eNeonatal Review

Jointly Presented by The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing

Supported by an educational grant from INO Therapeutics

January 2007 VOLUME 4, NUMBER 5

eNeonatal Review is proud to announce our accredited PODCASTS for 2007. Listen here.

Participants can now receive 0.5 credits per podcast after completing an online post test. In addition to our monthly newsletters, there will be six podcasts throughout the year.

The eNeonatal Review podcast is a lively discussion between our January authors and Robert Busker, eNeonatal Review's Medical Editor.

To learn more about podcasting and how to enjoy this exciting new feature of eNeonatal Review, please visit this page.

In this issue...

Patent ductus arteriosus (PDA) is a clinical diagnosis made within the first few days of life in a premature neonate in which failure to detect a PDA can result in severe clinical complications. The incidence of PDA is up to 60% in infants <28 weeks gestational age, compared to 20% in infants >32 weeks.[1] The first-line therapy for PDA closure has been intravenous indomethacin for the past 30 years with surgical ligation for pharmacological failures. Recently, a new formulation of intravenous ibuprofen has been approved that may provide a new and potentially safer treatment approach.

In this issue, we review the clinical trial information for intravenous ibuprofen (pharmacologically related to indomethacin) for the treatment and prophylaxis of PDA, and its effect on intraventricular hemorrhage (IVH) prophylaxis.

This Issue

Guest Editors of the Month

Commentary:
Carlton K.K. Lee, Pharm.D., MPH

Assistant Professor, Department of Pediatrics
School of Medicine
Johns Hopkins University
Clinical Specialist, Pediatrics
Department of Pharmacy
The Johns Hopkins Hospital

Program Information

CE Info
Accreditation
Credit Designation
Target Audience
Learning Objectives
Faculty Disclosure
Disclaimer Statement
Internet CE Policy

Length of Activity
1.0 hours

Expiration Date
January 19, 2009

Next Issue
February 15, 2007

Complete Post Test
and Receive CME/CE Credit

Newsletter Archive
Our comprehensive library of accredited programs

Course Directors

Edward E, Lawson, M.D.
Professor

Department of Pediatrics Neonatology
The Johns Hopkins University
School of Medicine

Lawrence M. Nogee, M.D.
Associate Professor

Department of Pediatrics Neonatology
The Johns Hopkins University
School of Medicine

Christoph U. Lehmann, M.D.
Assistant Professor

Department of Pediatrics,
Health Information
Science and Dermatology
The Johns Hopkins University
School of Medicine

Mary Terhaar, RN
Assistant Professor

Undergraduate Instruction,
The Johns Hopkins University
School of Nursing

Robert J. Kopotic, MSN, RRT, FAARC
Director of Clinical Programs

ConMed Corporation

Recommend to a Colleague

Reviews:
Melissa D. Meekins, Pharm.D.

Pediatric Specialty Resident
Department of Pharmacy
The Johns Hopkins Hospital

Guest Faculty Disclosure:
Carlton K.K. Lee, Pharm.D., MPH. No relationship with commercial supporters.

Melissa D. Meekins, Pharm.D. No relationship with commercial supporters.

Unlabelled/Unapproved Uses:
This presentation will include off-label and unapproved uses of intravenous Indomethacin and Ibuprofen for prophylaxis of PDA and intraventricular hemorrhage in premature neonates as well as NeoProfen as prophylaxis for intraventricular hemorrhage and PDA in premature neonates.

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 CME/CE activity.

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

- Discuss the efficacy of IV ibuprofen compared to IV indomethacin in the treatment of PDA
- Compare the use of IV ibuprofen for prophylaxis of PDA to IV indomethacin
- Identify the role of IV ibuprofen for intraventricular hemorrhage prophylaxis

Commentary

Ibuprofen lysine injection (NeoProfen®) was approved by the FDA on April 13, 2006 as a priority review and orphan drug. Approval was based on the review of a multi-center randomized double-blind placebo controlled trial conducted by the NICHD-Pediatric Pharmacology Research Unit Network in the United State.[1,2] This study enrolled 136 premature infants less than 30 weeks gestation with birth weights of 500-1000 grams. Infants were randomized to receive either a 3-day treatment course of IV ibuprofen at 10 mg/kg, followed by doses of 5 mg/kg at 24 and 48 hours after the initial dose (n=68), or saline placebo (n=68), within 72 hours of life. The primary outcome of this trial was the proportion of infants that required rescue treatment for PDA (IV indomethacin or surgery) on or prior to study day 14.[1,2] Patient demographics (mean +/- SD; range) of the infants enrolled include: gestational age 26.2 +/- 1.4; 23-30 weeks and birth weight 798+ 130.3; 530-1015 grams. Age at when the first dose of study drug was administered was 1.4 +/- 0.7 days. Demographics were similar in both groups. Ibuprofen significantly decreased the need for rescue therapy (25% vs 48%; $p<0.005$). Of the infants requiring rescue intervention, there was no difference between the 2 groups with respect to mean age at start of first rescue (8.7 days, range 4-15 days, for ibuprofen vs. 6.9 days, range 2-15 day for placebo).[1] Death, IVH, NEC, daily fluid intake/output, liver function, BPD, and ROP were not statistically significant between groups.[1,2]

The development of IV ibuprofen in the United States is a welcome addition to the Neonatal Pharmacopeia with equal efficacy, including duct reopening, and a more favorable renal side effect profile compared to the previous standard pharmacological agent IV indomethacin. The difference in renal side effect profile between the two drugs may be attributed to both indomethacin being more potent against cyclooxygenase-1 (COX-1) as well as COX-1 being apparently more involved in basal kidney physiology than cyclooxygenase-2 (COX-2).[3,4] However, in animal studies, both COX-1 and COX-2 seem to have a role in the pathophysiology of PDA.[5,6]

Interestingly, all reported comparative trials of ibuprofen and indomethacin for PDA treatment have been conducted internationally, in Europe (7 trials) and Asia (1 trial).[7] Will we experience similar comparative efficacy and the safer renal side effect profile in the much more ethnically diverse patient population in the United States? While long-term and widespread data do not yet exist, perhaps ibuprofen PDA outcomes may be explained by pharmacogenomics rather than the differences in ethnicity.

The molecular response to cyclooxygenase (COX) inhibition has been recently described in analgesic response to ibuprofen after minor oral surgery.[8] The level of COX-2 gene (PTGS2) expression was significantly higher at 2-4 hours after surgery for patients with the G/G allele at the nucleotide position of the -765G>C in the COX-2 gene ($p=0.012$) compared to patients with the G/C and C/C alleles.[8] The authors concluded that the wide variability in gene expression and functional polymorphisms in *PTGS2* may explain the interindividual variations in acute pain and analgesic efficacy of nonsteroidal anti-inflammatory drugs.[8] Ibuprofen and indomethacin have been shown, through in vitro studies, to be primarily metabolized by the hepatic cytochrome P450 2C9 isoenzyme system.[9,10] Genetic polymorphisms of the *2 and *3 alleles have reduced 2C9 activity.[11] Individuals carrying the homozygous *3/*3 genotype have been shown to have between a 5-

and 10- fold reduced activity depending on the particular drug.[11] Allele frequency for *2 and *3 have been reported at 11% and 7% in Caucasians and 4% and 2% in Africans, respectively.[11] A patient carrying this genotype may have reduced ibuprofen clearance leading to a potentially higher risk for side effects such as oliguria. Thus, the potential collective differences in COX-2 and cytochrome P450 2C9 genotype expressions may be responsible for the interpatient differences in the efficacy and safety with ibuprofen use in PDA. Follow-up phase IV US pharmacoepidemiology studies and pharmacogenetic evaluations should be performed such that potential differences in efficacy and safety can be identified.

There are two different formulations of intravenous ibuprofen, ibuprofen tris-hydroxyamino-methane (THAM) and ibuprofen L-lysine. Neonatal pulmonary hypertension had been a reported side effect in three infants treated with ibuprofen THAM and in one infant with the lysine formulation.[15] The cause of pulmonary hypertension with the THAM formulation has been thought to be related to the early administration of the drug (within 6 hours of life) or to the acid formulation of the product that could precipitate and result in microembolism in the lungs. It is unclear now at the present moment as to the true risk for pulmonary hypertension with the L-lysine product. Ibuprofen L-lysine is the formulation currently available in the United States.[7]

The lack of beneficial effects on IVH prophylaxis with ibuprofen would require Neonatal Intensive Care units to carry both ibuprofen and indomethacin. Heightened educational efforts are necessary for all healthcare providers involved in the prescribing, dispensing and administration of these sound alike medications so that that potential medication errors will be avoided. IV ibuprofen dosages are 5 or 10 mg/kg/dose and IV indomethacin dosages for IVH have ranged from 0.1 to 0.2 mg/kg/dose.[12,13] Recommended medication prevention strategies may include the use of tall man lettering (e.g. ibuPROfen, indoMETHacin), posting dosing charts to contrast the potential 100-fold difference (e.g. ibuprofen 10 mg/kg/dose vs. indomethacin 0.1 mg/kg/dose), dose warning limits checks in electronic physician order entry and pharmacy computer systems, and traditional in-service education.

IV ibuprofen (NeoProfen®) is available as single-use vials containing 2 mL of 10 mg/mL sterile solution and is manufactured by Ovation Pharmaceuticals. The recommended dosage for the treatment of PDA is 10 mg/kg/dose initially followed by single doses of 5 mg/kg/dose at 24 and 48 hours later. All doses should be based on the patient's birth weight. A second three-dose course may be administered if the PDA persists or reopens. Although not labeled as an approved use by the FDA, the aforementioned dosage recommendation for PDA treatment has been used for PDA prophylaxis.[14] IV ibuprofen is administered intravenously over 15 minutes and may be diluted with dextrose or saline. Diluted dosages should be administered within 30 minutes of preparation.[1] Contraindications to this medication include anuria or oliguria (urinary output <0.6 mL/kg/hr), active or suspected NEC, thrombocytopenia, coagulation defects, active IVH and GI bleeds, ductus arteriosus dependent congenital heart disease, and untreated infections.[1] Based on average wholesale pricing, IV ibuprofen lysine can be as high as 44% more expensive in drug costs alone when comparing an equipotent dose of IV indomethacin for the treatment of PDA. However, when factoring the cost savings with the lower risk of oliguria with ibuprofen, a more favorable overall cost benefit with ibuprofen is likely.

References:

1. Product information. NeoProfen® (ibuprofen lysine) injection. Ovation Pharmaceuticals. Deerfield, IL. April 2006.
2. Aranda JV for the IV Ibuprofen – PDA Study Team and for the Pediatric Pharmacology Research Unit Network (NICHD-PPRU). Multicenter Randomized Double-Blind Placebo Controlled Trial of Ibuprofen L-Lysine Intravenous Solution (IV Ibuprofen) in Premature Infants for the Early Treatment of Patent Ductus Arteriosus (PDA). SPR-PAS Annual Meeting, Washington DC, 2005.
3. Vane JR, Botting RM. Mechanism of action of anti-inflammatory drugs. In: Sinzinger H, Samuelsson B, Vane JR, Paoletti R, Ramwell P, Wong PY-K, eds. Recent advances in prostaglandin, thromboxane, and leukotriene research. Vol. 433 of Advances in experimental medicine and biology. New York: Plenum Press, 1997;137-8.
4. Smith WL, DeWitt DL. Biochemistry of prostaglandin endoperoxide H synthase-1 and synthase-2 and their differential susceptibility to nonsteroidal anti-inflammatory drugs. Semin Nephrol. 1995:15:179-94.
5. Loftin GD, Trivedi DB, Tiano HF, and et al. Failure of ductus arteriosus closure and remodeling in neonatal mice deficient in cyclooxygenase-1 and cyclooxygenase-2. Proc. Natl. Acad. Sci. 2001;98(3):1059-64.
6. Toyoshima K, Takeda A, Imarmura S, and et al. Constriction of the ductus arteriosus by selective inhibition of cyclooxygenase-1 and -2 in near-term and preterm fetal rats. Prostaglandins and other Lipid Mediators. 2006;79:34-42.
7. Thomas RL, Parker GC, Van Overmeire B, Aranda JV. A meta-analysis of ibuprofen versus indomethacin for closure of patent ductus arteriosus. Eur J Pediatr. 2005;164:135-40
8. Lee YS, Kim H, W TX, and et al. Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. Clinical Pharmacology and Therapeutics. 2006;79(5):407-18.
9. McGinnity DF, Parker AJ, Soars M, and Riley RJ. Automated Definition of the Enzymology of Drug Oxidation by the Major Human Drug Metabolizing Cytochrome P450s. Drug Metabolism and Disposition. 2000;28(11):1327-34
10. Nakajima M, Inoue T, Shimada N, et al. Cytochrome P450 2C9 Catalyzes Indomethacin O-Demethylation in Human Liver Microsomes. Drug Metabolism and Disposition. 1998;26(3):261-66
11. Kirchheiner J, Roots I, Goldammer M, et al. Effect of Genetic Polymorphisms in Cytochrome P450 (CYP) 2C9 and CYP2C8 on the Pharmacokinetics of Oral Antidiabetic Drugs. Clin. Pharmacokinet. 2005:44(12):1209-25

12. Yanowitz TD, Baker RW, Sobchak BB. Prophylactic indomethacin reduces grades III and IV intraventricular hemorrhages when compared to early indomethacin treatment of a patent ductus arteriosus. J Perinatol. 2003;23(4):317-22

13. Kumar N-PA, Pai MG, Gazil HA, and et al. Indomethacin prophylaxis for intraventricular hemorrhage in very low birth weight babies. Indian Pediatr. 2004;41(6):551-8

14. Ohlosson A, Walia R, Shah S. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants (Review). Cochrane Database Syst Rev. 2006 Jan 25;(1):CD004213

15. Bellini C, Campone F, Serra G. Pulmonary hypertension following L-lysine ibuprofen therapy in a preterm infant with patent ductus arteriosus. CMAJ. 2006 Jun 20;174(13):1843-4

INTRAVENOUS (IV) IBUPROFEN TREATMENT COMPARED TO IV INDOMETHACIN FOR PDA

Patel J, Marks KA, Roberts I et al. **Ibuprofen treatment of patent ductus arteriosus**. Lancet. 1995;346:255.

(For non-journal subscribers, an additional fee may apply for full text articles)

Article Options
View journal abstract

Van Overmeire B, Follens I, Hartmann, S et al. **Treatment of patent ductus arteriosus with ibuprofen.** Arch Dis Child. 1997;76:F179-F184.

(For non-journal subscribers, an additional fee may apply for full text articles)

Article Options
View journal abstract
View full article

Mosca F, Bray M, Lattanzio M et al. **Comparative evaluation of the effects of indomethacin and ibuprofen on cerebral perfusion and oxygenation in preterm infants with patent ductus arteriosus.** J Pediatr. 1997;131:549-54.

(For non-journal subscribers, an additional fee may apply for full text articles)

Article Options
View journal abstract

Pezzati M, Vangi V, Biagiotti R et al. **Effects of indomethacin and ibuprofen on mesenteric and renal blood flow in preterm infants with patent ductus arteriosus.** J Pediatr. 1999;135:733-8.

(For non-journal subscribers, an additional fee may apply for full text articles)

Article Options
View journal abstract

Van Overmeire B, Smets K, Lecoutere D et al. **A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus.** N Engl J Med. 2000;343:674-681.

(For non-journal subscribers, an additional fee may apply for full text articles)

Article Options
View journal abstract
View full article

Lago P, Bettiol T, Salvadori S et al. **Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: a randomised controlled trial.** Eur J Pediatr. 2002;161:202-207.

(For non-journal subscribers, an additional fee may apply for full text articles)

Article Options
View journal abstract

Su PH, Chen JY, Su CM et al. **Comparison of ibuprofen and indomethacin therapy for patent ductus arteriosus in preterm infants.** Pediatrics International. 2003;45:665-670.

(For non-journal subscribers, an additional fee may apply for full text articles)

Article Options
View journal abstract
View full article

Several randomized clinical trials have been conducted to compare the efficacy of IV ibuprofen with that of IV indomethacin in inducing closure of a PDA in premature infants. The alternative use of IV ibuprofen for PDA closure was first studied in 1995 by Patel J et al. Concerns related to the decline in cerebral perfusion and reduced oxygenation with the use of IV indomethacin resulted in a study of an alternative prostaglandin

inhibitor with a focus on potentially less concerning cerebral effects. Infants included were between 23 and 28 weeks gestation. The study compared the effects of two IV ibuprofen doses (5mg/kg (n=12) and 10mg/kg (n=6)) and indomethacin 0.1mg/kg (n=15). The results indicated that IV ibuprofen did not impair cerebral hemodynamics or oxygenation. The authors concluded that the cerebral effects of IV indomethacin must be unique to this specific prostaglandin inhibitor. Although the authors did find a difference in cerebral effects, there was no apparent difference in rate of PDA closure (57% closure in both indomethacin and ibuprofen treated infants).

In 1997, Van Overmeire et al conducted a study in 40 premature infants to evaluate if IV ibuprofen is as effective as IV indomethacin in closing a PDA. Secondary outcomes were adverse drug effects. Premature infants included in this study had a gestational age <33 weeks with respiratory distress syndrome and echocardiographically confirmed PDA. Infants were randomized at days 2 and 3 of life to receive 3 doses of IV indomethacin (0.2mg/kg every 12 hours) or IV ibuprofen (10mg/kg, followed by 5mg/kg after 24 and 48 hours). After receiving this treatment course, 15/20 (75%) infants in the IV indomethacin group and 16/20 (80%) infants in the IV ibuprofen group had PDA closure. Mosca et al evaluated 16 infants (<31 weeks gestation) receiving 0.2mg/kg IV indomethacin or 10mg/kg IV ibuprofen. Following the first dose, ductal closure occurred in 6/8 receiving IV indomethacin and 5/8 receiving IV ibuprofen. These results are consistent with other early studies evaluating PDA closure rates. In a small study by Pezzati M et al, PDA closure rates of 88% with indomethacin and 78% with ibuprofen were noted following the first dose.

Prior to 2000, the clinical trials evaluating IV ibuprofen were of small sample size (n of <100). In that year, the study by Van Overmeire et al comparing ibuprofen and indomethacin included 148 premature infants of gestational age 24 to 32 weeks with evidence of a PDA by echocardiogram, requiring respiratory support due to respiratory distress syndrome. Premature infants were randomly assigned to receive either IV indomethacin (0.2mg/kg every 12 hours for 3 doses) or IV ibuprofen (10mg/kg, followed by 5mg/kg after 24 and 48 hours). Rescue doses of indomethacin were indicated if there was no PDA closure and the infant continued to require respiratory support following the initial 3 study drug doses. Rescue doses were indomethacin (0.2mg/kg every 12 hours for 3 doses) and were given if indicated to both groups (indomethacin and ibuprofen) independent of the initial randomization.

In 2002, a second large, randomized clinical trial by Lago et al was conducted that included 175 premature infants (gestational age 23 to 34 weeks) with significant PDA and respiratory distress syndrome. The methods of this study were similar to the 2000 Van Overmeire study; however, in the event that rescue doses were indicated for a persistent PDA, three doses of the same initial randomization drug were given versus standard indomethacin. From previous trial results, the sample size for these 2000 and 2002 studies were calculated based on the ability to detect a difference of at least 20 percentage points in the closure rate between the ibuprofen and indomethacin groups. A more recent study, in 2003, was conducted by Su P et al in 63 premature infants with respiratory distress syndrome and a gestational age * 32 weeks. This study had the same methods of intervention as the 2000 and 2002 studies mentioned previously – however no rescue doses of drug were given for lack of PDA closure or reopening. In all of these aforementioned studies, premature infants with major congenital anomalies, bleeding risks, and renal impairment were excluded.

With the primary outcome of PDA closure in these comparative trials, IV ibuprofen has been found to be as efficacious as IV indomethacin. In 2000, Van Overmeire et al found the rate of ductal closure to be 66% (49/74) in the IV indomethacin group compared to 70% (52/74) in the IV ibuprofen group (p=0.41). In this same study, infants requiring rescue doses did not differ significantly between the two groups (12% IV indomethacin group vs. 16% IV ibuprofen group, p=0.48). Lago et al found similar closure rates of PDA following the initial three drug doses (69% IV indomethacin group vs. 73% IV ibuprofen group). Following three rescue doses, PDA closure rates were similar (82% IV indomethacin vs. 86% with IV ibuprofen). In 2003, Su et al found PDA closure rates following three drug doses to be similar as well (80.6% IV indomethacin vs. 84.4% IV ibuprofen).

With respect to adverse effects, renal impairment was most commonly found to be significantly different between the IV ibuprofen and IV indomethacin groups. In the earlier Van Overmeire trial, premature infants receiving IV ibuprofen had increased urine output and no rise in serum creatinine compared to the IV indomethacin group. In the 2000 Van Overmeire trial, oliguria developed in 14 infants receiving indomethacin and 5 infants receiving ibuprofen during the three days following the start of treatment (p=0.03). A greater increase in serum creatinine from day 4 to day 8 also occurred in the indomethacin group (p=0.04). Lago et al found a similar difference in oliguria between groups, with oliguria noted to be higher in those infants receiving IV indomethacin (15% vs. 1% with IV ibuprofen, p=0.017). Consistent with previous adverse effects, Su et al found serum creatinine values to be lower in the ibuprofen group at 24, 48, and 72 hours after treatment compared to the indomethacin group ($p < 0.01$). Also, a significantly lower urine volume was found in the IV indomethacin group at 24 hours after treatment compared to the IV ibuprofen group ($p < 0.02$). In all of these studies, there were generally no differences between groups for developing necrotizing enterocolitis, intraventricular hemorrhage, etc.

In conclusion, IV ibuprofen has consistently been shown to be as effective as IV indomethacin for the closure of PDA in premature infants. Secondary outcomes of these comparative trials have primarily looked at adverse effects, finding that IV ibuprofen has less adverse effects on renal function compared to IV indomethacin. In summary, IV ibuprofen has been shown to be as efficacious as the gold standard for treatment of PDA, IV indomethacin, with improved adverse effects on renal function.

INTRAVENOUS (IV) IBUPROFEN PROPHYLAXIS FOR PDA IN PREMATURE NEONATES

Varvarigou A, Bardin CL, Beharry K et al. **Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants.** JAMA. 1996;275(7):539-44.

(For non-journal subscribers, an additional fee may apply for full text articles)

Article Options
View journal abstract

De Carolis MP, Romagnoli C, Polimeni V et al. **Prophylactic ibuprofen therapy of patent ductus arteriosus in preterm infants.** Eur J Pediatr. 2000;159:364-368.

(For non-journal subscribers, an additional fee may apply for full text articles)

Article Options
View journal abstract
View full article

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

(For non-journal subscribers, an additional fee may apply for full text articles)

Article Options
View journal abstract
View full article

Although IV ibuprofen has shown to be efficacious for treatment of PDA in premature infants, the role for IV ibuprofen prophylaxis has less evidence to date in the literature. Several studies comparing IV ibuprofen prophylaxis to placebo have demonstrated efficacy in reducing the incidence of PDA. However, not all studies have shown a benefit without the risk of adverse effects.

A prospective, controlled trial with three treatment arms was conducted by Varvarigou et al in 1996. Thirty-four premature infants (mean gestational age 26.9 weeks, range 22.4 to 31.0 weeks) were assigned within 3 hours of birth to a treatment, receiving either three doses of IV ibuprofen (10mg/kg, followed by 5mg/kg after 24 and 48 hours), one dose of IV ibuprofen (10mg/kg), or saline. The incidence of PDA did not differ between the infants receiving one dose of IV ibuprofen or the saline group. However, those infants that received three doses of IV ibuprofen had no PDA, which was a statistically significant finding compared to the saline group (0/12 vs. 7/11, $p < 0.02$). No adverse effects were noted to be associated with IV ibuprofen in this study. A similar study was conducted in 2000 by De Carolis et al, in which IV ibuprofen prophylaxis was given as 3 standard doses (10mg/kg, followed by 5mg/kg after 24 and 48 hours). Forty-six premature infants (<31 weeks gestation) were randomly assigned to treatment at 2 hours of life. The control group received no placebo. At 72 hours of life, a greater number of infants in the IV ibuprofen group versus the control group were found to have no presence of PDA [20/23 (87%) vs. 7/23 (30.4%)]. No significant adverse effects were noted to occur with IV ibuprofen.

Until recently, IV ibuprofen for PDA prophylaxis had shown consistent efficacy with little reports of adverse effects. In 2004, the larger, randomized, double-blind, placebo-controlled trial performed by Gournay et al was stopped early following the enrollment of 135 premature infants, in which three cases of severe pulmonary hypertension were noted to occur in the IV ibuprofen group. This trial included premature infants <28 weeks gestation receiving either three doses of ibuprofen (10mg/kg, followed by 5mg/kg after 24 and 48 hours) or placebo within 6 hours of birth. IV ibuprofen prophylaxis appeared to reduce the rate of surgical ligation (9% placebo vs. 0% IV ibuprofen, $p=0.03$), but survival with IV ibuprofen was not improved compared to the placebo group due to the frequency of adverse effects.

In summary, IV ibuprofen has been shown to have beneficial effects in decreasing the occurrence of PDA when compared to placebo. No significant adverse effects were generally noted, but there have been cases of severe pulmonary hypertension related to prophylaxis with IV ibuprofen. Additional data are needed to determine the safety of ibuprofen before it can be recommended in the prophylaxis of PDA.

INTRAVENOUS (IV) IBUPROFEN LACKS EFFICACY FOR INTRAVENTRICULAR HEMORRHAGE (IVH) PROPHYLAXIS

Van Overmeire B, Allegaert K, Casaer A et al. **Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial.** Lancet. 2004;364:1945-49.

(For non-journal subscribers, an additional fee may apply for full text articles)

Article Options
View journal abstract
View full article

Dani C, Bertini G, Pezzati M et al. **Prophylactic ibuprofen for the prevention of intraventricular hemorrhage among preterm infants: a multicenter, randomized study.** Pediatrics. 2005;115:1529-1535.

(For non-journal subscribers, an additional fee may apply for full text articles)

Article Options
View journal abstract
View full article

Mosca F, Bray M, Lattanzio M et al. **Comparative evaluation of the effects of indomethacin and ibuprofen on cerebral perfusion and oxygenation in preterm infants with patent ductus arteriosus.** J Pediatr. 1997;131:549-54.

(For non-journal subscribers, an additional fee may apply for full text articles)

Article Options
View journal abstract

Patel J, Roberts I, Azzopardi D et al. **Randomized double-blind controlled trial comparing the effects of ibuprofen with indomethacin on cerebral hemodynamics in preterm infants with patent ductus arteriosus.** Pediatr Res. 2000;47:36-42.

(For non-journal subscribers, an additional fee may apply for full text articles)

Article Options
View journal abstract

Gournay V, Roze JC, Kuster A et al. **Prophylactic ibuprofen versus placebo in very premature infants: a randomized, double-blind, placebo-controlled trial.** Lancet. 2004;364:1939-44.

(For non-journal subscribers, an additional fee may apply for full text articles)

Article Options
View journal abstract
View full article

Indomethacin has also been used for IVH prophylaxis in premature infants. However, the beneficial use of indomethacin is often limited due to the adverse effects on renal and gastrointestinal function, apparently related to interference with perfusion and oxygen delivery. Prospective, randomized trials have been conducted to assess the efficacy of IV ibuprofen for IVH prophylaxis, while other studies have looked at the effects of IV ibuprofen on cerebral hemodynamics. Like indomethacin, IV ibuprofen has been shown to be efficacious in the treatment and prevention of PDA, although with an improved adverse effect profile.

In 2004, Van Overmeire et al studied the efficacy of early IV ibuprofen in reducing the frequency of severe IVH in 415 infants (gestational age <31 weeks). Infants were randomized to receive IV ibuprofen (10mg/kg, followed by 5mg/kg after 24 and 48 hours) or placebo within 6 hours after birth. Severe IVH was noted in 17/205 (8%) infants in the IV ibuprofen group and 18/210 (9%) infants in the placebo group.

In 2005, a multicenter, prospective, double-blind randomized controlled trial conducted by Dani et al hypothesized that prophylactic IV ibuprofen would reduce the occurrence of IVH and make the worsening of IVH toward grades 2 to 4 less likely among premature infants. Premature infants of gestational age <28 weeks received IV ibuprofen or placebo within the first 6 hours of life. Infants received the same doses prescribed in previous studies (10mg/kg, followed by 5mg/kg after 24 and 48 hours). Of the 155 infants included in this study, grade 2 to 4 IVH developed in 21% in the IV ibuprofen group compared to 17% in the placebo group. Comparing the IVH rates at baseline, 24 hours, 48 hours, and at 7 days of life, the investigators found no difference in rates between the IV ibuprofen and placebo groups.

With respect to cerebral hemodynamics, Mosca et al's 1997 study compared the effects of IV indomethacin and IV ibuprofen on cerebral perfusion and oxygenation in premature infants. In this study of 16 infants (<31 weeks gestation), treatment with IV ibuprofen did not significantly reduce cerebral perfusion and oxygen availability. These results were further confirmed in a prospective, randomized controlled trial by Patel J et al in 2000. The investigators measured cerebral hemodynamics in 33 preterm infants during treatment of PDA with IV ibuprofen or IV indomethacin. Following the first dose of IV ibuprofen, no change was noted in cerebral oxygen delivery. However, cerebral oxygen delivery changed significantly after the first dose of IV indomethacin: while cerebral blood volume was reduced with IV indomethacin by a mean decrease of-0.5mL/100Gm, no significant reduction was observed with IV ibuprofen (p=0.022). Following the 24 hour dose of IV indomethacin, significant reductions in cerebral blood flow, cerebral blood volume, and cerebral oxygen delivery were noted. In contrast, no significant changes were seen with IV ibuprofen.

In 2004, Gournay et al evaluated the effects of prophylactic IV ibuprofen on IVH in 135 premature infants (<28 weeks gestation). The need for surgical ligation of PDA was chosen as the primary endpoint, as the sample size needed for prevention of IVH as a primary endpoint was determined to be too large. Although underpowered, as a secondary endpoint a decrease in the rate of grade 3 or 4 IVH was seen with prophylactic IV ibuprofen compared to placebo (11% vs. 23%, p=0.10). The overall rate of IVH was similar between both groups.

In conclusion, IVH prophylaxis with IV ibuprofen has been shown to be ineffective and is not recommended. In animal studies, indomethacin has vasoconstrictive effects in the brain – however ibuprofen is not known to cause these same effects. Although ibuprofen has an improved safety profile, especially in regards to renal and gastrointestinal function, the lack of efficacy in IVH prophylaxis does not warrant its use. With no alternative for IVH prophylaxis, the risks and benefits of IV indomethacin must be considered.

Ask the Authors

LAST MONTH'S Q & A January 2006 - Volume 4 - Issue 5

In our January 2007 issue, we reviewed the clinical trial information for intravenous ibuprofen (pharmacologically related to indomethacin) for the treatment and prophylaxis of PDA, and its effect on intraventricular hemorrhage (IVH) prophylaxis.

Commentary:
Carlton K.K. Lee, Pharm.D., MPH

Assistant Professor, Department of Pediatrics
School of Medicine
Johns Hopkins University
Clinical Specialist, Pediatrics
Department of Pharmacy
The Johns Hopkins Hospital

Reviews:
Melissa D. Meekins, Pharm.D.

Pediatric Specialty Resident
Department of Pharmacy
The Johns Hopkins Hospital

Our readers asked the January faculty the following questions:

Q Is there any evidence that oral ibuprofen is as effective as IV ibuprofen in the treatment of PDA for preemies?

A The experience with oral ibuprofen in treating PDA for preemies is currently limited to four small clinical trials: two open-labeled studies and two comparison trials to indomethacin. When combining the subjects of the two open label trials, ductal closure was achieved in 91.4% (32 of 35) of patients[1,2]. Ductal reopening did not occur in one of these studies (N=22)[1] and was not reported in the other (N=13)[2]. There were no drug related side effects of oliguria or bleeding[1,2].

The comparison pilot studies of oral ibuprofen to indomethacin have reported statistically similar rates of ductal closure at 77.8% (7/9) vs. 88.9% (8/9)[3] and 46.7% (7/15) vs. 66.7% (10/15)[3,4], respectively (p=NS for both). Slightly favorable response rates with indomethacin in both of these trials may be attributed to better drug absorption with the intravenous (IV) route of administration compared to oral ibuprofen. Indomethacin subjects in the Supapannachart et al[3] trial received their doses by either IV or PO, and indomethacin was administered exclusively intravenously in the study by Chotigeat et al[4]. Ductal reopening was statistically similar at 40% vs 33% (p=NS), ibuprofen vs indomethacin respectively, in one of these studies[4]. In regards to adverse drug events, favorable renal effects were observed with ibuprofen. Ibuprofen use was associated with higher urine output (with no significant increase in serum creatinine or blood urea nitrogen)[3]; and significantly less diuretic (furosemide) use ($p<0.01$)[4] Despite the lack of statistical significance, a higher rate of NEC was also observed with indomethacin (66.7% vs 40%) in the study by Chotigeat and associates[4].

Despite promising closure rates as high as 90% with open-labeled studies, unanswered issues in regards to dosing and other potential side effects still remain. Three different oral ibuprofen dosing regimens were used in the four aforementioned trials; 10 mg/kg/dose x 1 followed by 5 mg/kg/dose x 2 given every 24 hours (same as the IV treatment dose), or every 12 hours, or 10 mg/kg/dose x 3 given every 24 hours. A PO/IV bioavailability study is needed to determine the proper oral dose. Spontaneous intestinal perforation, without signs of NEC, has been reported in two very-low birth-weight infants receiving oral ibuprofen for PDA treatment[5].

References:

1. Heyman E, Morag I, Batash D et al. Closure of patent ductus arteriosus with oral ibuprofen suspension in premature newborns: a pilot study. Pediatrics. 2003;112:354-358.
2. Hariprasad P, Sundarrajan V, Srimathy G, et al. Oral ibuprofen for closure of hemodynamically significant PDA in premature neonates. Indian Pediatrics. 2002;39(1):99-100.
3. Supapannachart S, Limrungsiul A, Khowsathit P. Oral ibuprofen and indomethacin for treatment of patent ductus arteriosus in premature infants: a randomized trial at Ramathibodi Hospital. J Med Assoc Thai. 2002;85(Suppl 4):S1252-8.
4. Chotigeat U, Jirapapa K, Layangkool, T. A comparison of oral ibuprofen and intravenous indomethacin for closure of patent ductus arteriosus in preterm infants. J. Med Assoc Thai. 2003;86 (Suppl 3):S563-9.
5. Tatli MM, Kumral A, Duman N, et al. Spontaneous intestinal perforation after oral ibuprofen treatment of patent ductus arteriosus in two very-low-birthweight infants. Acta Paediatr. 2004;93(7):999-1001.

Q As a prophylactic protocol, is there any evidence that oral ibuprofen may be beneficial when the IV preparation is not available?

A The available clinical data on oral ibuprofen use with PDA prophylaxis is currently limited to a small, randomized, controlled study conducted in Thailand[6]. Twenty-two neonates between 28-32 weeks gestational age with a birth weight of approximately 1500 grams received PO ibuprofen, while 20

neonates of similar age, birth weight, and other clinical characteristics received placebo. An oral ibuprofen dosage of 10 mg/kg/dose every 24 hours for 3 doses, with the first dose initiated within 24 hours of life, was given. The investigators found the prevalence of symptomatic PDA to be lower in the ibuprofen prophylaxis group compared to placebo (0/22 vs. 5/22, $p<0.05$)[6]. Although there were no significant side effects, gastrointestinal bleeding did occur more frequently with ibuprofen (12/22 vs. 6/20, $p=0.196$)[6].

It is also important to consider the unpredictability of the oral administration of drugs in infants. Infants, especially premature infants, may have irregular gastric emptying and decreased intestinal and/or biliary function. Additionally, in the presence of a PDA, decreased mesenteric blood flow may also play a role in altering absorption. The pharmacokinetics of oral ibuprofen have been studied in premature infants and results have shown large inter-individual variability with respect to drug exposure, area under the curve (AUC), and peak plasma concentration (C_{max}). In a pharmacokinetic study by Sharma et al, the coefficient of variation was 88.5% for AUC and 74.1% for C_{max}[7]. This is quite variable considering a relatively homogeneous patient population [mean gestational age 30.45 +/- 1.48 weeks (range 26 to 32 weeks) and mean birth weight 1262.5 +/- 247.76 grams (range 750 to 1900 grams)]. Additional oral pharmacokinetic studies are needed to fine-tune the dosing strategy with oral ibuprofen by reducing the inter-individual variability of drug exposure (AUC and C_{max}).

References:

6. Sangtawesin V, Sangtawesin C, Raksasinborisuc C, et al. Oral ibuprofen prophylaxis for symptomatic patent ductus arteriosus of prematurity. J. Med Assoc Thai. 2006;89(3):314-21.
7. Sharma PK, Garg SK, Narang A. Pharmacokinetics of oral ibuprofen in premature infants. J Clin Pharmacol. 2003;43(9):968-73.

Complete Post Test and Receive CME/CE Credit **Recommend eNeonatal Review to a Colleague**

Accreditation • **back to top**
Physicians
The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Nurses
The Institute for Johns Hopkins Nursing is accredited as provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

Respiratory Therapists
Respiratory Therapists should visit this page to confirm that AMA PRA category 1 credit is accepted toward fulfillment of RT requirements.

Credit Designations • **back to top**
Physicians
The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurses
This 1.0 contact hour (for each eNewsletter or a maximum of 6 contact hours for all twelve eNewsletters) Educational Activity (Provider Directed/Learner Paced) is provided by The Institute for Johns Hopkins Nursing.

Respiratory Therapists
Respiratory Therapists should visit this page to confirm that your state will accept the CE Credits gained through this program.

Target Audience • **back to top**
This activity has been developed for Neonatologists, NICU Nurses and Respiratory Therapists working with Neonatal patients. There are no fees or prerequisites for this activity.

Learning Objectives • **back to top**
At the conclusion of this activity, participants should be able to:

- Discuss the efficacy of IV ibuprofen compared to IV indomethacin in the treatment of PDA
- Compare the use of IV ibuprofen for prophylaxis of PDA to IV indomethacin
- Identify the role of IV ibuprofen for intraventricular hemorrhage prophylaxis

Statement of Responsibility • **back to top**
The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing takes responsibility for the content, quality, and scientific integrity of this CME/CNE activity.

Faculty Disclosure Policy Affecting CE Activities • back to top

As providers accredited by the Accreditation Council for Continuing Medical Education and American Nursing Credentialing Center's Commission of Accreditation, it is the policy of The Johns Hopkins University School of Medicine and The Institute of Johns Hopkins Nursing to require the disclosure of the existence of any significant financial interest or any other relationship a faculty member or a provider has with the manufacturer(s) of any commercial product(s) discussed in an education presentation. The presenting faculty reported the following:

- 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.
- Dr. Lehmann has indicated a financial relationship in the form of honorarium from the Eclipsys Corporation.

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.

Unlabelled/Unapproved Uses • back to top

This presentation will include off-label and unapproved uses of intravenous Indomethacin and Ibuprofen for prophylaxis of PDA and intraventricular hemorrhage in premature neonates as well as NeoProfen as prophylaxis for intraventricular hemorrhage and PDA in premature neonates.

Disclaimer Statement • back to top

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing name implies review of educational format design and approach. Please review the complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings and adverse effects before administering pharmacologic therapy to patients.

Internet CE Policy • back to top

The Offices of Continuing Education (CE) at The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing are committed to protect the privacy of its members and customers. The Johns Hopkins University maintains its Internet site as an information resource and service for physicians, other health professionals and the public.

The Johns Hopkins University School of Medicine and The Institute For Johns Hopkins Nursing will keep your personal and credit information confidential when you participate in a CE Internet based program. Your information will never be given to anyone outside The Johns Hopkins University program. CE collects only the information necessary to provide you with the service you request.

Created by DKBmed.