REVIEW ARTICLE

Clinical Experience with Intravenous Ibuprofen Lysine in the Pharmacologic Closure of Patent Ductus Arteriosus

Evelyn R. Hermes-DeSantis, PharmD[1] and Jacob V. Aranda, MD, PhD, FRCPC[2]

[1]Department of Pharmacy Practice and Administration, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, New Jersey, [2]Pediatric Pharmacology Research Unit Network, Children's Hospital of Michigan, Detroit, Michigan

Patent ductus arteriosus (PDA) is the failure of the ductus that arises from the distal dorsal aortic arch to close during the first few days of life. The treatment options for PDA include "watchful waiting," pharmacologic therapy with cyclooxygenase (COX) inhibitors (COX-1 and COX-2), such as indomethacin or intravenous (IV) ibuprofen lysine, and surgery when medical interventions have proved ineffective. The clinical trials evaluating the utilization of IV ibuprofen lysine focus on either preventing the persistence of a PDA or treating the PDA in premature infants in whom the ductus does not close within 48 hours of birth. Although the role of COX inhibitors in prophylaxis of PDA has been studied, it has not been clearly delineated. Treatment of PDA in preterm low birth weight infants from the second day of life on with IV ibuprofen lysine has been studied in 4 major and 3 smaller clinical trials. Overall, in 7 studies with 492 patients, the closure rate of PDA was 75.1% with IV ibuprofen lysine compared to 73.5% with indomethacin. In addition, neonates treated with IV ibuprofen lysine had significantly better creatinine clearance, urine output, serum creatinine, and blood urea nitrogen (BUN) profiles than indomethacin-treated patients. Overall, IV ibuprofen lysine is as effective as indomethacin for closure of PDA, yet is associated with a better safety profile with fewer negative side effects when compared to indomethacin.

KEYWORDS clinical efficacy, ibuprofen, IV ibuprofen lysine, patent ductus arteriosus

J Pediatr Pharmacol Ther 2007;12:171-182

INTRODUCTION

Patent ductus arteriosus (PDA) is the failure of the ductus that arises from the distal dorsal aortic arch to close during the first few days of life. In utero, the ductus is well developed by the sixth week of gestation. During gestational development, the lungs are not yet required for respiration, as the placenta oxygenates the blood. In order to shunt the blood around the lungs, the ductus provides the necessary bridge between the pulmonary artery and the dorsal aorta. At birth, low birth weight premature neonates may experience a ductus that remains open with a left-to-right shunt.[1,2]

Treatment options for PDA include conservative "watchful waiting," surgery, and drug therapy. Surgical intervention to close the PDA is necessary only when medical interventions have proved ineffective.[3] Surgical ligation improves lung compliance and hemodynamics and reduces the duration of mechanical ventilation.[3, 4,5] Medical intervention is centered on the administration of either intravenous (IV) indomethacin (Indomethacin, Ovation Pharmaceuticals, Deerfield, IL) or IV ibuprofen lysine (NeoProfen, Ovation Pharmaceuticals, Deerfield, IL). While these 2 COX inhibitors

Address correspondence to: Evelyn R. Hermes-DeSantis, PharmD, BCPS, Department of Pharmacy Practice and Administration, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, 160 Frelinghuysen Road, Piscataway, NJ 08854, email: ehermesd@rci.rutgers.edu

are structurally different, their pharmacologic effects are very similar. Indomethacin, a COX inhibitor with a greater effect at COX-1, has been the standard medical treatment for PDA in preterm neonates since the 1970s.[6] It has proven efficacy rates of between 66% and 80%.[7,8,9,10] In recent studies, IV ibuprofen lysine, a COX inhibitor with less COX-1 activity compared to indomethacin, was as effective as indomethacin in treatment of PDA with similar ductal closure rates.[10] The differences in COX-1 and COX-2 sensitivity may result in different pharmacological perfusion effects. Indomethacin has a host of adverse side effects that include altered platelet function; decreased gastrointestinal, cerebral, and renal blood flow; oliguria; and gastrointestinal perforation or hemorrhage.[11] Neonates treated with IV ibuprofen lysine had lower serum creatinine values, improved urine output, fewer vasoconstrictive adverse events, and less undesirable reduced organ blood flow.[12]

ABBREVIATIONS BUN, blood urea nitrogen; CBF, cerebral blood flow; CBFV, cerebral blood flow velocity; CBV, cerebral blood volume; CBVR, carbon dioxide tension; COX, cyclooxygenase; $CytO_2$, oxidized cytochrome aa_3; FDA, Food and Drug Administration; IV, intravenous; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NNT, number needed to treat; NSAIDs, nonsteroidal anti-inflammatory drugs; PDA, patent ductus arteriosus; PGE, prostaglandins; PMA, postmenstrual age; PPHN, persistent pulmonary hypertension of the newborn; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; THAM, trishydroxyaminomethane; US, United States

This article reviews the pharmacology, clinical efficacy, and safety issues of IV ibuprofen lysine. Although ibuprofen has been employed for years as an oral pain medication, its utilization in the management of PDA is only recent in the United States (US). In clinical trials, comparison to placebo has been used for early closure or prophylaxis therapy, while treatment trials have focused on comparison to indomethacin. These clinical trials will be reviewed, and the safety advantages of IV ibuprofen lysine will be explored.

IV IBUPROFEN LYSINE PHARMACOLOGY

Both ibuprofen and indomethacin are COX inhibitors that achieve their pharmacological effect by the inhibition of COX-1 and COX-2. COX-1, found primarily in systemic circulation, and COX-2, thought to be primarily responsible for ductal patency during fetal development, are potent endogenous vasodilators. However, little is known regarding whether COX-1 or COX-2 or both affect the patency of the ductus during the postnatal period.[13] Another contributory mechanism related to the failure of the ductus to close involves high levels of endogenous vasodilators such as nitric oxide and prostaglandins (PGE), including both PGE_1 and PGE_2. PGE_2 may be more specific in maintaining ductal patency. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, effectively inhibit the action of COX and, in doing so, interfere with the synthesis of PGEs (Figure 1).[14]

In addition to the blockade of COX and synthesis of PGE_1 and PGE_2, indomethacin may also work by affecting vascular endothelium, resulting in increased circulating levels of endothelins, which could explain the increased frequency of adverse events with IV indomethacin vs. IV ibuprofen lysine.[10,13] Ibuprofen appears to have a different influence on regional circulation. In addition, IV ibuprofen lysine has not been associated with decreased platelet adhesion and associated bleeding disorders that plague other NSAIDs. Dani and colleagues showed no difference in serial platelets between IV ibuprofen lysine and placebo.[13] Ibuprofen also has inhibition of leukocyte function, antiinflammatory, analgesic, and antipyretic effects.[15]

CLINICAL EXPERIENCE OF IV IBUPROFEN LYSINE

The clinical trials evaluating the utilization of IV ibuprofen lysine are divided between prophylactic use to prevent the development of PDA and treatment of PDA in premature infants in whom the ductus does not close within 48 hours of birth. These differences in clinical trials have translated into clinical practice; however, the first step in assessing therapy is identifying the optimal dose of IV ibuprofen lysine.

Dose-ranging study

Desfrere et al. evaluated 4 dosing regimens

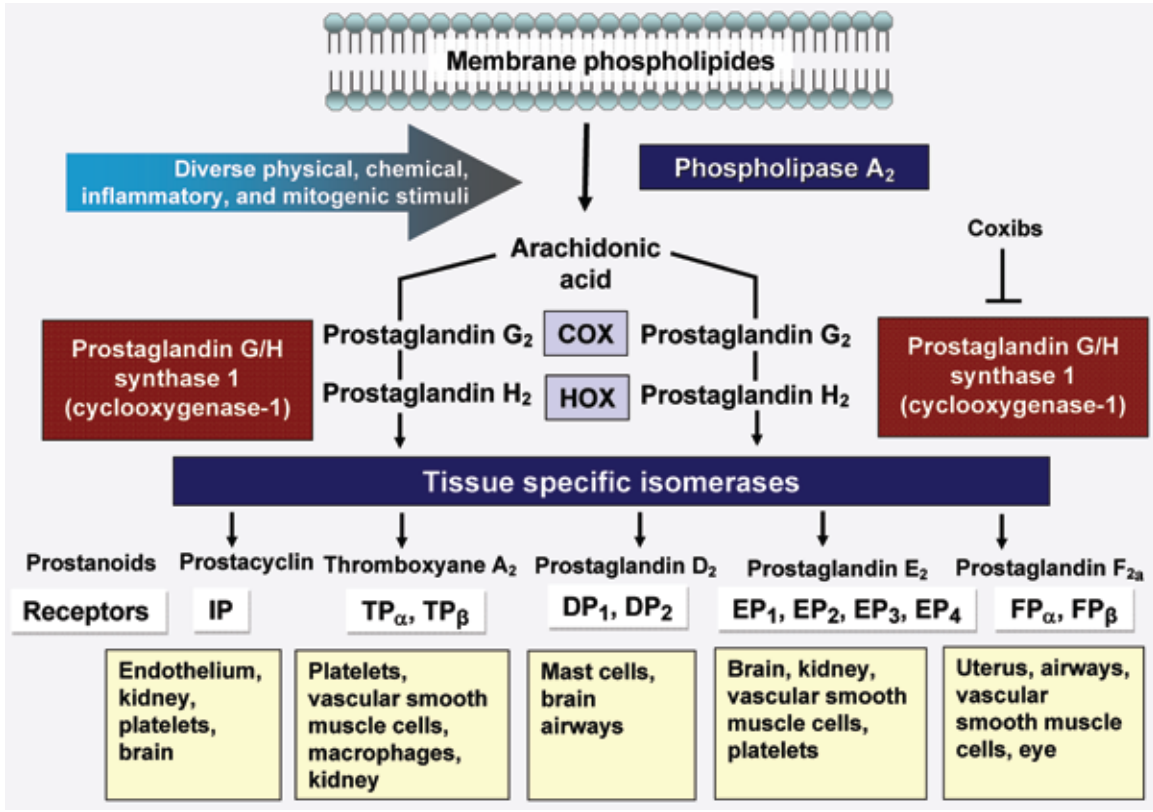

Figure 1. Production and actions of prostaglandins and thromboxane. Arachidonic acid, a 20-carbon fatty acid containing 4 double bonds, is liberated from the *sn*2 position in membrane phospholipids by phospholipase A_2, which is activated by diverse stimuli. Arachidonic acid is converted by cytosolic prostaglandin G/H synthases, which have both cyclooxygenase (COX) and hydroperoxidase (HOX) activity, to the unstable intermediate prostaglandin H_2. The synthases are colloquially termed cyclooxygenases and exist in 2 forms, cyclooxygenase-1 and cyclooxygenase-2. Coxibs selectively inhibit cyclooxygenase-2. Prostaglandin H_2 is converted by tissue-specific isomerases to multiple prostanoids. These bioactive lipids activate specific cell-membrane receptors of the superfamily of G-protein–coupled receptors. Some of the tissues in which individual prostanoids exert prominent effects are indicated. IP denotes prostacyclin receptor, TP thromboxane receptor, DP prostaglandin D_2 receptor, EP prostaglandin E_2 receptor, and FP prostaglandin F_2 receptor. Fitzgerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med 345: 433-42. Copyright © 2001 Massachusettes Medical Society. All Rights Reserved.

of IV ibuprofen lysine in 40 infants in a double-blind dose-ranging study.[16] The target closure rates varied with postmenstrual age (PMA); in neonates with a PMA of 27-29 weeks, a closure rate of 80% was targeted; in neonates with PMA less than 27 weeks, the target was 50%. Twenty infants in each PMA group with PDA between 3 and 5 days of life received a loading dose of 5, 10, 15 or 20 mg/kg of IV ibuprofen lysine, followed by 2 doses of half of the loading dose at 24-hour intervals. The efficacy of each dose regimen was evaluated by echocardiography 24 hours after the third infusion.

In the PMA of 27-29 weeks group, the minimum effective dose regimen of 10 mg/kg followed by 5 mg/kg at 24 and 48 hours (10-5-5 mg/kg) had a probability of success of 77% (95% credibility interval, 56-92%). The 15-7.5-7.5 mg/kg dose had a better probability of success of 88%. In the PMA less than 27 weeks group, the minimum effective dose was the 20-10-10 mg/kg regimen, with a probability of success of 54.8% (95% credibility interval, 22-84%). Failure to close the PDA occurred in 70% of patients of less than 27 weeks PMA. Renal adverse effects occurred in the 27-29 weeks PMA as the IV ibuprofen lysine dose increased, whereas renal effects occurred more frequently at all dosing regimens in patients less than 27 weeks. These all returned to normal within 24

hours. This study concluded that the appropriate dosing regimen is 10 mg/kg IV ibuprofen lysine followed by 5 mg/kg at 24 and 48 hours to treat and prevent PDA, while keeping adverse effects to a minimum.[16]

Prophylaxis of PDA: Placebo-controlled studies

Placebo-controlled trials with IV ibuprofen lysine have evaluated the efficacy of prophylaxis for the development of PDA. IV ibuprofen lysine was compared to saline or no treatment in 4 studies and demonstrated efficacy in the prevention of PDA compared to placebo.[1]

Varvarigou et al. conducted a prospective sequential, controlled 3-armed trial in 34 infants, dosed 0-3 hours after birth.[17] The mean birth weight was 913 g (range 565-1460 g) with a gestational age of 26.9 weeks (range 22.4-31 weeks). Patients received either IV ibuprofen lysine 10 mg/kg followed by 5 mg/kg at 24 and 48 hours (n = 12), 1 dose of IV ibuprofen lysine 10 mg/kg (n = 11), or saline (n = 11). No patients in the 3-dose regimen developed PDA, whereas 7 patients in each of the other groups developed PDA (P < .02). The 3-dose regimen of IV ibuprofen lysine within the first 3 hours of life resulted in a statistically significant reduction in the incidence of PDA in infants weighing less than 1460 g and less than 31 weeks of gestational age. Treatment was achieved without any significant adverse symptoms of intestinal, hepatic, neurologic or hematologic complications.[17]

De Carolis et al. evaluated the efficacy in preventing PDA of IV ibuprofen lysine 10 mg/kg followed by 2 doses of 5 mg/kg at 24-hour intervals in 23 preterm infants with a gestational age of less than 31 weeks.[18] Therapy was initiated within 2 hours of life. IV ibuprofen lysine was effective in closing PDA, reducing the need for backup treatment or surgical ligation, and was not associated with significant adverse effects (Table 1).

Van Overmeire et al. evaluated IV ibuprofen 10 mg/kg followed by 5 mg/kg at 24 and 48 hours in an intent-to-treat study in 415 low birth weight infants treated within 6 hours of life.[19] The primary endpoint of the study was the occurrence of intraventricular hemorrhage (IVH); secondary endpoints were the occurrence of PDA or adverse side effects of IV ibuprofen lysine. Of the 205 infant treated with IV ibuprofen lysine, 17 (8%) developed severe IVH, vs. 18 (9%) of the 210 saline-treated infants (relative risk 0.97, 95% CI 0.51-1.82). On day 3, 172 (84%) of the infants in the IV ibuprofen lysine group vs. 126 (60%) of the saline-treated infants had a closed ductus (P < .0001) (Table 1). No statistically significant adverse effects were noted in either group except for a lower urine production on day 1 (1.4 mL/kg/hr IV ibuprofen lysine vs. 2.3 mL/kg/hr saline, P < .0001) and a higher concentration of serum creatinine on day 3 in the IV ibuprofen lysine group (101 μmol/L vs. 88 μmol/L, P < .0001).

In the Trial of Indomethacin Prophylaxis in Preterms (TIPP), indomethacin use for prophylaxis demonstrated a significant reduction in the incidence of PDA but no difference in mortality or survival without impairment.[20] Recently, a retrospective cohort study compared indomethacin prophylaxis to early indomethacin therapy and noted that the incidences of PDA, necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH) were similar between the 2 groups.[21] However, when confounding variables were controlled for, there was a significant difference in the incidence of symptomatic PDA with early treatment compared to prophylaxis (RR 1.79, 95% CI 1.09-2.96, P = .02). The US Food and Drug Administration (FDA) has not approved either IV ibuprofen lysine or indomethacin for prophylaxis in preterm infants at risk for PDA.

One additional study that address efficacy utilizes the European formulation, ibuprofen trishydroxyaminomethane (THAM). Gournay et al. conducted a randomized, double-blind, placebo-controlled study with prophylactic IV ibuprofen THAM (Pedeaprofen, Orphan Drugs, France) in 131 infants of less than 28 weeks gestational age.[22] A total of 65 infants received IV ibuprofen THAM and 66 received IV placebo initiated within 6 hours of life. Surgical ligation was reduced from 6 in the saline-treated group to none in the IV-ibuprofen-THAM-treated group (9% vs. 0%, respectively, P = .03). In addition, IVH occurred in 15 of the saline-treated infants compared to 7 of the IV-ibuprofen-THAM-treated patients (23% vs. 11%, respectively, P = .10) (Table 1). Survival, however, was not improved (IV ibuprofen THAM 71% vs. placebo 72%), due to the high frequency of digestive, respiratory, and renal

Table 1. IV ibuprofen lysine prophylaxis studies

Reference (Study design)	Treatment (sample size) [age;wt]	Ductus closure at 72 hr (%)
13, (Parallel randomized to treatment vs prevention)	Saline (n = 78) [29.2 wk; 1231g]	70
	IBU (n = 77) [29.6 wk; 1226 g]	90
		P =. 0019
17, (Open, non-randomized)	Saline (n = 11) [27.3 wk; 843 g]	64
	IBU 1 dose (n = 11) [26.6 wk; 909 g]	54
	IBU 3 doses (n = 12) [26.5 wk; 948 g]	100
		P = .002 vs. saline*
18, (Parallel randomized blinded)	Untreated (n = 23) [28 wk; 998 g]	30.4
	IBU (n = 23) [28.1 wk; 934 g]	87
		P < .0002
19, (Multicenter, randomized, double blinded, placebo)	Saline (n = 210) [28.1 wk;1065 g]	60
	IBU (n = 205) [28.1 wk; 1047 g]	84
		P < .0001
22, (Parallel randomized, double blinded, placebo Ibuprofen-THAM)	Saline (n = 66) [26 wk; 851 g]	45
	IBU (n = 65) [26.3 wk; 844 g]	72
		P = .0018

IBU, Ibuprofen; INDO, indomethacin
** for significant PDA*

adverse events. The study was stopped prematurely because 3 of the 65 infants developed pulmonary hypertension in the IV ibuprofen THAM group. Ibuprofen THAM is not currently available in the US.

Treatment of PDA: Comparison to indomethacin

Overall, IV ibuprofen lysine is effective in the treatment of PDA based on systematic reviews, meta-analysis, and evidence-based-medicine reviews. Recent trials demonstrate that IV ibuprofen lysine is at least as effective as indomethacin for closure of PDA. Speculation that IV ibuprofen lysine may have a more favorable side effect profile has been validated in the majority of the clinical trials. The data from these trials are suggestive of a safety benefit that IV ibuprofen lysine provides over indomethacin for the closure of PDA in selected populations (Table 2).

Individual clinical trials

A specific review of the 4 main peer-reviewed clinical trials with closure of PDA as the primary outcome follows. In all of these treatment studies, the dose of IV ibuprofen lysine was 10 mg/kg followed by 5 mg/kg 24 and 48 hours later, and the dosing of indomethacin

Table 2. Parallel randomized blinding controlled trials for the treatment of PDA

Ref	Groups (number) [age*; wt]	PDA Closure Rate (%)	Ligation Rate (%)	Death (%)
2†	Ibuprofen (n = 18) [26 wk; 790 g]	78	17	NR
	Indomethacin (n = 15) [26.7 wk;838 g]	93	0	
9†	Ibuprofen (n = 74) [29 wk;1230 g]	66	14	12
	Indomethacin (n = 74) [29 wk;1230 g]	70	12	11
10†	Ibuprofen (n = 94) [28 wk;1126]	73	12	12
	Indomethacin (n = 81) [29 wk;1214 g]	69	15	9
11†	Ibuprofen (n = 20) [29 wk;1270 g]	80	10	5
	Indomethacin (n = 20) [28.7 wk;1210 g]	75	15	15
23†	Ibuprofen: (n = 32) [28.7 wk;1134 g]	84	3	3
	Indomethacin (n = 31) [28.2 wk;1110 g]	81	6	13
24‡	Ibuprofen (n = 8) [29 wk;855 g]	100	—	NR
	Indomethacin (n = 8) [28 wk; 820 g]	100	—	
25‡	Ibuprofen (n = 9) [29.1 wk;1151 g]	100	—	NR
	Indomethacin (n = 8) [29.5 wk;1277 g]	100	—	
Overall calculated percentage				
	Ibuprofen	75.1	10.7	9.9
	Indomethacin	73.5	11.8	11.0

NR, not reported
** Mean gestational age*
† Indomethacin, dose was 0.2 mg/kg per 12 hours for 3 doses
‡ Indomethacin, dose was 0.2 mg/kg for first dose, then 0.1 mg/kg per 24 hours for next 2 doses

was a 3-dose regimen of 0.2 mg/kg every 12 hours. These doses are in compliance with FDA-approved dosing. PDA was confirmed by a complete echocardiographic and Doppler evaluation.

Van Overmeire et al. compared indomethacin to IV ibuprofen lysine in 40 preterm infants less than 33 weeks of gestational age in a randomized clinical trial. In addition to gestational age and confirmed PDA, the criteria also required the infants to have respiratory distress syndrome (RDS).[11] The ductus closure rates were similar between the 2 groups (75% indomethacin vs. 80% IV ibuprofen lysine). Rescue indomethacin treatment was required in 7 infants: 3 in the indomethacin group and 4 in the IV ibuprofen lysine group. Five infants needed surgical ligation: 3 in the indomethacin group and 2 in the IV ibuprofen lysine group. The study concluded that IV ibuprofen lysine is as effective as indomethacin in the closure of PDA. In addition, infants treated with IV ibuprofen lysine had better urine output and lower serum creatinine levels than those in the indomethacin group.

In another study, Van Overmeire et al. com-

pared indomethacin and IV ibuprofen lysine in 148 preterm infants between 24 and 32 weeks of gestational age in a multicenter, randomized clinical trial.[9] In addition to a confirmed PDA by echocardiogram, the criteria required the infants to have RDS. All medication was started on the third day of life. In the indomethacin treated group, 66% (49/74) compared to 70% (52/74) of the IV-ibuprofen-lysine-treated group had successful closure of the ductus (RR 0.94; 95% CI, 0.76-1.17; P = .41). The rates of secondary medication intervention (33% vs. 25% respectively) and surgical ligation (12% vs. 14% respectively) did not differ significantly between groups. Fourteen indomethacin-treated infants developed oliguria compared to 5 on IV ibuprofen lysine (P = .03). The study concluded that IV ibuprofen lysine is as effective as indomethacin in the closure of PDA without reducing renal or mesenteric blood flow and that significantly fewer infants treated with IV ibuprofen lysine compared to indomethacin experienced oliguria.

Lago et al. compared the efficacy of indomethacin and IV ibuprofen lysine in 175 preterm infants between 23 and 34 weeks of gestational age in a randomized, controlled trial.[10] All patients had persistent, hemodynamically significant PDA, as well as RDS. Treatment was started on the second or third day of life. In the indomethacin-treated group 69% (56/81) of infants, and in the IV-ibuprofen-lysine-treated group 73% (69/94) of infants, had a closed PDA after 3 standard doses. In addition, it was noted that closure of the PDA occurred with a higher incidence in infants born at a gestational age of at least 28 weeks compared to gestational age less than 28 weeks (P < .05). Infants receiving indomethacin had a significant increase in serum creatinine compared to infants receiving IV ibuprofen lysine (post-treatment creatinine 89 vs. 81 mmol/L, P = .03). A lower fractional excretion of sodium was also noted with indomethacin (3% vs. 4%, P = .08) although this difference was not statistically significant. More patients on indomethacin developed oliguria compared to IV ibuprofen lysine (15% vs. 1%, P = .017). The study concluded that IV ibuprofen lysine is as effective as indomethacin in the closure of PDA with fewer side effects on renal function related to urine output and fluid retention.

Su et al. compared indomethacin to IV ibuprofen lysine in 63 infants with a significant PDA who were less than 32 weeks gestational age and who weighed less than 1,500 g in a randomized clinical study.[23] All medication was started between the second and seventh day of life. All the infants were on continuous positive airway pressure with supplemental oxygen at least 30% or receiving mechanical ventilation. Prior to therapy, infants had serum creatinine levels less than 1.5 mg/dL and serum platelet count of at least 100,000/μL. No infant had a grade 3-4 IVH before randomization. A total of 27 (84.4%) infants in the IV-ibuprofen-lysine-treated group had PDA closure vs. 25 (80.6%) infants in the indomethacin-treated group. In addition, at 24, 48, and 72 hours the IV ibuprofen lysine group had lower serum creatinine (1.3, 1.48, and 1.66 mg/dL IV ibuprofen lysine vs. 1.71, 2.03, and 1.67 mg/dL indomethacin, respectively, for each time comparison P < .01) and BUN levels (19.8, 22.5, and 26.5 mg/dL vs. 25.8, 31.9, and 32.5 mg/dL, respectively, for each time comparison P < .01) compared to the indomethacin group. Urine output and creatinine clearance levels were higher in the IV ibuprofen lysine group as well (urine output at 24 hours, 3.6 mL/kg/hr vs. 2.8 mL/kg/hr respectively, P < .02; at 72 hours, 4.1 mL/kg/hr vs. 3.4 mL/kg/hr respectively, P = ns; creatinine clearance at 48 hours, 6.8 vs. 5.0 mL/min/1.73 m^2, P < .01; at 72 hours, 7.2 vs. 5.3 mL/min/1.73 m^2, P < .01).[23]

As demonstrated by the clinical trials reviewed above and additional trials evaluating safety concerns with closure of PDA as a secondary outcome,[24,25] IV ibuprofen lysine is as effective as indomethacin in treating PDA in preterm infants and may have a better safety profile.

Evidence-based medicine review/meta-analysis

A Cochrane review evaluated 11 randomized and quasi-randomized, controlled trials conducted in preterm infants with PDA that were less than 37 weeks gestational age or with birth weights less than 2,500 g. The trials evaluated the safety and effectiveness of ibuprofen, both IV and oral, compared to placebo or indomethacin. The dosing of IV ibuprofen lysine was 10 mg/kg followed by 5 mg/kg at 24 and 48 hours. Indomethacin was dosed at 0.2 mg/kg every 12

hours for a total of 3 doses.[7]

Overall, from this review there were no significant differences in outcomes, including failure to close PDA, surgical ligation, mortality, periventricular leukomalacia (PVL), NEC, IVH, retinopathy of prematurity (ROP), sepsis, and number of days on supplemental oxygen.[7] However, for oliguria, IV-ibuprofen-lysine-treated patients fared better, with the number needed to treat (NNT) calculated as 9 (95% CI, 5-14).

In addition to the Cochrane review, other systematic reviews and meta-analyses have been conducted on the various clinical trials. Aranda et al. conducted a systematic review of 9 trials, 2 double-blind studies and 7 open studies, comparing ibuprofen to placebo or indomethacin.[26] Many of the articles reviewed in that article are reviewed in depth elsewhere in this publication. Their analysis concluded that ibuprofen and indomethacin have similar effects on closure in neonates with PDA. Evaluating pre- and post-treatment Doppler blood flow and near infrared spectroscopy on cerebral and/or mesenteric hemodynamics reveals that ibuprofen has minimal negative effect on organ blood flow. In addition, IV ibuprofen lysine reduces the risk of oliguria by increasing urine output, reduces serum creatinine levels, and has less negative effect on organ blood flow compared to indomethacin. Adverse events such as persistent pulmonary hypertension of the newborn (PPHN) have been reported primarily with ibuprofen trishydroxyaminomethane, or THAM (Pedea, Orphan Europe, S.a.r.l., Paris, France); however, one possible case of PPHN in a newborn treated with ibuprofen lysine has also been reported (discussed later in this paper). After evaluating all of the variables, including therapy and adverse effects, the authors suggest that there is a more positive profile for the use of IV ibuprofen over indomethacin.

Thomas et al. conducted a meta-analysis of ibuprofen vs. indomethacin for closure of PDA using 9 trials involving 566 infants less than or equal to 37 weeks gestational age and less than or equal to 2,500 g of weight with a confirmed PDA by echocardiography.[12] The meta-analysis revealed that the efficacies of ibuprofen and indomethacin in closure of PDA were similar. In 2 trials containing 188 infants, significantly more infants required oxygen therapy for at least 28 days, indicating chronic lung disease, in the ibuprofen group than in the indomethacin group (55.3% vs. 40.4%, $P < .05$). In addition, infants on ibuprofen had lower serum creatinine levels, higher urine output, and fewer organ blood flow and vasoconstrictive adverse effects.

SAFETY OVERVIEW

IV ibuprofen lysine is relatively well-tolerated. Overall, there were no serious adverse effects occurring in a greater number of IV-ibuprofen-lysine-treated infants than in those receiving placebo.[13,17-19] Table 3 lists some of the adverse effects that occurred more frequently in clinical trials with IV ibuprofen lysine than placebo, as reported without regard to causality in the package insert.[27] Additional clinical trials have focused more closely on the organ perfusion issues comparing IV ibuprofen lysine to indomethacin.[2,24,25,28] In all of these studies, closure rates of the PDA were similar between IV ibuprofen lysine and indomethacin.

Pezzati et al. evaluated the effect of IV ibuprofen lysine and indomethacin for the treatment of PDA on mesenteric and renal blood flow velocity in 17 preterm (less than 33 weeks of gestation) infants.[25] Preterm infants received either 10 mg/kg ibuprofen lysine (n = 9), or indomethacin 0.2 mg/kg over 15 minutes (n = 8). Mesenteric and renal blood velocity was measured by Doppler ultrasonography. Ibuprofen lysine did not negatively affect blood velocity 30 minutes after administration, and blood flow actually increased 120 minutes after administration. Indomethacin, however, revealed a significant reduction in both mesenteric and renal blood flow velocity 30 minutes after administration, and blood velocity failed to return to normal levels at 120 minutes after administration.

In addition to mesenteric and renal blood flow, cerebral perfusion is a concern with COX inhibitors. In a small study, cerebral blood volume was evaluated 15 minutes after an infusion of IV ibuprofen lysine 5 mg/kg (n = 12), 10 mg/kg (n = 6), or indomethacin 0.1 mg/kg (n = 15) in infants with a median gestational age of 26 weeks (23-28 weeks) and confirmed PDA.[28] The effects of cerebral blood flow were

Table 3. Adverse effects reported in clinical trials[27]

Adverse event	Ibuprofen* (%)	Placebo (%)
Sepsis	43	37
Anemia	32	25
Total bleeding	32	29
Intraventricular hemorrhage, all grades	29	24
Apnea	28	26
Gastrointestinal disorders	22	18
Renal events	21	15

** There was not statistically significant difference in adverse events in those given ibuprofen and those receiving placebo.*
Reproduced with permission of Ovation Pharmaceuticals

measured using near-infrared spectroscopy to evaluate cerebral perfusion by its effect on cerebral blood volume (CBV) and cerebral mitochondrial oxygenation, measured by changes in concentrations of oxidized cytochrome aa_3 ($CytO_2$). The index of dynamic cerebrovascular control was evaluated by the response of CBV to changes in carbon dioxide tension (CBVR). Both doses of IV ibuprofen lysine produced no median changes in CBV or in cerebral mitochondrial oxygenation. In addition, the CBVR increased from 0.13 mL/100 g^{-1} kPa^{-1} before treatment with IV ibuprofen lysine to 0.16 mL/100 g^{-1} kPa^{-1} post treatment. However, indomethacin infusions produced significant decreases in CBV (–0.4 mL/100 g) and $CytO_2$ (–0.2 µmol/L). The CBVR fell from 0.17 mL 100 g^{-1} kPa^{-1} before treatment to 0.06 mL 100 g^{-1} kPa^{-1} ($P < .001$). No apparent differences were observed in the efficacy of IV ibuprofen lysine and indomethacin in the closure of PDA**.** Overall, IV ibuprofen lysine was as efficacious as indomethacin in its ability to close PDA without the negative effects of impairing cerebral hemodynamics and oxygenation associated with indomethacin.

Patel et al. evaluated the effects of the first dose of IV ibuprofen lysine and indomethacin on cerebral blood flow (CBF) and CBV in 33 preterm infants.[2] Upon completion of the drug regimen, PDA closure rates were also evaluated. The mean CBF was 13.6 mL·100 g^{-1} min^{-1} before and 8.3 mL·100 g^{-1} min^{-1} after the first dose of indomethacin ($P < .001$), whereas the IV ibuprofen lysine group had no significant difference in CBF (13.3 vs. 14.9 mL·100 g^{-1} min^{-1}). The differences in median interquartile range values were statistically significant between the groups for cerebral flow volume (CFV) after first dose for indomethacin and IV ibuprofen lysine (–0.4 mL/100 g and 0.0 mL/100 g, respectively), in favor of IV ibuprofen lysine. Attenuated CBF was also noted in the indomethacin group at the 24-hour mark. No significant difference was noted relative to PDA closure between the groups. The study concluded that IV ibuprofen lysine is equally effective at closing the PDA but does not cause significant decreases in CBF and CBV in premature infants.

Mosca et al. evaluated the cerebral perfusion and oxygenation of indomethacin 0.2 mg/kg and IV ibuprofen lysine 10 mg/kg in 16 preterm infants (less than 31 weeks of gestation) with PDA on mechanical ventilation in a randomized study.[24] The trial measured cerebral blood volume (CBV), changes in oxidized cytochrome oxidase concentrations, and PDA closure. The indomethacin group showed statistically significant reductions in both cerebral oxygen availability and perfusion compared to the IV ibuprofen lysine group at 1, 5, 30 and 60 minutes after infusion. The absolute mean value reduction of CBV in the indomethacin groups translated into a 21% decrease from pretreatment values. The study concluded that IV ibuprofen lysine is as effective as indomethacin when used for PDA closure and does not have a negative effect of cerebral perfusion and oxygen availability.

PPHN has been reported in patients receiving IV ibuprofen, particularly with the THAM formulation; however, 1 case was reported with ibuprofen lysine. In the Gournay study,[22] 3 infants developed PPHN after receiving ibuprofen THAM prophylactically within 6 hours of birth. The early administration of ibuprofen THAM may have stalled the normal decrease in pulmonary vascular resistance that would have avoided this adverse event. Bellini

et al. reported that 1 neonate out of 169 in a study developed PPHN after the second dose of ibuprofen lysine.[29] Prior to treatment with ibuprofen lysine for PDA, the neonate had severe pulmonary distress syndrome at birth, which was treated with surfactant (200 mg/kg) on 2 occasions. In addition, the neonate was on a mechanical ventilator. After the second dose of ibuprofen lysine at postnatal age of 4 days, the neonate developed PPHN, which was successfully treated with nitric oxide with resolution of the PPHN. This neonate died of overwhelming sepsis at day 5, suggesting the potential role of sepsis in the pathogenesis of PPHN in this infant.[27]

Drug interactions with ibuprofen lysine are limited. It is a highly protein-bound drug, similar to indomethacin, and can, at concentrations greater than 100 mg/L, affect the site where bilirubin binds to albumin. The resultant displaced bilirubin has the potential to cause hyperbilirubinemia. However, plasma levels of ibuprofen lysine usually do not exceed 50 mg/L. All NSAIDs may increase the gastrointestinal toxicity of corticosteroids; IV ibuprofen lysine is no different. Peltoniemi et al. reported that 3 of 4 infants who developed gastrointestinal perforations while on hydrocortisone were receiving a COX inhibitor.[30] One patient received IV ibuprofen, and the other two received IV indomethacin.

Overall, IV ibuprofen lysine appears to be safe and well tolerated. However, long-term follow-up after the use of any COX inhibitor in the treatment of PDA has not been sufficiently studied.[1,12]

CONCLUSION

In this review of the literature, IV ibuprofen lysine is considered safe and effective in the management of PDA. Both IV ibuprofen lysine and indomethacin achieve their pharmacologic effect by the inhibition of COX-1 and COX-2, which have vasodilatation effects. IV ibuprofen lysine may have a greater effect on COX-2, a potent endogenous vasodilator primarily intrinsic to the ductus that is responsible for ductal patency during fetal development, without interfering with cerebral, mesenteric, or renal blood flow, as is seen with indomethacin. The dose of IV-ibuprofen-lysine established in clinical trials is 10 mg/kg as an initial dose followed by 5 mg/kg at 24 and 48 hours. When one is considering prophylaxis of PDA, IV ibuprofen lysine may have a place in therapy, although no studies have compared IV ibuprofen lysine to indomethacin for this indication.

IV-ibuprofen-lysine-treated patients also had better creatinine clearance, urine output, serum creatinine and BUN profile than indomethacin-treated patients. Although prophylactic use of COX inhibitors has not been delineated, IV ibuprofen lysine treatment of PDA in preterm low birth weight infants from the second day of life on has been shown to be a first-line therapy that is efficacious with fewer adverse side effects than indomethacin. IV ibuprofen lysine has been shown to significantly reduce PDA requiring rescue and has not been associated with PPHN or hemorrhage. Its safety profile shows no statistically significant differences vs. placebo in the incidence of IVH, NEC, lung disease or ROP. In addition, the renal effects of IV ibuprofen lysine are significantly better than the adverse impact of indomethacin. There is ongoing research to further elucidate the answers to the questions that still remain concerning the use of ibuprofen lysine for the treatment of PDA.

DISCLOSURE Dr. DeSantis received an honorarium from Akita Biomedical Consulting.

Dr. Aranda served as an unpaid (pro bono) and paid (small grants, honoraria) consultant on drug and protocol development for various Pharmaceutical companies (Purdue, Farmacon, Mead Johnson, Whitehall Robins, Pfizer, Aventis, Merck, Bristol Myers Squibb-Mead Johnson, Glaxo, AstraZeneca etc.).

ca: 120 Clinical Trials from Phase 1 to Phase 4 (1999-2007).

Support for clinical studies from various pharmaceutical companies for trials performed independently or with the NIH Pediatric Pharmacology Research Network (NICHD-PPRU).

Consultant–Educational Program–Ross Abbott(12/05 only) and Ovation Pharma (2006-2007).

REFERENCES

1. Shah SS, Ohlsson A. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2006,(1):CD004213.pub2.

2. 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.
3. Cotton RB, Stahlman MT, Bender HW, et al. Randomized trial of early closure of symptomatic patent ductus arteriosus in small preterm infants. J Pediatr 1978;93:647-651.
4. Naulty CM, Horn S, Conry J, et al. Improved lung compliance after ligation of patient ductus arteriosus in hyaline membrane disease. J Pediatr 1978;93:682-684.
5. Lee SK, McMillan DD, Ohlsson A, Pendray M, Synnes A, Whyte R, et al. Variations in practice and outcomes in the Canadian NICU network: 1996-1997. Pediatrics 2000;106:1070-1079.
6. Friedman WF, Hirschklau MJ, Printz MP, et al. Pharmacologic closure of patent ductus arteriosus in the premature infant. N Engl J Med 1976;295:526-529.
7. Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2005,(4):CD003481.pub2.
8. Gersony WM, Peckham GJ, Ellison RC, et al. Effects of indomethacin in premature infants with patent ductus arteriosus: Results of a national collaborative study. J Pediatr 1983;102:895-905.
9. 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.
10. 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.
11. Van Overmeire B, Follens I, Hartmann S, et al. Treatment of patent ductus arteriosus with ibuprofen. Arch Dis Child Fetal Neonatal Ed 1997;76:179-184.
12. Thomas RL, Parker GC, Van Overmeire B, et al. A meta-analysis of ibuprofen versus indomethacin for closure of patent ductus arteriosus. Eur J Pediatr 2005;164:135-140.
13. Dani C, Bertini G, Pezzati M, et al. Prophylactic ibuprofen for the prevention of intraventricular hemorrhage (IVH) among preterm infants: A multicenter, randomized study. Pediatrics 2005;115:1529-1535.
14. Hermes-DeSantis ER, Clyman RI. Patent ductus arteriosus: Pathophysiology and management. J Perinatol 2006;26:S14-S18.
15. Lacy CF, Armstrong LL, Goldman MP, et al. Drug Information Handbook, 14th ed. Hudson, OH: Lexi-Comp; 2006-2007:806-808.
16. Desfrere L, Zohar S, Morville P, et al. Dose-finding study of ibuprofen in patent ductus arteriosus using the continual reassessment method. J Clin Pharm Ther 2005;30:121-132.
17. Varvarigou A, Bardin CL, Beharry K, et al. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. JAMA 1996;275:539-544.
18. 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.
19. Van Overmeire B, Allegaert K, Casaer A, et al. Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2004;364:1945-1949.
20. 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;344:1966-1972.
21. Cordero L, Nankervis CA, DeLooze D, et al. Indomethacin prophylaxis or expectant treatment of patent ductus arteriosus in extremely low birth weight infants? J Perinatol 2007, 27:158-163.

22. 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;364:1939-1944.
23. Su P-H, Chen J-Y, Su C-M, et al. Comparison of ibuprofen and indomethacin therapy for patent ductus arteriosus in preterm infants. Pediatr Int 2003;45:665-670.
24. 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;131:549-554.
25. 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;135:733-738.
26. Aranda JV, Thomas R. Systematic review: intravenous ibuprofen in preterm newborns. Semin Perinatol 2006;30:114-120.
27. Ovation Pharmaceuticals. NeoProfen (ibuprofen lysine) package insert. Deerfield, IL ; May 2006.
28. Patel J, Marks KA, Roberts I, et al. Ibuprofen treatment of patent ductus arteriosus. Lancet 1995;346:255.
29. Bellini C, Campone F, Serra G. Pulmonary hypertension following L-lysine ibuprofen therapy in a preterm infant with patent ductus arteriosus. CMAJ 2006;174:1843-1844.
30. Peltoniem IO, Kari MA, Heinonen K, et al. Pretreatment cortisol values may predict responses to hydrocortisone administration for the prevention of bronchopulmonary dysplasia in high-risk infants. J Pediatr 2005;146:632-637.