



eNeonatal Review

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In this issue...Volume 2, Number 8

In the fetus, the ductus arteriosus (DA) connects the pulmonary artery to the aorta. The subsequent right-to-left shunt through the DA is critical for maintaining systemic circulation. A brief period of right-to-left shunting after birth may also be important as the left ventricle adapts to its new role as the dominant pumping chamber. Thereafter, in healthy term infants, the DA closes, usually by three days of life. However, in preterm infants, particularly those with lung disease, there is a tendency for the DA to remain open. Hence, "patent ductus arteriosus" (or PDA) is a common diagnosis in these infants.

There is a strong association between the presence of a patent ductus arteriosus (PDA) in preterm infants and the development of chronic lung disease (CLD). The association with other morbidities is less clear. In addition, in some animal models, left-to-right shunting through a PDA results in abnormalities in pulmonary function. These observations have led many clinicians to conclude that a PDA contributes to the pathophysiology of CLD and that treatments to prevent or close the PDA will reduce the likelihood of CLD (and perhaps other morbidities). These treatments include the use of prostaglandin inhibitors such as indomethacin (and, less commonly, ibuprofen), as well as surgical ligation. However, despite nearly three decades of research, the question of whether these treatments improve outcome remains unanswered. The lack of placebo controlled trials without significant treatment of infants in the control group creates a challenge for clinicians who must decide whether or when to treat a PDA.

In this month's issue, we review treatment strategies for closing the PDA. These strategies are divided into a) preventive or prophylactic treatment designed to affect closure and prevent left-to-right shunting, and b) treatment strategies designed to close the PDA after documentation of patency. Herein we review evidence regarding the effect of these treatments on morbidities associated with prematurity and the limitations of these studies.

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Learning Objectives

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CE activity.

At the conclusion of this activity, participants should be able to:

- Identify common management strategies for treatment of the patent ductus arteriosus;
- Identify the effect of treatment of the patent ductus arteriosus on neonatal morbidities;
- Understand the limitations of the studies of treatment of the patent ductus arteriosus.

Program Information

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→ **PROPHYLACTIC IBUPROFEN THERAPY**

→ **INDOMETHACIN THERAPY FOR ASYMPTOMATIC PDA**

Guest Editors of the Month



Commentary

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Reviews

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Guest Faculty Disclosure

Carl L. Bose, MD

Faculty Disclosure: No relationship with commercial supporters.

Matthew M. Laughon, MD, MPH

Faculty Disclosure: No relationship with commercial supporters.

Unlabelled/Unapproved Uses:

The following faculty members have disclosed that their presentation will reference unlabeled/unapproved use of drugs or products.

Carl L. Bose, MD

Has indicated that the presentation includes information on uses of indomethacin and ibuprofen that are not approved in children.

Matthew M. Laughon, MD, MPH

Has indicated that the presentation includes information on uses of indomethacin and ibuprofen that are not approved in children.

0.5 hours

EXPIRATION DATE

April 15, 2007

NEXT ISSUE

May 15, 2005

COMMENTARY

In preterm infants, patency of the DA has been associated with a variety of morbidities, most notably chronic lung disease (CLD)¹. Because of this association, many clinicians assume that the PDA is pathologic and contributes to the development of these morbidities. Belief in this principle has been so well established for such a long period of time that virtually all clinical trials in the modern era have focused on determining the most expeditious way in which to close a PDA. None have addressed the more fundamental question of whether

closing the PDA improves outcome. The trials that included control groups treated with a placebo permitted, in fact prescribed, treatment of any PDA that persisted for even a brief period after study enrollment. This study design has resulted in high rates of cross-over (usually in the range of 40%) and has markedly handicapped our ability to answer the core question of whether closure of the PDA influences outcome. Additionally, our ability to detect adverse effects of treatment is equally compromised. Further, the message from clinical trials is not encouraging: meta-analyses and large randomized, controlled trials of the use of medical therapies for the prevention and treatment of PDAs have not documented a decrease in the incidence of significant morbidities following treatment, despite success in closure of the PDA²⁻⁶.

Patency of the DA may represent normal physiologic adaptation during the early hours of life, and may be critical for maintenance of systemic circulation in the presence of severe lung disease. Therefore, closure under these circumstances may be hazardous (although outside of these limited settings, the risks may be less). Unfortunately, the use of prostaglandin inhibitors is not benign. These drugs have potent effects on vasculature and organ perfusion, an association between their use and necrotizing enterocolitis has been reported, and recent data suggests that the coincidental use of indomethacin and corticosteroids may cause intestinal perforation⁷.

From the research presented, we believe that prophylactic treatment of the PDA with prostaglandin inhibitors is contraindicated, particularly in the first day of life, and that therapies designed to close the DA should not be considered a "standard of care" until such time as these therapies have been proven to decrease long term clinical morbidities in properly controlled trials. Clinicians who treat a PDA should have a clear and important objective of treatment (e.g. reduction of a significant morbidity) and understand that the treatment will have uncertain benefit and risk.

SOURCES FOR ADDITIONAL INFORMATION:

1. **Rojas MA, Gonzalez A, Bancalari E, Claire N, Poole C, Silva-Neto G.** [Changing trends in the epidemiology and pathogenesis of neonatal chronic lung disease.](#) J Pediatr 1995; 126:605-10
2. **Fowlie PW, Davis PG.** [Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants.](#) Cochrane Database Syst Rev 2002:CD000174.
3. **Schmidt B, Davis P, Moddemann D, et al.** [Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants.](#) N Engl J Med 2001; 344:1966-72.
4. **Cooke L, Steer P, Woodgate P.** [Indomethacin for asymptomatic patent ductus arteriosus in preterm infants.](#) Cochrane Database Syst Rev 2003:CD003745.
5. **Gournay V, Roze JC, Kuster A, et al.** [Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial.](#) Lancet 2004; 364:1939-44.
6. **Van Overmeire B, Allegaert K, Casaer A, et al.** [Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial.](#) Lancet 2004; 364:1945-9.
7. **Watterberg KL, Gerdes JS, Cole CH, et al.** [Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial.](#) Pediatrics 2004; 114:1649-57.

OVERVIEW OF TREATMENT STRATEGIES OF THE PDA

Laughon MM. Simmons MA. Bose CL.
Patency of the ductus arteriosus in the premature infant: is it pathologic? Should it be treated?



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Current Opinion in Pediatrics. 2004 Apr;16(2):146-51.
(For non-journal subscribers, an additional fee may apply for full text articles)

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Knight DB.

The treatment of patent ductus arteriosus in preterm infants. A review and overview of randomized trials.

Seminars in Neonatology. 2001; 6:63-73.

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Reviewing the Pathophysiology of PDA and the impact of treatment strategies on outcomes.

While a PDA is associated with the development of CLD, Laughon et al. stress that treatment does not modify the risk of this disease. In addition, although the treatment of a PDA with the goal of closure is a common practice, it should not be considered a "standard of care". Finally, the authors emphasize the need for randomized, controlled trials to determine the risks and benefits of treatment of a PDA that examine not only short-term outcomes (closure of PDA, PDA ligation), but more importantly longer-term, clinically relevant endpoints (CLD, neurodevelopmental outcome).

The systematic review by Knight identified all of the randomized controlled trials up to 2001 of indomethacin for treatment of the PDA. The author divided 22 trials into three groups: prophylactic therapy, pre-symptomatic therapy, and symptomatic therapy. There was heterogeneity in the selection criteria, treatment regimens, and endpoints. The only consistent, significant result was the decreased incidence of PDA in the indomethacin groups (Risk Ratio or RR of 0.32 for prophylaxis and symptomatic treatment and 0.38 for pre-symptomatic treatment). There were no differences in death, retinopathy of prematurity, or necrotizing enterocolitis between the groups. Thus, the author concludes that, even though a prolonged PDA is associated with respiratory disease, closure at any particular time seems to have no influence on the development of CLD.

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PROPHYLACTIC INDOMETHACIN THERAPY

Fowlie PW. Davis PG.

Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants.

The Cochrane Database of Systematic Reviews 2002, Issue 3. CD000174

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Schmidt B. Davis P. Moddemann D et al.

Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants.

NEJM. 2001 Jun 28;344(26):1966-72.

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Schmidt B, Asztalos EV, Roberts RS, Robertson CM, Sauve RS, Whitfield MF; Trial of Indomethacin Prophylaxis in Preterms (TIPP) Investigators.

Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms.

JAMA. 2003 Mar 5;289(9):1124-9.

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Accumulating data about both long term and large scale prophylactic indomethacin use.

The Cochrane review was performed to determine the risks and benefits of prophylactic intravenous indomethacin in preterm infants. This review included only randomized, controlled trials of indomethacin therapy given within 24 hours of life. The review identified 19 studies. Although most of these studies were of high quality, the dosing regimen varied between studies and the majority examined short-term clinical outcomes only.

Treatment with prophylactic indomethacin significantly reduced the incidence of symptomatic PDA (RR = 0.44, Risk Difference or RD = -0.24) and reduced the incidence of PDA ligation (RR = 0.51, RD = -0.05). The numbers needed to treat were 4 to prevent a symptomatic PDA and 20 to prevent a PDA ligation. In addition, treatment with prophylactic indomethacin reduced all grades of intraventricular hemorrhage (RR = 0.88, RD = 0.04) and grade 3 and 4 intraventricular hemorrhage (RR = 0.66, RD = -0.05).

In the Cochrane review, the authors determined that treatment with prophylactic indomethacin did not reduce mortality or the incidence of the following morbidities: pneumothorax, duration of ventilation, duration of supplemental oxygen, or incidence of CLD (at 28 days or at 36 weeks post-menstrual age), severe developmental delay, cerebral palsy, blindness, deafness, necrotizing enterocolitis, intestinal perforation, bleeding diathesis, sepsis, or retinopathy of prematurity. In addition, prophylactic indomethacin was associated with an increase in the incidence of oliguria.

Schmidt et al performed the largest study to date investigating the risks and benefits of prophylactic indomethacin therapy in premature infants, the Trial of Indomethacin Prophylaxis in Preterms, (the TIPP study). The TIPP study was designed to determine whether the prophylactic administration of indomethacin improved survival without neurosensory impairment. This trial randomized 1202 infants with birth weights of 500 to 999 grams to receive indomethacin or placebo within 6 hours of birth. Although its primary purpose was not to investigate the effect of indomethacin on the PDA, this study adds considerably to our understanding of the effect of treatment because of the large sample size, detailed reporting correlating the PDA with a large number of neonatal morbidities, and the evaluation of long term outcome. The primary outcome was death before a corrected age of 18 months or one of the following: cerebral palsy, cognitive delay, hearing loss requiring amplification, and bilateral blindness.

In this study, administration of prophylactic indomethacin reduced the incidence of PDA, subsequent medical treatment of the PDA, and subsequent PDA ligation, but it did not reduce the incidence of CLD or other morbidities historically or putatively associated with a PDA (e.g. necrotizing enterocolitis, feeding intolerance, or retinopathy or prematurity). The estimate for the effect (risk ratio or relative risk) of prophylactic indomethacin on the development of CLD was 1.2 with a 95% confidence interval of 0.9-1.5, suggesting that the use of prophylactic indomethacin was just as likely to have had a 10% reduction as well as a 50% increase in the incidence of CLD.

These studies demonstrate that prophylactic indomethacin reduces short term morbidities such as symptomatic PDA and intraventricular hemorrhage, but does not improve long-term outcome, specifically poor neurodevelopment. Interestingly, even though prophylactic indomethacin reduces the incidence of a symptomatic PDA, it does not reduce the incidence of any pulmonary morbidity, suggesting that a causal link between PDA and CLD may not exist. In nearly all of these studies, infants in the control groups were eligible for "rescue" indomethacin treatment if they developed a PDA. Therefore, in each study, a portion of the control group was "contaminated" or "crossed-over" by receiving indomethacin treatment outside of the confines of the study. This design typically resulted in high rates of cross-over, e.g. 46%, in the TIPP Trial.

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PROPHYLACTIC IBUPROFEN THERAPY

Gournay V. Roze JC. Kuster A et al.
Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial.

Lancet. 2004 Nov 27;364(9449): 1939-44.
(For non-journal subscribers, an additional fee may apply for full text article)

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Van Overmeire B. Allegaert K. Casaer A et al.
Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial.

Lancet. 2004 Nov 27;364(9449): 1945-9.
(For non-journal subscribers, an additional fee may apply for full text article)

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Shah SS, Ohlsson A.
Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants.

Cochrane Database Syst Rev 2003; (2): CD004213.
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Reporting on a variety of prophylactic ibuprofen treatment modalities.

Two recent studies investigate the effect of prophylactic ibuprofen on preterm infants. Based on earlier small studies, compared to indomethacin, ibuprofen was presumed to have less effect on renal and mesenteric blood flow and therefore may present a lower risk profile compared to indomethacin.

Gournay et al conducted a randomized, masked, placebo-controlled trial to determine if prophylactic ibuprofen versus early curative ibuprofen in infants less than 28 weeks gestation would decrease the need for surgical ligation. Ibuprofen or placebo was administered prior to 6 hours of life. At three days of life, an echocardiogram was performed and infants with a PDA were given open-label ibuprofen. This trial enrolled 135 patients but was terminated early because of three cases of severe pulmonary hypertension in the prophylactic ibuprofen group.

Prophylactic ibuprofen decreased the incidence of PDA on the third day of life (18/65 patients [28%] in the ibuprofen group versus 36/66 [55%] in the placebo group, RR = 0.51, RD = -0.52, p=0.0018) and subsequent surgical ligation (0/65 in the ibuprofen group versus 6/66 [9%] in the placebo group, p=0.0277). There was no difference in intraventricular hemorrhage, periventricular leukomalacia, CLD at 36 weeks, duration of mechanical ventilation, survival at 36 weeks, or survival without morbidity. There was a significant increase in the prophylactic group in the incidence of oliguria, elevated creatinine, and necrotizing enterocolitis.

Van Overmeire et al also conducted a randomized, masked, placebo-controlled trial to determine if prophylactic ibuprofen versus placebo in infants 24-30 weeks gestation would decrease the incidence of severe intraventricular hemorrhage (grade 3 or 4). Ibuprofen or placebo was administered prior to 6 hours of life. At three days of life, an echocardiogram was performed and infants with a PDA were given open-label ibuprofen or indomethacin. This trial enrolled 415 patients. Prophylactic ibuprofen significantly reduced the incidence of PDA (33/205 [16%] had an open PDA at three days of life in the ibuprofen group versus 84/210 [40%] in the placebo group, RR = 0.4, RD = -0.24, p = 0.0001) and there was a trend toward significance for PDA ligation (5/205 [2%] in the ibuprofen group versus 10/210 [5%] in the placebo group, RR = 0.51, RD = -0.03, p = 0.21). There was no difference in the primary

outcome of grade 3 or 4 intraventricular hemorrhage or any of the following secondary outcomes: mortality, death, periventricular leukomalacia, or a combined outcome of CLD or death at 36 weeks post-menstrual age. There was an increase in the incidence of oliguria and elevated creatinine in the prophylactic group.

These studies suggest that prophylactic ibuprofen reduces the incidence of PDA and PDA ligation, but has no influence on clinically important outcomes such as mortality or CLD. In addition, ibuprofen inhibits renal function more frequently than previously thought. These studies also had a high rate of cross-over in the placebo groups, 38% in Gournay's study and 40% in Van Overmeire's study. Therefore, any conclusions about lack of benefit or risk should be interpreted with caution. However, at a minimum, one might safely conclude that prophylactic treatment adds no additional benefit to rescue treatment (an obligatory element of the study designs) and may be hazardous in some infants.

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INDOMETHACIN THERAPY FOR ASYMPTOMATIC PDA

Cooke L, Steer P, Woodgate P.
Indomethacin for asymptomatic patent ductus arteriosus in preterm infants.

The Cochrane Database of Systematic Reviews 2003, Issue 1. CD003745.

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Does avoiding prophylactic indomethacin preserve the therapeutic advantage?


This Cochrane review was performed to determine if the treatment of an asymptomatic (non-hemodynamically significant) PDA with indomethacin decreased mortality and morbidity in preterm infants. The rationale for this review was that, by avoiding prophylactic indomethacin and narrowing the population that received indomethacin, the therapeutic advantage might be preserved without exposing infants to the risks of therapy who would never appreciate the benefits. In order to avoid trials where indomethacin was given prophylactically, this review only included randomized, controlled trials of indomethacin therapy given after 24 hours of life.

The review identified three randomized, placebo-controlled trials with a total of 97 infants. As one might expect, there was a significant reduction in the incidence of symptomatic PDA (RR = 0.36, RD = -0.35). Interestingly, there was no significant difference between the groups in the number of PDA ligations. Additionally, there was no significant difference between treatment or control groups for the following endpoints: mortality, CLD defined as oxygen requirement at 28 days, retinopathy of prematurity (all grades), intraventricular hemorrhage (all grades), necrotizing enterocolitis, length of ventilation, or length of hospital stay. There was a small but statistically significant reduction in the duration of supplemental oxygen therapy (mean difference = -14.7 days, -28.4 to -0.98). The studies did not report neurodevelopmental outcome. As with the prophylactic trials, in all of these studies, a high proportion of infants in the control group received indomethacin. An additional caution is the lack of contemporary literature using this study design, in that the most recent study in this review was performed on relatively large infants over 15 years ago, an era prior to the use of antenatal steroids and surfactant therapy.

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Respiratory Therapists

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- Dr. Nogee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

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Matthew M. Laughon, MD, MPH

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