrics; Notes: ULHT journal article requests. Complete the online form to obtain articles.

10. Efficacy and safety of oral versus intravenous ibuprofen in very low birth weight preterm infants with patent ductus arteriosus.

**Author(s)** Gokmen T, Erdeve O, Altug N, Oguz SS, Uras N, Dilmen U

**Citation:** Journal of Pediatrics, April 2011, vol./is. 158/4(549-554.e1), 0022-3476;1097-6833 (2011 Apr)

**Publication Date:** April 2011

**Abstract:** OBJECTIVE: To compare oral ibuprofen with intravenous ibuprofen for closure of patent ductus arteriosus in very low birth weight (VLBW) preterm infants.STUDY DESIGN: In a prospective, randomized study, 102 VLBW preterm infants with patent ductus arteriosus received either intravenous or oral ibuprofen at an initial dose of 10 mg/kg, followed by 5 mg/kg at 24 and 48 hours. The success rate and evaluation of renal tolerance using cystatin-C were the major outcomes.RESULTS: Patent ductus arteriosus closure rate was significantly higher with oral ibuprofen (84.6% versus 62%) after the first course of the treatment (P = .011). The cystatin-C level increased significantly after treatment in the oral group (P = .001), but did not change with intravenous ibuprofen (P = .4).CONCLUSIONS: Oral ibuprofen is more effective than intravenous ibuprofen for ductal closure in VLBW infants. The increase in the cystatin-C level with oral treatment suggests that patients with borderline renal function should be evaluated and followed closely.

**Source:** Medline

Available in print from Journal of Pediatrics; Notes: ULHT journal article requests. Complete the online form to obtain articles.
11. Network meta-analysis of indomethacin versus ibuprofen versus placebo for PDA in preterm infants.

Author(s) Jones LJ, Craven PD, Attia J, Thakinstian A, Wright I

Citation: Archives of Disease in Childhood -- Fetal & Neonatal Edition, 01 January 2011, vol./is. 96/1(0 - ), 13592998

Publication Date: 01 January 2011

Abstract: Objectives To evaluate the effects of indomethacin or ibuprofen compared with placebo on closure, morbidity and mortality in preterm infants <37 weeks' gestation with echocardiographically and/or clinically important patent ductus arteriosus (PDA) at >24 h of life. Data sources MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, CINAHL, Cochrane Library, clinicaltrials.gov, controlled-trials.com, American Pediatric and European Paediatric Research Societies and Effective Care of the Newborn Infant. Review methods Systematic review with network meta-analysis of randomised studies comparing intravenous indomethacin, ibuprofen or placebo for PDA in preterm infants at >24 h of life. Results Ten trials compared intravenous indomethacin versus intravenous ibuprofen, nine intravenous indomethacin versus placebo and one intravenous ibuprofen versus placebo. Both intravenous indomethacin (pooled RR 2.39 (95% CI 2.05 to 2.78)) and intravenous ibuprofen (RR 2.40 (95% CI 2.03 to 2.84)) closed a PDA more effectively than placebo. Intravenous ibuprofen was associated with approximately 30% greater risk of chronic lung disease than intravenous indomethacin (RR 1.28 (95% CI 1.03 to 1.60)) or placebo (RR 1.29 (95% CI 0.99 to 1.70)). Differences in risk or benefit were not significant between any combination of intravenous indomethacin, intravenous ibuprofen or placebo groups for intraventricular haemorrhage, necrotising enterocolitis and death. Reporting on neurological outcomes was insufficient for pooling. Conclusions Intravenous indomethacin or ibuprofen administered to preterm infants for PDA at >24 h of life promoted ductal closure, but other short-term benefits were not seen. Treatment with intravenous ibuprofen may increase the risk of chronic lung disease. Good-quality evidence of treatment effect on morbidity, mortality and improved neurodevelopment is urgently needed.

Source: CINAHL

Available in fulltext from Archives of Disease in Childhood - Fetal and Neonatal Edition at Highwire Press

Available in print from Archives of Disease in Childhood -- Fetal & Neonatal Edition; Notes: ULHT journal article requests. Complete the online form to obtain articles.

12. Patent ductus arteriosus in the preterm infant: to treat or not to treat?

Author(s) Noori, S

Citation: Journal of Perinatology, 02 October 2010, vol./is. 30/(0 - ), 07438346

Publication Date: 02 October 2010

Abstract: Pharmacological and/or surgical closure of a hemodynamically significant patent ductus arteriosus (PDA) in the very preterm infant has been the standard of care over the past few decades. However, the rationale for closure of PDA has recently been challenged. In this article, the factors that have fueled the controversy of the approach to the management of PDA and the gap in our knowledge are reviewed in detail. In addition, the pros and cons of the different treatment strategies applied in clinical care are evaluated with a focus on discussing the available evidence in the literature.

Source: CINAHL

Available in print from Journal of Perinatology; Notes: ULHT journal article requests. Complete the online form to obtain articles.

13. Treatment of patent ductus arteriosus: indomethacin or ibuprofen?
Abstract: We compared ibuprofen and indomethacin for the treatment of patent ductus arteriosus (PDA) in preterm infants. A retrospective comparative study was conducted at a pediatric tertiary center in preterm infants diagnosed with PDA. Infants born from January 2000 to June 2003 were treated with indomethacin, whereas infants born from July 2003 to November 2005 were treated with ibuprofen. The two treatment groups were compared. Demographic data and clinical, laboratory, and outcome data were collected from the medical files. Seventy-three infants were included in the ibuprofen group and 46 in the indomethacin group. No significant difference in efficacy was found between indomethacin and ibuprofen. Compared with ibuprofen, indomethacin treatment was associated with significantly higher mean creatinine levels and a higher percent of infants with creatinine >1.2 mg/dL, hyponatremia <120 mmol/L, and platelet level <100,000 platelets/mL (3). There were no significant differences in bilirubin levels, incidence and grade of intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, rate of surgical duct ligation, sepsis, length of hospital stay, or mortality. Indomethacin and ibuprofen are equally effective for PDA closure in premature infants. Treatment with ibuprofen is safer, decreasing the risk of renal failure, thrombocytopenia, and hyponatremia. © Thieme Medical Publishers.

Source: CINAHL

Available in print from American journal of perinatology; Notes: ULHT journal article requests. Complete the online form to obtain articles.


Author(s) Simeoni U.

Citation: Journal of Maternal-Fetal and Neonatal Medicine, May 2010, vol./is. 23/(81), 1476-7058 (May 2010)

Publication Date: May 2010

Abstract: cerebral hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia and death. Consequently, prophylactic or curative treatment has been advocated before the critical left-to-right shunting occurs. A host of studies has shown that both pharmacological agents and surgical closure are effective in closing the ductus arteriosus in premature infants. Indomethacin has long been the drug of choice. However, renal and cerebral haemodynamic side effects have been frequently reported. Strategies to minimise adverse effects of indomethacin, such as the association with frusemide, dopamine or the use of low-dose prolonged treatment with indomethacin have failed or shown partial benefit. Other NSAIDs have been investigated. But either the profile of adverse effects was unfavourable, as in the case of mefenamic acid, or their efficacy was less than that of indomethacin for PDA closure. More recently, ibuprofen has been proposed for the treatment of PDA as it was shown to induce less adverse effects on cerebral blood flow, intestinal and renal hemodynamics, while retaining similar efficacy to indomethacin. However, since renal perfusion, GFR and diuresis in early neonatal life strongly depend on the vasodilator effects of PGs on the afferent glomerular arterioles, ibuprofen, as other COX-inhibitors may not be exempt of some renal undesirable effects. While numerous studies have shown that PDA is a risk factor associated with immaturity and with increased incidence of complications of preterm birth, including broncho-pulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis and death, there is little evidence that such association is causative. Moreover, still little evidence exists from randomized controlled trials that the pharmacological closure of PDA benefits to premature infants in terms of clinically significant short-term or medium-term outcomes, beyond a positive effect on DA patency. The use of COX-inhibitors for the prophylaxis or closure of PDA during the first hours or days of life should thus be cautious and based on an individual evaluation of benefit and risk. Considering areas for future research, there is an urgent need of randomized, placebo-controlled trials designed to assess the benefits in terms of mortality and morbidity.
outcomes of an early, or even very early pharmacological closure of PDA in extremely low gestational age infants.

Source: EMBASE
Available in print from Journal of Maternal-Fetal & Neonatal Medicine; Notes: ULHT journal article requests. Complete the online form to obtain articles.
Available in fulltext from Journal of Maternal-Fetal and Neonatal Medicine at EBSCOhost

15. Ibuprofen in very preterm infants impairs renal function for the first month of life.
Author(s) Vieux R, Desandes R, Boubred F, Semama D, Guillemin F, Buchweiller MC, Fresson J, Hascoet JM
Citation: Pediatric Nephrology, February 2010, vol./is. 25/2(267-74), 0931-041X;1432-198X (2010 Feb)
Publication Date: February 2010
Abstract: We carried out a study aiming to determine the renal effect of ibuprofen treatment for patent ductus arteriosus (PDA) in very preterm infants during the first month of life. Infants aged 27-31 weeks gestation were enrolled from October 2004 to August 2006. They were assigned to two different groups according to ibuprofen exposure during care of their PDA status assessed by echocardiography. Infants of both groups were matched based on gestational age, Clinical Risk Index for Babies score, birth weight and inclusion center. Renal function was evaluated at baseline and weekly for 1 month. One hundred and forty-eight infants were enrolled. Glomerular filtration rate (GFR) was significantly decreased in the ibuprofen group after treatment withdrawal (GFR on day 7, ibuprofen versus no ibuprofen: 12.8 +/- 6.2 vs. 18.1 +/- 12.1 ml/min/1.73 m(2); P < 0.001). Adjusted analysis proved this decrease to be sustained during the first month of life. Tubular function was also impaired during the first month in ibuprofen-treated infants. Ibuprofen administered for PDA is associated with a decreased GFR during the first month of life. Renal function of infants receiving ibuprofen should be carefully monitored and drugs that are eliminated by glomerular filtration handled cautiously during this period.
Source: Medline
Available in fulltext from Pediatric Nephrology at EBSCOhost
Available in print from Pediatric nephrology (Berlin, Germany); Notes: ULHT journal article requests. Complete the online form to obtain articles.

16. Effect of indomethacin infused over 30 minutes on cerebral fractional tissue oxygen extraction in preterm newborns with a patent ductus arteriosus.
Author(s) Keating P, Verhagen E, van Hoften J, ter Horst H, Bos AF
Citation: Neonatology, 2010, vol./is. 98/3(232-7), 1661-7800;1661-7819 (2010)
Publication Date: 2010
Abstract: BACKGROUND: A significant patent ductus arteriosus (PDA) is a common finding in the first days of life and, if persistent, is associated with an increased morbidity and mortality in the preterm newborn.OBJECTIVES: Our aim was to investigate, using near-infrared spectroscopy, the effect of indomethacin on the fractional tissue (cerebral) oxygen extraction (FT(c)OE) in a group of preterm newborns undergoing medical treatment for a PDA.METHODS: This is a prospective, observational study. A cohort of 18 preterm newborns (<32 weeks) undergoing treatment for a PDA with indomethacin were monitored continuously for mean arterial blood pressure, arterial oxygen saturation (SpO(2)) and regional cerebral oxygen saturation (r(c)SO(2)). Measurements were started 1 h before and continued for 4 h after the first indomethacin dose. A final measurement (1 h) was made within 24 h of completing the full course. FT(c)OE = [SpO(2) - r(c)SO(2)]/SpO(2) was then calculated. To analyze the data, we chose to average the measurements over 1-hour
**RESULTS:** There was a significant increase in the FT(c)OE (0.06, 95% CI 0.04-0.09, \( p < 0.001 \)) noticeable within the 1st hour after the start of indomethacin administration, which peaked in the 2nd hour (FT(c)OE increased by 0.08, 95% CI 0.04-0.11, \( p < 0.001 \)) and lasted for the full 4-hour period measured.

**CONCLUSION:** Indomethacin, infused over 30 min, significantly increased the FT(c)OE in the preterm newborn, the effect lasting at least 4 h. This may represent a protective response to the indomethacin-induced reduction in cerebral blood flow demonstrated by others and warrants further investigation. Copyright Copyright 2010 S. Karger AG, Basel.

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**17. Intravenous ibuprofen and closure of patent ductus arteriosus in preterm infants**

**Author(s)** Pedersen L., Madsen L., Ebbesen F.

**Citation:** Cardiology in the Young, November 2009, vol./is. 19/(144), 1047-9511 (November 2009)

**Publication Date:** November 2009

**Abstract:** Background: Spontaneous closure of patent ductus arteriosus (PDA) in preterm infants is delayed or does not occur. Its incidence in preterm infants is between 30 and 70%, being higher the lower gestational age. A PDA will lead to left to right shunt, increasing risk of intraventricular hemorrhage, necrotising enterocolitis (NEC) and bronchopulmonary dysplasia. We report our experience with IV ibuprofen (Pedea) treatment in a danish neonatal intensive care unit with a mixed population of preterm infants. Methods: During the period december 2006 to July 2008, 199 infants were born before full 34 gestational weeks. PDA was diagnosed clinically and echocardiographically in 31 infants with an incidence of 16%. The PDA was evaluated as moderate or severe, if the 2D diameter was >2mm, left atrium/aorta ratio >1.3 and the gradient through the duct >20mmHg. Eighteen infants had a hemodynamical significant PDA and received ibuprofen at median 11 days of life (range 2-20). It was given IV as recommended in doses of 10mg/kg followed by 5mg/kg after 24 and 48 hours. Ratio girls/boys was 11/7, median birth weight 1092 g (range 810-1700) and median gestational age 28.4 weeks (range 25.9-33.6). Thrombocyte count, serum INR, creatinin/urea, sodium, potassium, body weight and 24 hour-urine output were controlled before, during and after treatment. Echocardiography was repeated 24 to 72 hours after the last ibuprofen dosis. In all infants with PDA at discharge, clinical and echocardiographical follow-up was undertaken after 6 and 12 months or until the PDA was closed. Results: After the ibuprofen treatment, PDA was only closed in 2 infants (11%), was smaller in 10 (56%), although still moderate in 2, unchanged in 5 (28%) and larger in one infant (6%). Six infants received a second treatment with ibuprofen and after that the PDA was smaller in one and unchanged moderate in 5 patients. Of the 16 infants in whom the ductus was patent after ibuprofen, 3 infants had a large PDA with clinical symptoms and underwent surgical closure (17%), 3 closed spontaneous before discharge, 3 closed spontaneous after discharge, 1 is referred to transcatheter closure, 3 has a small PDA, one is missing to control and one died suddenly after discharge and the PDA was found closed at the autopsy. One infant with a small PDA died of NEC 17 days after ibuprofen treatment. Three others developed NEC, one before treatment and 2 others 5 and 15 days after ibuprofen treatment. No serious side effects were observed. Conclusion: Our rate of pharmacological closure of PDA withibuprofen was surprisingly low. There are several randomized controlled trials in preterm infants, which showed a rate of closure of 60-80%. In all these series a very restricted population of preterm infants were included and the treatment given at 48-72 h of life. We believe that when ibuprofen is given so early, many infants in whom the PDA would close spontaneously, will be treated unnecessary. On the other hand, in our series the treatment was possibly given too late, as the effect is better in the first week of life. Our surgical closure rate was similar to those found in the literature. The ideal timing for treatment is probably between 3 and 7 days of life, and a routine echocardiography in this period will help in decision-making.
18. A second course of ibuprofen is effective in the closure of a clinically significant PDA in ELBW infants.

Author(s) Richards J, Johnson A, Fox G, Campbell M

Citation: Pediatrics, 01 August 2009, vol./is. 124/2(0-), 00314005

Publication Date: 01 August 2009

Abstract: OBJECTIVES: There are few published data on the efficacy of ibuprofen in the most immature infants and no data on repeated courses. Our objectives were to describe PDA closure rates in a population of infants <1000 g birth weight after repeated courses of ibuprofen, to examine the effect of gestation, and to document plasma markers of renal function and platelet counts. METHODS: This was a single center observational study. We collected data on infants weighing <1000 g at birth who were treated with ibuprofen for a clinically significant PDA. A successful outcome was defined as resolution of clinical symptoms such that no additional treatment was required. Serum biochemistry and hematology data were analyzed and compared with controls. RESULTS: We identified 160 infants with a mean +/- SD birth weight of 757 +/- 127 g and gestation of 25.6 +/- 1.4 weeks. Seventy infants closed their PDA after a single course of ibuprofen (45%) and 32/80 (40%) following a second. Infants of <26 weeks' gestation (n = 83) were less likely to respond after both the first (27.7% vs 63.6%; P < .001) and second (30.9% vs 60.0%; P = .026) courses. The postnatal decrease in plasma creatinine was delayed by ibuprofen treatment, while platelet counts and other plasma markers were unaffected. CONCLUSIONS: In our study population, PDA closure was gestation dependant, with a cumulative closure rate of 65%. A similar proportion of infants closed their PDA following the first and second courses regardless of gestation. These data suggest that a second course of ibuprofen may be effective in closing a PDA in even the most preterm infant.

Source: CINAHL

Available in print from Pediatrics; Notes: ULHT journal article requests. Complete the online form to obtain articles.

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Available in fulltext from Pediatrics at American Academy of Pediatrics

19. Ibuprofen versus continuous indomethacin in premature neonates with patent ductus arteriosus: is the difference in the mode of administration?.

Author(s) Hammerman C, Shchors I, Jacobson S, Schimmel MS, Bromiker R, Kaplan M, Nir A

Citation: Pediatric Research, September 2008, vol./is. 64/3(291-7), 0031-3998;1530-0447 (2008 Sep)

Publication Date: September 2008

Abstract: Ibuprofen has been proposed as a preferential alternative to indomethacin in treating patent ductus arteriosus (PDA), because it is purported to have less renal, mesenteric, and cerebral vasoconstrictive effects. However, short and long-term safety concerns regarding ibuprofen remain. Continuous slow infusion of indomethacin also eliminates peripheral vasoconstriction and may thus offer similar benefits to ibuprofen without safety concerns. In this study, our objective was to show that treating a PDA with continuous indomethacin is similar to ibuprofen in its effect on urine output, renal function, and blood flow velocities in the renal, superior mesenteric, and anterior cerebral arteries.
Sixty four prematures with PDA were randomly, prospectively assigned to either treatment. PDA closure rates were similar (74 versus 59%; p = 0.123). Nine indomethacin-treated babies (29%) versus twelve ibuprofen babies (38%) underwent repeated therapy (p = 0.656). Two indomethacin and four ibuprofen infants required surgical ligation (p = 0.672). Serum creatinine, oliguria, estimated glomerular filtration rate, and fractional excretion of sodium were similar in both groups, as were blood flow velocity parameters in the vessels studied. There were no differences in necrotizing enterocolitis, BPD, intraventricular hemorrhage, and/or retinopathy of prematurity. In conclusion, PDA treatment with either continuous indomethacin infusion or ibuprofen was equally devoid of adverse renal effects and/or peripheral vasoconstrictive effects.

Source: Medline

Available in print from Pediatric research; Notes: ULHT journal article requests. Complete the online form to obtain articles.

20. Treatment of patent ductus arteriosus: indomethacin or ibuprofen?

Author(s) Sekar KC, Corff KE

Citation: Journal of Perinatology, 02 May 2008, vol./is. 28/(0-), 07438346

Publication Date: 02 May 2008

Abstract: Persistent patent ductus arteriosus (PDA) in preterm infants can result in serious hemodynamic changes causing respiratory, gastrointestinal and renal morbidities if not treated within the first week of life. The treatment options available are a conservative approach, pharmacological treatment with cyclo-oxygenase (COX) inhibitors and surgical ligation. The COX inhibitors approved for use in the United States are indomethacin and ibuprofen lysine. Both of these drugs are equally effective in closing the PDA. Subtle differences exist between these two preparations. Indomethacin has a protective effect on the incidence of intraventricular hemorrhage (IVH) but reduces the blood flow to the kidneys and the brain. Ibuprofen is less toxic but has no effect on IVH. Efficacy of pharmacological treatment is influenced by timing of initiation of therapy. Surgical treatment is the only option when pharmacological treatment fails to close the PDA in symptomatic infants. Long-term neurological and respiratory morbidities are associated with surgical ligation. This paper reviews these medical considerations in the treatment options for PDA in premature infants.

Source: CINAHL

Available in print from Journal of Perinatology; Notes: ULHT journal article requests. Complete the online form to obtain articles.

21. An optimized ibuprofen dosing scheme for preterm neonates with patent ductus arteriosus, based on a population pharmacokinetic and pharmacodynamic study.

Author(s) Hirt D, Van Overmeire B, Treluyer JM, Langhendries JP, Marguglio A, Eisinger MJ, Schepens P, Urien S

Citation: British Journal of Clinical Pharmacology, May 2008, vol./is. 65/5(629-36), 0306-5251;1365-2125 (2008 May)

Publication Date: May 2008

Abstract: UNLABELLED: WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT: Ibuprofen is a nonsteroidal anti-inflammatory agent that induces closure of the patent ductus arteriosus in neonates. Few studies of ibuprofen pharmacokinetics have been performed and were limited to small groups of preterm infants, showing a large intersubject variability and an increase in clearance with either postnatal or gestational age.WHAT THIS STUDY ADDS: A population pharmacokinetic study was performed on 66 neonates to characterize the concentration-time courses of ibuprofen. Ibuprofen clearance significantly increased from postnatal age day 1 to day 8, but not with gestational age. A relationship was shown between ibuprofen area under the curve (AUC) and patent ductus arteriosus...
closure rate, and an effective threshold AUC was evidenced. Dosing schemes were proposed as a function of postnatal age, to achieve this AUC and to improve the efficacy of treatment for patent ductus arteriosus in neonates. AIMS To describe ibuprofen pharmacokinetics in preterm neonates with patent ductus arteriosus (PDA) and to establish relationships between doses, plasma concentrations and ibuprofen efficacy and safety. METHODS: Sixty-six neonates were treated with median daily doses of 10, 5 and 5 mg kg(-1) of ibuprofen-lysine by intravenous infusion on 3 consecutive days. A population pharmacokinetic model was developed with NONMEM. Bayesian individual pharmacokinetic estimates were used to calculate areas under the curve (AUC) and to simulate doses. A logistic regression was performed on PDA closure. RESULTS: Ibuprofen pharmacokinetics were described by a one-compartment model with linear elimination. Mean population pharmacokinetic estimates with corresponding intersubject variabilities (%) were: elimination clearance CL = 9.49 ml h(-1) (62%) and volume of distribution V = 375 ml (72%). Ibuprofen CL significantly increased with postnatal age (PNA): CL = 9.49*(PNA/96.3)(1.49). AUC after the first dose (AUC1D), the sum of AUC after the three doses (AUC3D) and gestational age were significantly higher in 57 neonates with closing PDA than in nine neonates without PDA closure (P = 0.02). PDA closure was observed in 50% of the neonates when AUC1D < 600 mg l(-1) h (or AUC3D < 900 mg l(-1) h) and in 91% when AUC1D > 600 mg l(-1) h (or AUC3D > 900 mg l(-1) h) (P = 0.006). No correlation between AUC and side-effects could be demonstrated. CONCLUSIONS: To achieve these optimal AUCs, irrespective of gestational age, three administrations at 24 h intervals are recommended of 10, 5, 5 mg kg(-1) for neonates younger than 70 h, 14, 7, 7 mg kg(-1) for neonates between 70 and 108 h and 18, 9, 9 mg kg(-1) for neonates between 108 and 180 h.

Source: Medline
Available in fulltext from British Journal of Clinical Pharmacology at National Library of Medicine
Available in print from British journal of clinical pharmacology; Notes: ULHT journal article requests. Complete the online form to obtain articles.
Available in fulltext from British Journal of Clinical Pharmacology at EBSCOhost
When the echocardiographic PDA flow pattern was used as a guide for PDA treatment, fewer doses of drugs were needed to achieve acceptable closing rates.

Source: EMBASE

Available in fulltext from Archives of Disease in Childhood. Fetal and Neonatal Edition at National Library of Medicine

Available in fulltext from Archives of Disease in Childhood - Fetal and Neonatal Edition at Highwire Press

Available in print from Archives of Disease in Childhood -- Fetal & Neonatal Edition

Notes: ULHT journal article requests. Complete the online form to obtain articles.

23. Comparison of oral ibuprofen and indomethacin therapy for patent ductus arteriosus in preterm infants.

Author(s) Fakhraee SH, Badiee Z, Mojtahedzadeh S, Kazemian M, Kelishadi R

Citation: Zhongguo Dangdai Erke Zazhi, October 2007, vol./is. 9/5(399-403), 1008-8830;1008-8830 (2007 Oct)

Publication Date: October 2007

Abstract: OBJECTIVE: Intravenous indomethacin is the conventional treatment for patent ductus arteriosus (PDA) in preterm infants; however its use is associated with various side effects such as oliguria, gastrointestinal bleeding and reduction of cerebral perfusion. Intravenous ibuprofen has recently been used to treat PDA in preterm infants without reducing cerebral blood flow or affecting intestinal or renal hemodynamics. Intravenous forms of indomethacin and ibuprofen are not available in Iran. This study aimed to examine and compare the efficacy and safety of oral ibuprofen and oral indomethacin for the treatment of PDA in preterm infants.METHODS: Thirty-six infants (gestational age less than 34 weeks) who had echocardiographically confirmed PDA were enrolled in this study. The patients were randomly administered with three oral doses of either indomethacin (0.2 mg/kg, at an interval of 24 hrs) or ibuprofen (a first dose of 10 mg/kg, followed at an interval of 24 hrs by two doses of 5 mg/kg each) (n=18 each group). The rate of ductal closure, side effects, complications, and the infants’ clinical course were recorded.RESULTS: The ductus was closed in all of 18 patients (100%) in the ibuprofen group and in 15 (83.3%) patients in the indomethacin group (P > 0.05). There were no significant differences in the levels of serum blood urea nitrogen and creatinine between the two groups before and after treatment. Necrotizing enterocolitis (NEC) occurred in 3 patients in the indomethacin group and none in the ibuprofen group (P < 0.05). The survival rate at 1 month after treatment was 94% (17/18) in both groups. One infant in the ibuprofen group died from sepsis and one in the indomethacin group died as a result of NEC.CONCLUSIONS: Oral ibuprofen is as effective as oral indomethacin for the treatment of PDA in preterm infants. Oral ibuprofen therapy is associated with a lower incidence of NEC.

Source: Medline


Author(s) Cherif A, Jabnoun S, Khrouf N

Citation: American Journal of Perinatology, 01 June 2007, vol./is. 24/6(339-345), 07351631

Publication Date: 01 June 2007

Abstract: Intravenous indomethacin and intravenous ibuprofen are widely used for the treatment of patent ductus arteriosus (PDA) in premature infants. Intravenous indomethacin may lead to renal impairment, enterocolitis, and intraventricular hemorrhage. Intravenous ibuprofen was shown to be as effective and to cause fewer side effects. If ibuprofen is
effective intravenously, it will probably be effective orally, too. This study was conducted to
test oral ibuprofen in early curative closure of PDA in very premature infants hoping for a
to the same efficacy as intravenous ibuprofen. Forty very premature
infants (mean gestational age: 29.4 +/- 1 to 2 weeks [range: 26 to 31.5 weeks]; mean
weight: 1237.2 +/- 198 g [range: 650-1770 g]) with PDA and respiratory distress were
studied prospectively. They received, while between 48 and 96 hours old, oral ibuprofen at
a dose of 10 mg/kg, followed, if needed, at 24-hour intervals by one or two additional doses
of 5 mg/kg each. Color Doppler echography of the heart, brain, and abdomen were
performed before treatment and after each dose administration. Ductal closure, early
outcome (1 week after treatment), and late outcome were recorded. Thirty-eight patients
(95%) achieved pharmacological closure. Two patients did not respond to the treatment:
One required surgical ligation of the ductus, and the other patient received and well
tolerated ductal shunting. Twenty-four patients were treated with one dose of oral
ibuprofen, 10 were treated with two doses, and 6 were treated with three doses. Early
outcome showed no case of renal impairment, no significant differences in serum creatinine
levels, nine cases (22.5%) of intraventricular hemorrhage, three cases (7.5%) of necrotizing
enterocolitis, and two cases (5%) of gastrointestinal bleeding. Late outcome showed 15
cases (37.5%) of nosocomial sepsis, 3 cases (7.5%) of chronic lung disease, 2 cases (5%)
of periventricular leukomalacia, and 17 cases of death. In this study, oral ibuprofen was
effective and well tolerated for early curative closure of PDA in very premature infants.
Nevertheless, larger randomized comparative studies with pharmacokinetics measures are
warranted.

Source: CINAHL
Available in print from American journal of perinatology; Notes: ULHT journal article
requests. Complete the online form to obtain articles.

25. Safety and efficacy of ibuprofen versus indomethacin for the treatment of patent
ductus arteriosus in the preterm infant: reviewing the evidence.

Author(s)
Citation: Neonatal Network, 01 May 2007, vol./is. 26/3(187-200), 07300832
Publication Date: 01 May 2007
Source: CINAHL
Available in print from Neonatal Network: the Journal of Neonatal Nursing; Notes: ULHT
journal article requests. Complete the online form to obtain articles.
Available in fulltext from Neonatal Network at EBSCOhost
Available in print from Neonatal Network: the Journal of Neonatal Nursing; Notes: Use
the link to request articles from the library. Complete the appropriate online form and press
'Send'.

26. Oral Ibuprofen and ductus arteriosus in premature infants: a randomized pilot
study.

Author(s) Aly H, Lotfy W, Badrawi N, Ghawas M, Abdel-Meguid IE, Hammad TA
Citation: American Journal of Perinatology, May 2007, vol./is. 24/5(267-70), 0735-
1631;0735-1631 (2007 May)
Publication Date: May 2007
Abstract: The purpose of this study was to evaluate the feasibility of the use oral ibuprofen
suspension (OIS) in the treatment of patent ductus arteriosus (PDA) in premature infants.
Premature infants (<35 weeks) age 2 to 7 days who suffered from respiratory distress
and had been diagnosed with PDA were included in this study. Color Doppler
echocardiography (ECHO) was used to measure the internal ductal diameter, pressure
gradient, and the ratio of left atrial to aortic root diameters (La/Ao). Infants were randomly assigned to one of two groups: group I received three doses of intravenous (IV) indomethacin (0.2 mg/kg at 12-hour intervals) and group O received an initial dose of OIS (10 mg/kg), followed by two doses of 5 mg/kg each, after 24 and 48 hours. A follow-up ECHO was done after treatment by the same pediatric cardiologist who was blinded to the assignment of the study groups. Changes in blood platelet count, hematocrit, blood urea nitrogen, and creatinine were compared between groups. In total, 78 premature infants were screened: 21 had been diagnosed with PDA. Infants in group I (n = 9) and group O (n = 12) did not differ in birthweight (1884 +/- 485 versus 1521 +/- 398 g [mean +/- SD]; P = 0.13), gestational age (32.9 +/- 1.6 versus 31.2 +/- 2.5 weeks; P = 0.07), internal diameter of PDA (2.3 +/- 0.5 versus 2.1 +/- 0.5 mm; P = 0.34), pressure gradient across PDA (12.83 +/- 6.46 versus 11.11 +/- 4.5 mm Hg; P = 0.48), and La/Ao ratio (1.26 +/- 0.21 versus 1.17 +/- 0.12; P = 0.25). Closure of PDA was achieved in 78% (seven of nine) of infants in group I and in 83% (10 of 12) of infants in group O. Comparisons of laboratory changes following treatment in group I and group O were as follows: decrease in hematocrit (-6.5 +/- 6.6 versus -1.2 +/- 4.2; P = 0.04) and in platelet count (-54 +/- 67 versus -1 +/- 53 x 10^3/muL; P = 0.24), and increase in blood urea nitrogen (16.4 +/- 16.4 versus 2.1 +/- 17.4 mg/dL; P = 0.06) and serum creatinine (0.12 +/- 0.22 versus -0.06 +/- 0.19 mg/dL; P = 0.13). Two infants in group I had severe pulmonary hemorrhage, whereas there were none in the group O. Oral ibuprofen could be an easy-to-administer and efficacious alternative in the treatment of PDA.

Source: Medline
Available in print from American journal of perinatology; Notes: ULHT journal article requests. Complete the online form to obtain articles.


Author(s) Markham M
Citation: Newborn & Infant Nursing Reviews, 01 September 2006, vol./is. 6/3(151-157), 15273369
Publication Date: 01 September 2006
Abstract: The ductus arteriosus (DA) connects the main pulmonary artery and the aorta in the fetus. Although the term infant DA almost always closes in the first three days of postnatal life, that of the preterm infant can be present for weeks to months. The frequency of diagnosis and rate of complications due to patent ductus arteriosus (PDA) are inversely proportional to gestational age. This vascular connection between pulmonary and systemic circulations can lead to the "stealing" of blood from systemic organs supplied by the aorta. Furthermore, with left-to-right shunting across the DA, the preterm lung is challenged with increased pulmonary blood flow. Although these complications can be serious, many infants with a PDA are asymptomatic. Despite monumental advances in neonatal care over the last 20 years, the best approach to management of PDA in preterm infants remains unclear. Clinical practice still varies widely with regard to treatment. Copyright © 2006 by Elsevier Inc.

Source: CINAHL
Available in print from Newborn & Infant Nursing Reviews; Notes: ULHT journal article requests. Complete the online form to obtain articles.

28. Pulmonary hypertension following L-lysine ibuprofen therapy in a preterm infant with patent ductus arteriosus.

Author(s) Bellini C, Campone F, Serra G
Citation: CMAJ Canadian Medical Association Journal, June 2006, vol./is. 174/13(1843-4), 0820-3946;1488-2329 (2006 Jun 20)
Abstract: Patent ductus arteriosus is one of the most common congenital abnormalities found in premature infants. Ibuprofen, a nonsteroidal drug that is commonly used as an antipyretic, analgesic and anti-inflammatory agent, is also used to induce closure of symptomatic patent ductus arteriosus in preterm infants. Recently, we gave L-lysine ibuprofen to a preterm infant with respiratory distress to induce closure of a patent ductus arteriosus, and the infant experienced pulmonary hypertension. Only 3 cases of pulmonary hypertension following early administration of an ibuprofen solution buffered with tromethamine have previously been reported. However, this severe side effect has never been observed in multicentre, randomized, double-blind controlled trials, nor in recent reviews or meta-analyses of L-lysine ibuprofen use.

Source: Medline
Available in fulltext from CMAJ: Canadian Medical Association Journal at EBSCOhost


Author(s) Sangtawesin V, Sangtawesin C, Raksasinborisut C, Sathirakul K, Kanjanapattanakul W, Khorana M, Horpaopan S

Citation: Journal of the Medical Association of Thailand, March 2006, vol./is. 89/3(314-21), 0125-2208;0125-2208 (2006 Mar)

Publication Date: March 2006

Abstract: BACKGROUND: The oral suspension form of ibuprofen has been shown to have the same efficacy and safety as indomethacin in the treatment of symptomatic PDA, however its role is still questionable in the prophylaxis of symptomatic PDA.OBJECTIVES: 1. To assess the efficacy and safety of the drug in the prevention of symptomatic PDA in premature infants. 2. To study its pharmacokinetics-pharmacodynamics relationship.MATERIAL AND METHOD: A randomized, single-blinded, controlled study was performed on premature neonates with a gestational age between 28-32 weeks, birthweight < or = 1500 grams at the neonatal unit, Queen Sirikit National Institute of Child Health from July 2003 to April 2004. Three doses of ibuprofen suspension or placebo were given 24 hours apart. Clinical evaluation was performed daily until the 28th day of life. Echocardiogram was performed prior to the drug administration, on the 3rd and 7th day of life.RESULTS: There were 22 and 20 cases in the ibuprofen and control group respectively. The epidemiologic data between the groups before enrollment showed no significant differences. Prevalence of symptomatic PDA was lower in the ibuprofen than in the control group without any significant side effects (0/22 vs 5/20, p = 0.015 on day 3 and 0/22 vs 6/20, p = 0.006 on day 7). Comparing with the pharmacokinetic study in older children and adult, the present study revealed nearly the same Cmax but longer Tmax and T1/2 in premature neonates.CONCLUSION: Oral ibuprofen suspension could reduce the prevalence of symptomatic PDA without any significant side effects.

Source: Medline
Available in print from Journal of the Medical Association of Thailand = Chotmaihet thangphaet; Notes: ULHT journal article requests. Complete the online form to obtain articles.

30. Effects of ibuprofen and indomethacin on urinary antidiuretic hormone excretion in preterm infants treated for patent ductus arteriosus.
Author(s) Zanardo V, Vedovato S, Lago P, Piva D, Faggian D, Chiozza L

Citation: Fetal Diagnosis & Therapy, November 2005, vol./is. 20/6(534-9), 1015-3837;1015-3837 (2005 Nov-Dec)

Publication Date: November 2005

Abstract: OBJECTIVE: To compare the effects of intravenous ibuprofen and indomethacin for treatment of patent ductus arteriosus (PDA) on urinary antidiuretic hormone (ADH) excretion, as a cause of oliguria.STUDY DESIGN: Forty-four respiratory distress syndrome prematures (<or=34 weeks' gestation) with PDA received either ibuprofen (n = 22) in an initial dose of 10 mg/kg followed by two doses of 5 mg/kg each after 24 and 48 h or three doses at 12-hour intervals of indomethacin (n = 24), 0.2 mg/kg, both infused continuously over a period of 15 min. Urinary ADH excretion, diuresis, serum creatinine, urinary sodium, fractional excretion of sodium, and urinary osmolality were measured before and after treatment.RESULTS: Indomethacin treatment caused a significant decrease in urinary ADH excretion (21.8 +/- 20.8 vs. 13.8 +/- 12.9 pg/ml; p < 0.05), along with a significant reduction in urinary sodium (92.1 +/- 36.1 vs. 64.8 +/- 35.6; p < 0.05), fractional excretion of sodium (68.5 +/- 37.1 vs. 45.6 +/- 37.1; p < 0.05), and urinary osmolality (276.2 +/- 103.9 vs. 226.4 +/- 60.3; p < 0.05). Ibuprofen treatment did not modify urinary ADH excretion and caused a statistically insignificant decrease in urinary sodium and in fractional excretion of sodium.CONCLUSIONS: Compared with ibuprofen, indomethacin caused a significant reduction in urinary ADH excretion and a significant decrease in urinary sodium and osmolality. Copyright (c) 2005 S. Karger AG, Basel.

Source: Medline

Available in print from Fetal diagnosis and therapy; Notes: ULHT journal article requests. Complete the online form to obtain articles.

Available in fulltext from Fetal Diagnosis and Therapy at EBSCOhost

31. Prophylactic ibuprofen in premature infants: A multicentre, randomised, double-blind, placebo-controlled trial

Author(s) Van Overmeire B., Allegaert K., Casaer A., Debauche C., Decaluwe W., Jespers A., Weyler J., Harrewijn I., Langhendries J.-P.

Citation: Lancet, November 2004, vol./is. 364/9449(1945-1949), 0140-6736 (27 Nov 2004)

Publication Date: November 2004

Abstract: Background Ibuprofen is used for treatment and prevention of patent ductus arteriosus in low-birthweight infants. Its effects on regional circulations differ from those of indometacin. Because prophylactic indomelacin reduces the frequency of severe intraventricular haemorrhage and patent ductus arteriosus, we aimed to study the efficacy of early ibuprofen in reducing these outcomes in a double-blind, multicentre trial. Methods Within 6 h after birth, 415 low-birthweight infants (gestational age <31 weeks) were randomly allocated ibuprofen-lysine (10 mg/kg then two doses of 5 mg/kg after 24 h and 48 h) or placebo intravenously. The primary outcome was occurrence of severe intraventricular haemorrhage; secondary outcomes were occurrence of patent ductus arteriosus and possible adverse effects of ibuprofen. Analysis was by intention to treat. Findings 17 (8%) of 205 infants assigned ibuprofen and 18 (9%) of 210 assigned placebo developed severe intraventricular haemorrhage (relative risk 097 [95% CI 051-182]). In 172 (84%) infants of the ibuprofen group, the ductus was closed on day 3 compared with 126 (60%) of the placebo group (relative risk 140 [123-159] ). No important differences in other outcomes or side-effects were noted; however, urine production was significantly lower on day 1 and concentration of creatinine in serum was significantly higher on day 3 after ibuprofen. Interpretation Ibuprofen prophylaxis in preterm infants does not reduce the frequency of intraventricular haemorrhage, but does decrease occurrence of patent ductus arteriosus.

Source: EMBASE

Available in print from Lancet; Notes: Use the link to request articles from the library.
32. Spontaneous intestinal perforation after oral ibuprofen treatment of patent ductus arteriosus in two very-low-birthweight infants.

Author(s): Tatli MM, Kumral A, Duman N, Demir K, Gurcu O, Ozkan H

Citation: Acta Paediatrica, July 2004, vol./is. 93/7(999-1001), 0803-5253;0803-5253 (2004 Jul)

Publication Date: July 2004

Abstract: AIM: To discuss intestinal side effects of ibuprofen in the treatment of patent ductus arteriosus, after having observed two cases of spontaneous intestinal perforation following ibuprofen treatment. METHODS: Clinical and laboratory records of two preterm infants, who developed intestinal perforation after ibuprofen administration, were evaluated. RESULTS: Gestational ages of infants were 29 wk (male) and 30 wk (female). Both infants developed intestinal perforations without signs of necrotizing enterocolitis. The perforations cured with Penrose drainage alone. CONCLUSION: Although ibuprofen is a reasonable treatment alternative to indomethacin, randomized controlled trials, which address potential adverse effects including spontaneous intestinal perforation, are needed.

Source: Medline

Available in print from Acta paediatrica (Oslo, Norway : 1992); Notes: ULHT journal article requests. Complete the online form to obtain articles.

Available in fulltext from Acta Paediatrica at EBSCOhost

33. Is indomethacin or ibuprofen better for medical closure of the patent ductus arteriosus?

Author(s): Swartz EN

Citation: Archives of Disease in Childhood, 01 December 2003, vol./is. 88/12(1134-1135), 00039888

Publication Date: 01 December 2003

Source: CINAHL

Available in fulltext from Archives of Disease in Childhood at National Library of Medicine

Available in print from Archives of disease in childhood; Notes: ULHT journal article requests. Complete the online form to obtain articles.

Available in fulltext from Archives of Disease in Childhood at Highwire Press

Available in fulltext from Archives of Disease in Childhood at Highwire Press
34. Closure of patent ductus arteriosus with oral ibuprofen suspension in premature newborns: a pilot study.

Author(s) Heyman E, Morag I, Batash D, Keidar R, Baram S, Berkovitch M

Citation: Pediatrics, 02 November 2003, vol./is. 112/5(0-), 00314005

Publication Date: 02 November 2003

Abstract: OBJECTIVE: Patent ductus arteriosus (PDA), a common finding among premature infants, is conventionally treated by intravenous indomethacin. Intravenous ibuprofen was recently shown to be as effective and to have fewer adverse reactions in preterm infants. If equally effective, then oral ibuprofen for PDA closure would have several important advantages over the intravenous route. This study was designed to determine whether oral ibuprofen treatment is efficacious and safe in closure of a PDA in premature infants with respiratory distress syndrome. METHODS: Twenty-two preterm newborns (gestational age: 27.5 +/- 1.75 [range: 23.9-31 weeks]; weight: 979 +/- 266 [range: 380-1500 g]) with PDA and respiratory distress syndrome were studied prospectively. They received oral ibuprofen suspension 10 mg/kg/body weight for the first dose, followed at 24-hour intervals by 2 additional doses of 5 mg/kg each, if needed, starting on the second day of life. Echocardiography was performed before treatment and 24 hours after each dose. Every child underwent cranial ultrasonography before and after each ibuprofen dose. The rate of ductal closure, the need for additional treatment, side effects, complications, and the infants’ clinical courses were recorded. RESULTS: Ductal closure was achieved in all newborns except for 1 (95.5%), in whom clinically nonsignificant ductal shunting persisted. No infant required surgical ligation of the ductus. There was no reopening of the ductus after closure had been achieved. Fourteen newborns were treated with 1 dose of ibuprofen, 6 were treated with 2 doses, and the remaining 2 were treated with 3 doses. The survival rate at 1 month was 86.4% (19 of 22). Three (13.6%) infants died from the following causes: 1 who was born at 24 weeks’ gestation with a birth weight of 380 g died as a result of extreme prematurity complications, necrotizing enterocolitis, and low birth weight; 1 died as a result of Candida sepsis; and the third died as a result of Klebsiella sepsis. Intraventricular hemorrhage was observed in 7 infants. The classification was changed from grade 2 to grade 3 in 1 and from grade 0 to grade 1 or higher in 3 others. The rate of survival to discharge was 86.4% (19 of 22). No bronchopulmonary dysplasia was observed in the study group, and there was no case of tendency to bleed. There were no significant differences in the levels of serum creatinine before and after treatment with oral ibuprofen. CONCLUSIONS: Oral ibuprofen suspension may be an effective and safe alternative for PDA closure in premature infants with PDA. However, larger comparative studies are warranted.

Source: CINAHL

Available in print from Pediatrics; Notes: ULHT journal article requests. Complete the online form to obtain articles.

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Available in print from Pediatrics; Notes: Use the link to request articles from the library. Complete the appropriate online form and press ‘Send’.

Available in fulltext from Pediatrics at Highwire Press

Available in fulltext from Pediatrics at American Academy of Pediatrics

35. A comparison of oral ibuprofen and intravenous indomethacin for closure of patent ductus arteriosus in preterm infants.

Author(s) Chotigeat U, Jirapapa K, Layangkool T

Citation: Journal of the Medical Association of Thailand, August 2003, vol./is. 86 Suppl 3/(S563-9), 0125-2208:0125-2208 (2003 Aug)

Publication Date: August 2003
Abstract: BACKGROUND: Indomethacin is widely accepted as the treatment for patent ductus arteriosus (PDA) in preterm infants but it has various side effects. Ibuprofen is the alternative treatment and believed to be less likely to induce side effects. OBJECTIVE: To compare efficacy and side effects of ibuprofen versus indomethacin treatment for symptomatic patent ductus arteriosus (PDA) in preterm infants. METHOD: The authors studied 30 infants (gestational age ≤ 35 weeks, aged ≤ 10 days) who were diagnosed as having symptomatic PDA confirmed by echocardiogram. The infants were randomly assigned to receive three intravenous doses of indomethacin given at 12-hour intervals or three doses of ibuprofen given at 24-hour intervals, starting within ten days of life. The demographic data, rate of clinical closure, need for additional treatment, side effects, complications and the infants’ clinical course were recorded within 28 days. RESULTS: The rate of ductal closure was similar with the two treatment regimes. Ductal closure occurred in 7 of 15 infants given ibuprofen (46.67%) and 10 of 15 infants given indomethacin (66.67%). (Relative risk 0.669; 95% confidence interval, 0.328 to 1.364; p = 0.462) The number of infants who needed a second pharmacologic treatment was not significantly different between the two groups, (6 cases in the ibuprofen group, 5 cases in the indomethacin group) but surgical ligation was performed in two cases in the indomethacin group. There was a significant difference in using the diuretic drug (furosemide) in the indomethacin group (11 cases), compared to the ibuprofen group (3 cases), (p = 0.009). More cases of necrotizing enterocolitis were seen in the indomethacin group (66.67% compared to 40% in the ibuprofen group) but there was no statistically significant difference. CONCLUSION: Ibuprofen has the same efficiency as indomethacin for the treatment of symptomatic patent ductus arteriosus in preterm infants and less likely to induce necrotizing enterocolitis and renal toxicity than indomethacin.

Source: Medline
Available in print from Journal of the Medical Association of Thailand = Chotmaihet thangphaet; Notes: ULHT journal article requests. Complete the online form to obtain articles.

36. The use of ibuprofen in neonates in the treatment of patent ductus arteriosus

Author(s) Van Overmeire B.

Citation: International Journal of Clinical Practice, Supplement, April 2003, vol./is./135(23-27), 1368-504X (April 2003)

Publication Date: April 2003

Abstract: Indomethacin has long been used to treat patent ductus arteriosus but it is associated with a relatively high risk of adverse effects; recent evidence suggests that ibuprofen is effective and may be safer. In a randomised trial to compare the efficacy and safety of ibuprofen and indomethacin in the treatment of patent ductus arteriosus, 144 infants received three doses of ibuprofen lysine (10, 5 and 5 mg/kg) at 24-hour intervals or indomethacin 0.2 mg/kg at 12-hour intervals. Ductal closure occurred in 70% of children treated with ibuprofen and 66% of those given indomethacin on the first treatment (P =0.41). Nineteen children underwent surgical ligation, equally distributed between the treatment groups (P = 0.81). Urine production was significantly greater than in children given indomethacin from day 3 to day 7 and the serum creatinine concentration was significantly lower from day 7. Ductal closure was associated with higher serum concentrations of ibuprofen and a concentration of 10-12 mg/l appears to be the minimum level for efficacy. In a randomised, placebo-controlled, double-blind trial of prophylaxis with ibuprofen, the rate of patent ductus arteriosus associated with ibuprofen was 19% compared with 42% with placebo. Urine output was comparable in the two groups except on day 1, when it was significantly lower among infants given ibuprofen. Ibuprofen is therefore as effective as indomethacin in the treatment of patent ductus arteriosus, and effective as prophylaxis, in premature infants.

Source: EMBASE
Available in print from International journal of clinical practice, Supplement; Notes: ULHT journal article requests. Complete the online form to obtain articles.
37. Ibuprofen: alternative treatment for patent ductus arteriosus.

**Author(s)** Flores M

**Citation:** Neonatal Network, 01 March 2003, vol./is. 22/2(27-35), 07300832

**Publication Date:** 01 March 2003

**Abstract:** Patent ductus arteriosus (PDA) is a common problem for premature babies. Indomethacin, traditionally the treatment of choice for PDA closure, varies in effectiveness and can have serious side effects, such as intraventricular cerebral hemorrhage and decreased mesenteric and renal blood flow. Researchers abroad are examining the efficacy and safety of ibuprofen as an alternative PDA therapy. Their findings have been promising and indicate the need for clinical trials in the U.S.

**Source:** CINAHL

Available in print from Neonatal Network: the Journal of Neonatal Nursing; Notes: ULHT journal article requests. Complete the online form to obtain articles.

38. Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: a randomised controlled trial.

**Author(s)** Lago P, Bettiol T, Salvadori S, Pitassi I, Vianello A, Chiandetti L, Saia OS

**Citation:** European Journal of Pediatrics, April 2002, vol./is. 161/4(202-7), 0340-6199;0340-6199 (2002 Apr)

**Publication Date:** April 2002

**Abstract:** Indomethacin (INDO) and, more recently, ibuprofen (IBU) have been used to treat haemodynamically significant patent ductus arteriosus (PDA) in preterm infants. Both are cyclo-oxygenase blockers, but seem to have a different influence on regional circulation. In a prospective, randomised, controlled study, we compared INDO and IBU with regard to efficacy and safety for the early non-invasive treatment of PDA. Doppler echocardiography was used to study 232 preterm infants (gestational age 23-34 weeks) with respiratory distress syndrome of whom 175 had persistent, haemodynamically significant PDA at 48-72 h of life. They were randomised to receive three intravenous doses of either INDO (0.2 mg/kg, at 12 h intervals) or IBU (a first 10 mg/kg dose followed by two doses of 5 mg/kg at 24 h intervals), recording rate of ductal closure, need for additional treatment, side-effects and clinical course. The efficacy of the pharmacological treatment was similar in the two groups (56/81, 69% INDO; 69/94, 73% IBU). Patients treated with INDO showed a significant increase in serum creatinine (89 +/- 24 versus 82 +/- 20 mmol/l, P = 0.03) and a near-significant tendency for a lower fractional excretion of sodium (3 +/- 3 versus 4 +/- 2%, P = 0.08); moreover, 12/81 (15%) INDO patients versus 1/94 (1%) IBU patients became oliguric (< 1 ml/kg per h) during treatment (P = 0.017).

**CONCLUSION:** Our findings confirm that, by comparison with indomethacin, ibuprofen has fewer effects on renal function in terms of urine output and fluid retention, with much the same efficacy and safety in closing patent ductus arteriosus in preterm infants with respiratory distress syndrome. In particular, no increased incidence of intracranial haemorrhage was observed after ibuprofen treatment.

**Source:** Medline

Available in print from European journal of pediatrics; Notes: ULHT journal article requests. Complete the online form to obtain articles.
Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial.


Citation: Lancet, January 0001, vol./is. 364/9449(1939-44), 0140-6736;1474-547X (2004 Nov 27-Dec 3)

Publication Date: January 0001

Abstract: BACKGROUND: Patent ductus arteriosus is a common complication of prematurity that frequently requires surgical or medical treatment. The benefit of prophylactic treatment by indometacin, a cyclo-oxygenase inhibitor, remains uncertain compared with curative treatment. This benefit could be improved with ibuprofen, another cyclo-oxygenase inhibitor with fewer adverse effects than indometacin on renal, mesenteric, and cerebral perfusion. We aimed to compare prophylactic and curative ibuprofen in the treatment of this abnormality in very premature infants.

METHODS: We did a randomised controlled trial in infants younger than 28 weeks of gestation, who were randomly assigned to receive either three doses of ibuprofen or placebo within 6 h of birth. After day 3, symptomatic patent ductus arteriosus was treated first by open curative ibuprofen, then back-up indometacin, surgery, or both. The primary endpoint was need for surgical ligation. Analysis was per protocol.

FINDINGS: The study was stopped prematurely after 135 enrollments because of three cases of severe pulmonary hypertension in the prophylactic group. 65 infants received prophylactic ibuprofen, and 66 received placebo. Prophylaxis reduced the need for surgical ligation from six (9%) to zero (p=0.03), and decreased the rate of severe intraventricular haemorrhage from 15 (23%) to seven (11%) (p=0.10). However, survival was not improved (47 [71%] placebo vs 47 [72%] treatment, p=1.00), because of high frequency of adverse respiratory, renal, and digestive events.

INTERPRETATION: In premature infants, prophylactic ibuprofen reduces the need for surgical ligation of patent ductus arteriosus, but does not reduce mortality or morbidity. Therefore, it should not be preferred to early curative ibuprofen.

Source: Medline

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... preterm neonates. KEYWORDS. Ibuprofen - patent ductus arteriosus - premature newborn - cyclooxygenase inhibitors - randomized clinical trial.