REVIEW ARTICLE

Clinical Considerations for the Pharmacologic Management of Patent Ductus Arteriosus with Cyclooxygenase Inhibitors in Premature Infants

Karen E. Corff, MS, ARNP and Kris C. Sekar, MD

Department of Pediatrics, Neonatal-Perinatal Medicine,University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

When medical management is warranted for closure of a persistent patent ductus arteriosus (PDA) in premature infants, treatment with a cyclooxygenase (COX) inhibitor is indicated. Indomethacin, available since 1976, has been the conventional pharmacologic treatment for PDA, but its use is associated with vasoconstrictive effects that impair renal, mesenteric and cerebral blood flow. Intravenous (IV) ibuprofen lysine, approved in the United States in 2006, has less severe vasoconstrictive effects on these vital organs than IV indomethacin. Clinical trials have shown both of these COX inhibitors to be equally effective in closing the PDA in approximately 70%-80% of treated infants, with less vasoconstrictive and adverse renal effects occurring with IV ibuprofen lysine.[1,2] Several clinical considerations are important in the process of medical decision-making when faced with the need for PDA treatment with one of these pharmacologic agents in the premature infant. This paper focuses on these clinical considerations, including cerebral, renal and mesenteric blood flow, renal function, pulmonary effects, protein-binding capacity as it relates to hyperbilirubinemia, and platelet aggregation. No differences in chronic lung disease, pulmonary hypertension, hyperbilirubinemia and coagulopathy were observed in clinical trials when comparing these 2 COX inhibitors; however, significant differences have been observed in arterial blood flow to the cerebral, renal and mesenteric organs, suggesting that IV ibuprofen lysine may be the more favorable agent.

KEYWORDS ibuprofen, indomethacin, patent ductus arteriosus, prematurity

J Pediatr Pharmacol Ther 2007;12:147-157

INTRODUCTION

In term infants, the ductus arteriosus (DA) typically closes in the first day of life, but in preterm infants, closure is often either delayed or does not occur at all.[3] Persistence of the DA is inversely related to gestational age. Spontaneous patent ductus arteriosus (PDA) closure occurs in up to 40% of prematurely born infants, but up to 70% of those born weighing less than 1,000 g require some form of intervention due to significant hemodynamic symptomatology.[4] The persistence of the PDA puts the infant at

ABBREVIATIONS BPD, bronchopulmonary dysplasia; BUN, blood urea nitrogen; CBF, cerebral blood flow; CBV, cerebral blood volume; CLD, chronic lung disease; COX, cyclooxygenase; DA, ductus arteriosus; FDA, Food and Drug Administration; IV, intravenous; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; $PaCO_2$, partial arterial pressure of carbon dioxide; PDA, patient ductus arteriosus; PMA, postmenstrual age; PPHN, persistent pulmonary hypertension of the newborn; SE, standard error; THAM, trishydroxyamino-methane

Address correspondence to: Karen E. Corff, MS, ARNP, 1200 Everett Drive, 7th Floor North Pavilion, Oklahoma City, OK 73104, email: Karen-Corff@ouhsc.edu

higher risk for undesirable pulmonary, hemodynamic, gastrointestinal, and renal effects including intraventricular hemorrhage (IVH), pulmonary edema, congestive heart failure, cerebral vascular accidents, necrotizing enterocolitis (NEC), poor weight gain, bronchopulmonary dysplasia (BPD), and death.[2,5]

Available treatment options include conservative medical management, pharmacologic therapy, and surgical ligation. There is a high failure rate with conservative medical management, which involves watchful waiting, fluid restriction, and possibly mechanical ventilation, especially in very low birth weight infants.[4] Surgical ligation in infants of less than 28 weeks gestation requires a thoracotomy and is associated with significant morbidities including pneumothorax, chylothorax, infection, laryngeal nerve paralysis, respiratory compromise, blood pressure fluctuation, intracranial hemorrhage, bronchopulmonary dysplasia, retinopathy of prematurity, neurosensory impairment, and even death.[4,6-8] Pharmacologic therapy involves the use of cyclooxygenase (COX) inhibitors, which have been shown to be safe and effective in 70%-80% of treated infants.[1,2]

Currently, there are 2 equally effective intravenous (IV) COX inhibitors available: IV indomethacin (Indocin; Ovation Pharmaceuticals, Deerfield, IL) and IV ibuprofen lysine (NeoProfen; Ovation Pharmaceuticals, Deerfield, IL).[1] Oral ibuprofen has been shown to be effective in closing PDAs in 3 studies; however, these were small, nonrandomized studies, and definite conclusions of efficacy and safety cannot be made from these trials.[9-11] Prior to 2006, when IV ibuprofen lysine was approved by the US Food and Drug Administration (FDA), IV indomethacin had been the standard of pharmacologic care for closure of PDA; however, adverse effects related to vasoconstriction of renal, mesenteric and cerebral blood flow caused by IV indomethacin left clinicians concerned about its use. Recent research has shown IV ibuprofen lysine to be associated with less of these adverse vasoconstrictive effects, making it a desirable alternative to indomethacin.

This review examines the clinical considerations surrounding the approved IV COX inhibitors, indomethacin and ibuprofen lysine. In particular, this article focuses on the safety and efficacy of these COX inhibitors with emphasis on the important differences demonstrated by clinical trials, including a comparison of these agents' effects on blood flow to the cerebral, renal and mesenteric arteries, and on renal function. Further, key clinical issues discussed in this paper include comparative effects on pulmonary outcomes, protein binding, platelet aggregation, gastrointestinal bleeding, and mortality.

CLINICAL CONSIDERATIONS IN THE MEDICAL MANAGEMENT OF PDA

Premature infants with respiratory distress and echocardiographically confirmed PDA warrant treatment with COX inhibitors to prevent the hemodynamic instability and undesirable sequelae associated with persistent PDA. IV ibuprofen lysine and IV indomethacin are chemically different and inhibit COX-1 and COX-2 isoforms to a different degree. By inhibiting COX-1 and COX-2 isoforms, prostaglandins, which support the patency of the DA, are inhibited.[8,12] Indomethacin has stronger COX-1 inhibition, which produces more severe gastrointestinal, cerebral, and renal side effects than COX-2 inhibition.[12] IV ibuprofen lysine inhibits both COX-1 and COX-2 enzymes but has less COX-1 inhibition than indomethacin, which results in less severe vasoconstrictive side effects on these vital organs.[13-17] IV ibuprofen lysine and indomethacin have been shown to be equally efficacious in the closure of PDA in preterm infants[1,2,8,18-25] and significantly more effective than placebo ($P < .0001$[26] and $P = .0018$,[27,28] respectively).

COMPARATIVE VASOCONSTRICTIVE EFFECTS

Clinical trials have shown that adverse vasoconstrictive effects to renal, cerebral and mesenteric vessels are less pronounced with the use of IV ibuprofen lysine than with IV indomethacin. Ibuprofen closes the DA in animals without affecting basal cerebral blood flow (CBF) or renal or intestinal hemodynamics during positive pressure ventilation.[29] Supporting this evidence, studies of premature infants have shown that IV ibuprofen lysine did not significantly reduce CBF.[30,31] In contrast, indomethacin induced significant reductions in CBF velocity in clinical trials.[32,33] Compara-

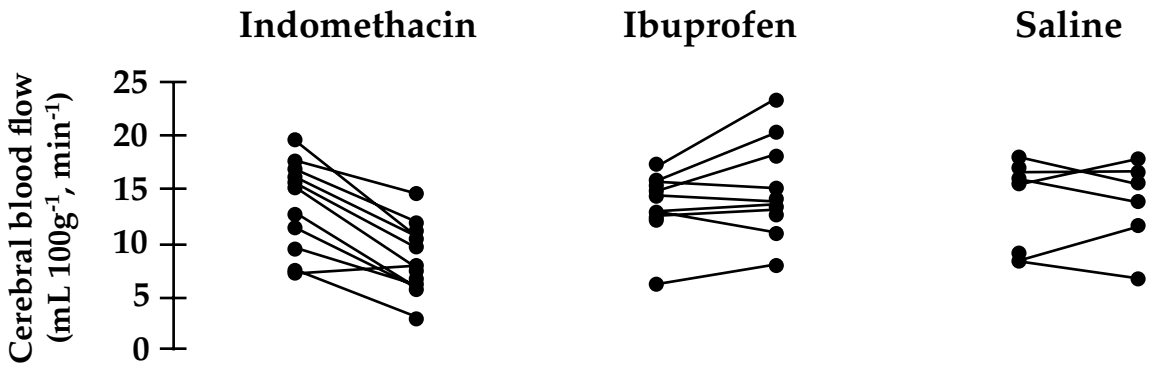

Figure 1. Effects of ibuprofen vs. indomethacin on cerebral perfusion. Indomethacin induced changes in cerebral circulation: decrease in blood flow, decreased cerebral blood volume, decreased oxygen delivery. Source: Patel J, Roberts I, Azzopardi D, et al. Randomized double-blind controlled trial comparing the effects of ibuprofen with indomethacin on cerebral hemodynamics in preterm infants with patent ductus arteriosus. Reprinted from reference 35 with permission of Lippincott Williams & Wilkins.

tive drug studies of IV ibuprofen versus IV indomethacin showed that indomethacin, but not ibuprofen, induced significant reductions in CBF (Figure 1).[34-36]

In addition, trials using indomethacin in preterm infants showed significant reduction in mesenteric [37,38] and renal[39] blood flow velocity measured by Doppler ultrasound.[17] Using indomethacin during positive pressure ventilation compromised regional hemodynamic blood flow to the kidneys (decreased 37%-57%), to the ileum (decreased 58%-74%), and to the colon (decreased 53%-71%) in a study by Malcolm.[13] A drug comparison trial of indomethacin vs. ibuprofen by Pezzati et al. confirmed that mesenteric and renal perfusion were more compromised with the use of indomethacin.[17]

Cerebral Effects

In animal studies, IV ibuprofen enhanced CBF[36] and cerebral autoregulation and protected neurologic functions after oxidative stress.[40] Animal and human newborn studies have shown that ibuprofen is efficacious in closing the PDA without reducing CBF[29,31,35,41,42] or altering cerebral vasoreactivity to carbon dioxide,[31] and that it may extend the range of blood pressures for which CBF is autoregulated.[16,35,40,41] This differs from the effects of indomethacin, which caused a significant and marked reduction in CBF, cerebral blood volume (CBV), response in CBV to changes in partial pressure of carbon dioxide ($PaCO_2$) velocity, and cerebral intracellular oxygenation (P = .022) compared to ibuprofen, as measured by Doppler ultrasound, near-infrared spectroscopy, and concentration of oxidized cytochrome oxidase.[41,43] Compared to indomethacin in drug comparison trials, treatment with ibuprofen did not significantly reduce cerebral perfusion or oxygen availability and had no adverse effects on cerebral hemodynamics (Figure 1).[35,41]

Indomethacin vs. placebo trials have shown a reduction in IVH among very low birth weight infants in prophylaxis.[44-47] The decrease in CBF caused by indomethacin may account for the decreased incidence of IVH seen in indomethacin-treated infants. Decreased CBF is accompanied by decreased cerebral oxygenation,[35] which could lead to cerebral ischemia.[48] Ohlsson argues that the positive effects of indomethacin on short-term reduction of IVH[44] may be outweighed by its longer-term effects on reducing CBF.[49] Several clinical trials studying indomethacin excluded infants who had preexisting IVH.[27,48] Two placebo-controlled trials with IV ibuprofen lysine did not show any statistically significant difference in incidence of any stage of IVH between the placebo- and IV-ibuprofen-lysine-treated infants.[26,50] Severe IVH (grade 3 or 4), as reported in 4 ibuprofen vs. placebo-control trials[24,26,28,50] and in the Cochrane[27] meta-analysis, showed no significant difference between groups.

Comparison trials of IV ibuprofen lysine and indomethacin showed no significant differences in the occurrence of initial IVH or the extension of IVH[1,2,18,19,41] between the 2 drugs. Incidence of periventricular leukomalacia (PVL), as reported in ibuprofen lysine vs. placebo trials,[24,26,28] in

IV ibuprofen lysine vs. indomethacin comparison trials,[1,18] and in a meta-analysis of 6 drug comparison trials,[25] was also not statistically different. Long-term neurologic outcomes after initial hospital discharge have not been sufficiently studied or reported to know if long term neurodevelopmental outcomes are affected by COX inhibitor treatment of PDA.[25,27]

Renal Effects

The greatest and most significant differences observed in clinical trials in patient tolerance of the 2 available COX inhibitors were in renal effects. When comparing renal and mesenteric blood flow using IV ibuprofen vs. IV indomethacin, Pezzati et al.[17] found significantly less decrease in renal blood flow ($P < .0001$) and mesenteric blood flow ($P < .0001$) with IV ibuprofen. The differential effects upon renal blood flow with IV indomethacin have been observed clinically. At the recommended dose of indomethacin, oliguria is a frequent side effect. In clinical settings, this often requires interruption of the treatment regimen. To counter this side effect, furosemide and/or dopamine are often used; however, use of furosemide increases circulating prostaglandin levels and may counteract treatment effectiveness.[51]

Decrease in urine output as a side effect of therapy was significantly less with IV ibuprofen lysine compared to indomethacin in a pooled analysis of 4 studies ($P < .00001$).[1,2,18,41] Infants treated with IV ibuprofen lysine had higher creatinine clearance, lower serum creatinine values ($P = .03$),[18] and lower blood urea nitrogen (BUN) values than infants treated with indomethacin.[19] Oliguria was significantly higher in the indomethacin group ($P = .017$).[18] Pezzati et al.[17] reported that urine output ($P < .05$) and serum creatinine ($P < .02$) were significantly affected by indomethacin; urine output took 7 days to return to pretreatment levels. Infants treated with indomethacin had a significant decrease in urine output on all 3 days of therapy ($P < .05$), while infants treated with IV ibuprofen lysine had a decrease only on day 1.[17] Patel et al.[35] found that infants developed oliguria and elevated serum creatinine after the first dose of indomethacin, while none of the ibuprofen infants in his study experienced adverse renal events.

Van Overmeire et al.,[1] in a comparison trial of IV ibuprofen lysine and IV indomethacin for closure of PDA (n = 148), showed significantly less oliguria with ibuprofen lysine ($P = .001$ over all treatment days) (Figure 2) and significantly lower serum creatinine concentrations in the indomethacin group ($P = .04$ overall) (Figure 3). A meta-analysis of 5 IV ibuprofen lysine vs. indomethacin trials (n = 443) confirmed these findings, revealing a smaller increase in serum creatinine ($P < .001$) and a significantly smaller decrease in urine output ($P < .001$) with IV ibuprofen lysine.[25] In multicenter trials of IV ibuprofen lysine, there was a small decrease in urinary output on days 2-6 of life in the ibuprofen groups with a compensatory increase on day 9; however, there were no statistically significant differences in total renal-related events between placebo and IV ibuprofen lysine.[20] These data underscore that IV ibuprofen lysine does not cause a reduction in renal blood flow velocity[1,17,30] as described under vasoconstrictive effects and is therefore associated with significantly less impairment of renal function in these tiny babies.

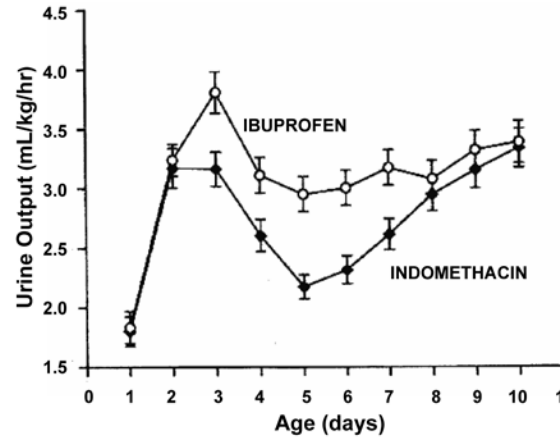

Figure 2. Urine output in the indomethacin and ibuprofen lysine groups. The values are means ± SE. There were significant differences between the treatment groups from day 3 to day 7 ($P < .001$ overall). Source: Van Overmeire, B, Smets, K, Lecoutere, D, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. N Engl J Med 2000;343:674-81.1 Copyright © 2000 Massachusetts Medical Society. All rights reserved.

Mesenteric Effects

NEC is one of the most common and devastating gastrointestinal complications of extreme prematurity. With mortality rates approaching 50% in infants with birth weight of less than

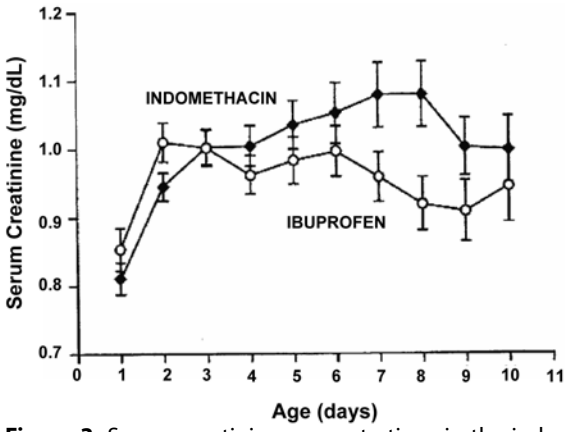

Figure 3. Serum creatinine concentrations in the indomethacin and ibuprofen lysine groups. Values are shown as means ± SE. There were significant differences between treatment groups from day 4 to day 8 (P = .04 overall). To convert values for creatinine to micromoles per liter, multiply by 88.4. Source: 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;343:674-81.1 Copyright © 2000 Massachusetts Medical Society. All rights reserved.

1,500 g,[52] the etiology of this disease remains unclear. Nonetheless, factors associated with NEC include PDA, low birth weight, immaturity of the gut with impaired immunologic defense, bacterial gut colonization, and enteral feedings.[52,53]

The literature is conflicting regarding the association of COX therapy and PDA as causative factors for NEC in premature neonates. It has been suggested that the combined mesenteric vasoconstriction created from the PDA and COX therapy with indomethacin may accentuate intestinal ischemia.[54] In a study of 17 mechanically ventilated preterm infants with a PDA, indomethacin, but not ibuprofen, was found to significantly decrease mesenteric blood flow (P < .0001).[17] This vasoconstriction was present within 30 minutes of administration, and had not returned to pretreatment levels within 120 minutes;[17] however, in very low birth weight infants, indomethacin without the presence of a PDA was not associated with an increased risk of NEC.[54]

Hypoperfusion of the gut with resulting mucosal hypoxia may lead to ischemia and ulceration, allowing bacterial invasion to occur.[55,56] Animal studies have demonstrated a significant reduction in mesenteric blood flow with the use of indomethacin.[14,15,57] In contrast, ibuprofen was observed not to alter mesenteric blood flow, but to possibly have a direct cytoprotective role in bowel ischemia.[14] One study showed ibuprofen was associated with an improved survival rate (P < .005) and a reduction in the incidence of bowel necrosis.[15]

Some clinical trials have shown an increased incidence of NEC[58] and gastrointestinal perforation[55] in low birth weight infants treated with indomethacin. However, a multicenter study on the long term effects of indomethacin prophylaxis indicated that the incidence of NEC was similar between indomethacin-treated and untreated infants.[59] Several systematic reviews of either symptomatic or prophylactic indomethacin therapy for PDA compared to no treatment or surgical intervention demonstrated no increased risk of NEC.[60-62] In a Cochrane review of 5 PDA treatment studies, no significant differences were found between IV indomethacin (n = 221) and IV ibuprofen lysine (n = 235) in the incidence of NEC, but there was a trend toward less NEC with ibuprofen lysine (P = .09).[23] Another systematic review of 4 PDA prevention trials that compared IV ibuprofen lysine (n = 333) and placebo or no therapy (n = 339) showed no significant difference in the incidence of NEC.[27] One of the studies included in the prevention meta-analysis found a higher incidence of NEC with ibuprofen trishydroxyamino-methane (THAM) (Pedea, Orphan Europe S.a.r.l., Paris, France) vs. placebo.[28] It is important to note that ibuprofen THAM is not the same formulation as IV ibuprofen lysine and is not available in the United States. A double-blind multicenter study of IV ibuprofen lysine vs. placebo (n = 136) for the early treatment of PDA in infants weighing less than 1,000 grams at less than 72 hours of age showed no statistically significant difference in the incidence of NEC between IV ibuprofen lysine and placebo.[20] Such data suggest that PDA is a major factor in the development of NEC and that effective closure of the PDA is benevolent medical management.

PULMONARY EFFECTS

Due to right-to-left cardiac shunting with a PDA, pulmonary function is compromised. The lower the gestational age of a prematurely born infant, the greater the occurrence of PDA, respiratory distress syndrome, and the greater

the risk of resulting chronic lung disease (CLD) or BPD. CLD in preterm infants has a multifactorial etiology. Genetics, oxygen exposure, mechanical ventilation, degree of immaturity, infection, and PDA are all compounding factors in the development of CLD. Perinatal steroids and tocolytics, coupled with postnatal surfactant and an increased use of noninvasive modes of respiratory support, have lowered the incidence and severity of CLD but have not eliminated it.

The definition of BPD or CLD differs among authors and clinicians. The definition of BPD/CLD as "the need for supplemental oxygen at 28 days of life" has been modified by clinicians who emphasize that an infant born at 24-25 weeks gestation is still 11-12 weeks premature at 28 days of life. Shennan et al.[63] found that the definition "the need for supplemental oxygen at 36 weeks postmenstrual age (PMA)" is a more accurate marker of adverse pulmonary outcome.

Chronic Lung Disease

The effect of COX inhibitors for PDA closure on the incidence of CLD has been analyzed in several meta-analyses. A Cochrane meta-analysis[23] of 2 controlled IV indomethacin vs. IV ibuprofen studies[1,2] reported a possible association of IV ibuprofen lysine with CLD when CLD is defined as the need for supplemental oxygen at 28 days of age.[23] However, neither of the original studies independently found a significant difference in oxygen use at 28 days of age.[1,2] It should be noted that the use of surfactant among patients in this review (n = 188) was greater in the indomethacin groups (87%) compared to the ibuprofen lysine groups (75%)[1,2] The same meta-analysis did not find a significant difference in CLD when defined as oxygen use at 36 weeks PMA.[23] A more recent Cochrane meta-analysis of PDA prevention studies did not find a significant difference between placebo and IV ibuprofen lysine in oxygen use at 28 days or at 36 weeks PMA.[27]

Persistent Pulmonary Hypertension of the Newborn

In a study in France using prophylactic ibuprofen THAM (n = 65) vs. placebo (n = 66) in very preterm infants, 3 cases of persistent pulmonary hypertension of the newborn (PPHN) were reported, and the study was stopped early as a safety measure.[28] Ibuprofen THAM (approved for use in Europe, but not in the United States) contains a buffer solution contraindicated in anuria and uremia, whereas ibuprofen lysine is a different agent (approved for use in the United States) containing an essential amino acid that is generally well tolerated in infants. Mosca et al. reported that in 227 mechanically ventilated preterm infants treated with IV ibuprofen lysine for documented PDA there was no causal association with pulmonary hypertension.[64] In another controlled, prophylactic IV ibuprofen lysine vs. placebo trial, 205 neonates received IV ibuprofen lysine with no associated hypoxemia events.[26]

One case report of PPHN has been reported following the use of IV ibuprofen lysine in a 1,600 g, 32 week gestational age infant who later died of sepsis at 4 days of life.[65] This finding has not been reported in any multicenter, randomized, double-blind, controlled trial.[65] The current US-approved labeling for IV ibuprofen lysine recommends treatment in infants weighing less than 1,500 g or less than 32 weeks gestational age based on studies in this age group for FDA approval.[66] The Cochrane review of 11 studies with 620 infants showed no cases of pulmonary-hypertension-induced severe hypoxemia.[23] In a pivotal placebo-controlled trial completed for FDA approval of IV ibuprofen lysine in the US, the number of cases of pulmonary hemorrhage and pulmonary hypertension by day 14 was similar for placebo- and IV-ibuprofen-lysine-treated infants.[66]

EFFECTS ON HEMOREGULATION

Both indomethacin and ibuprofen are COX inhibitors that block the conversion of arachidonic acid to prostaglandins. Their side effects include inhibition of platelet aggregation. In adult studies, IV ibuprofen lysine has a minimal effect on platelet aggregation that can cause a modest increase in bleeding time not exceeding the upper limit of normal, and these effects are short-lived and dissipate between 6 and 24 hours after dosing.[67] Indomethacin's effect on platelet aggregation persists longer, into the second day.[68] The pharmacodynamics and pharmacokinetics differ between adult and neonatal groups. Due to renal function immaturity, premature infants have substantially

slower elimination and prolonged half-life of these medications. Drug clearance increases and half-life decreases with advancing postnatal age, but in infants the half-life is generally more than 10 times greater than in adults.[66,69] Concerns regarding IVH due to the inhibition of platelet aggregation have led investigators to include IVH as an endpoint in clinical trials of both IV ibuprofen lysine and indomethacin. The relative risk for developing IVH is similar for both indomethacin- and ibuprofen-treated infants, and there may be a risk of increasing preexisting hemorrhages with the use of COX inhibitors. However, comparison trails of the 2 drugs showed no significant differences in the occurrence of initial IVH or the extension of IVH.[1,2,18,19,41] Even so, if a preexisting IVH is present, many practitioners will wait 24 hours before initiating treatment with COX inhibitors to prevent the risk of exacerbation of the IVH.

EFFECTS ON PROTEIN BINDING

COX inhibitors are highly protein-bound (95%-98%) drugs and can potentially displace bilirubin from its binding site on albumin, increasing free bilirubin levels. Hyperbilirubinemia is a common finding in premature infants, who are at increased risk for kernicterus. Unbound bilirubin that crosses the blood brain barrier is the best indicator of risk for kernicterus, but risk thresholds for adverse neurologic outcomes currently do not exist.[70] The degree of protein binding with COX inhibitors is concentration-dependent. At a bilirubin-to-albumin ratio of greater than or equal to 1 and a bilirubin concentration of greater than or equal to 10 mg/dL, potential displacement of serum bilirubin could occur with different serum concentrations of ibuprofen.[71] Studies in premature infants indicate that bilirubin can be displaced at an ibuprofen concentration of 100 mg/L, but not at 50 mg/L or below.[72,73] In the intended population, with the approved dose and infusion time of IV ibuprofen lysine, plasma levels of ibuprofen rarely exceed 50 mg/L.[66]

In clinical trials of IV ibuprofen lysine vs. placebo or no treatment, there were no clinically important differences in elevated bilirubin levels. In a pooled analysis of major studies, neonatal hyperbilirubinemia was reported in a lower percentage of infants receiving IV ibuprofen lysine than placebo or no treatment. A lower percentage of infants in the indomethacin comparator group experienced hyperbilirubinemia compared with infants receiving IV ibuprofen lysine, placebo or no treatment.[1,20,26,66] In 2 comparison studies by Van Overmeire, the incidence rates for neonatal hyperbilirubinemia were similar for infants treated with IV ibuprofen lysine or indomethacin[1] and infants treated with IV ibuprofen lysine or placebo.[26] A clinical trial of 15 preterm newborns tested for unbound bilirubin before and after IV ibuprofen administration at the recommended dosage showed no significant change in free or unbound bilirubin before or after ibuprofen infusion (1.07 μg/dL vs. 1.0 μg/dL).[74] These observations suggest that, at the doses recommended, IV ibuprofen lysine does not produce significant bilirubin-drug-albumin interactions.[21]

OTHER EFFECTS

Comparative clinical trials and meta-analyses of these studies have demonstrated that the 2 available COX inhibitors, IV ibuprofen lysine and IV indomethacin, are both safe and equally effective for PDA closure in preterm infants. Of the other multiple variables studied, significant differences were seen in maintenance of cerebral, mesenteric and renal blood flow and in less impairment of urine output and less elevation of creatinine levels favoring IV ibuprofen lysine.

No statistically significant differences in other adverse outcomes were found in any of the individual comparison trials or placebo-controlled trials or in meta-analyses.[23] The incidence of PDA reopening or the need for surgical PDA ligation were not statistically different in meta-analyses of IV ibuprofen lysine vs. placebo trials [27] or in drug comparison trials.[25] Neonatal mortality at less than 28 days of age,[23,24,27,50] at 36 weeks PMA,[27] or during the infants' initial hospital stay [24-26,50] showed no statistically significant differences between groups. Days on mechanical ventilation were similar in placebo-controlled [28,50] and comparison trials.[25] Gastrointestinal bleeding, defined as either occult blood in the stool, gastric bleeding, or localized bowel perforations, showed no statistically significant difference between trial groups using either COX inhibitor [25] or in trials

comparing IV ibuprofen lysine with placebo.[27] Occurrence of retinopathy of prematurity[50] or sepsis[24] was not significantly different in those trials reporting these variables or in 2 meta-analyses.[25,27] Time to reach full enteral feeding and length of hospital stay were not statistically different.[50] Outcomes after initial hospital discharge, including neurologic outcomes, have not been reported and require further study.

CONCLUSIONS

Persistent PDA in premature infants is associated with serious complications and adverse outcomes. Close medical monitoring and informed decision-making are essential in assuring the best treatment plan for optimal patient outcomes. Conservative medical treatment fails in two-thirds of infants delivered before 28 weeks gestation with birth weights less than 1,750 g.[28] Surgical ligation is associated with significant and serious short- and long-term morbidities.[4,6-8] When conservative measures fail to close the PDA, pharmacologic treatment with a COX inhibitor, IV Ibuprofen lysine or IV indomethacin, is recommended. Both agents are equally effective, closing the DA in 70%-80% of patients. Among the ibuprofen agents, only ibuprofen lysine is approved for use in the US.

Serious concerns with the use of these agents regarding renal compromise, PPHN, NEC, gastric perforation, IVH, CLD, hyperbilirubinemia, and coagulopathy have prompted multiple clinical trials. These studies have shown IV ibuprofen lysine to be more favorable in renal side effects, with significantly less rise in creatinine levels and less oliguria. PPHN has been seen only with ibuprofen THAM, which is not available in the US. There is no increase in the incidence of gastrointestinal complications with either agent. Prophylactic indomethacin has shown some protective properties against severe IVH, but concerns regarding treating children whose DAs might spontaneously close (60%) have prevented this from becoming widespread practice. Comparison treatment trials show no differences in the incidence of initial IVH or extension of existing IVH between the 2 drugs in treatment trials. There is no increase in the incidence of CLD at 36 weeks PMA with either drug, nor is there an increase in significant hyperbilirubinemia or bleeding dyscrasia. For treatment of PDA, IV ibuprofen lysine would be the treatment of choice due to significantly less renal side effects.

DISCLOSURE Dr. Sekar is on the speaker's bureau for Ovation and both authors have received honoraria from Akita Biomedical Consulting.

REFERENCES

1. 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.
2. Van Overmeire B, Follens I, Hartmann S, et al. Treatment of patent ductus arteriosus with ibuprofen. Arch Dis Child Fetal Neonatal Ed 1997:76: F179-F184.
3. Cardiac abnormalities. In: Gomella TL, Cunningham MD, Eyal FG, et al., eds. Neonatology: management, procedures, on-call problems, diseases, and drugs. 4th ed. Stamford, CT: Appleton & Lange; 1999:335-352.
4. Hermes-DeSantis ER, Clyman RI. Patent ductus arteriosus: pathophysiology and management. J Perinat 2006;26:S14-S18.
5. Cotton RB, Stahlman MT, Dovar I, et al. Medical management of small preterm infants with symptomatic patent ductus arteriosus. *J Pediatrics* 1979;2:467-473.
6. Clyman RI, Chorne N. Patent ductus arteriosus: Evidence for and against treatment. J Pediatrics 2007;150:216-219.
7. Kabra NS, Schmidt B, Roberts S, et al. Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: Results from the trial of indomethacin prophylaxis in preterms. J Pediatrics 2007;150:229-234.
8. Clyman RI. Ibuprofen and patent ductus arteriosus. N Engl J Med 2000;343:728-729.
9. 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 2004;86 (suppl 3): S563-S569.

10. Supapannachart S, Limrungsikul 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 (supp 4):S1252-S1258.
11. 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:e354.
12. Vane JR, Botting RM. Mechanism of action of anti-inflammatory drugs. In: Sinzinger H, Samuelsson B, Vane JR, et al., eds. Recent advances in prostaglandin, thromboxane, and leukotriene research, Vol. 433 of Advances in experimental medicine and biology. New York, NY: Plenum Press; 1997:131-138.
13. Malcolm DD, Segar JL, Robillard JE, et al. Indomethacin compromises hemodynamics during positive-pressure ventilation, independently of prostanoids. J Appl Physiol 1993;74:1672-1678.
14. Feigen LP, King LW, Ray J, et al. Differential effects of ibuprofen and indomethacin in the regional circulation of the dog. J Pharmacol Exp Ther 1981;219:679-684.
15. Grosfeld JL, Kamman K, Gross K, et al. Comparative effects of indomethacin, prostaglandin E_1, and ibuprofen on bowel ischemia. J Pediatr Surg 1983;18:738-742.
16. Speziale MV, Allen RG, Henderson CR, et al. Effects of ibuprofen and indomethacin on the regional circulation in newborn piglets. Biol Neonate 1999;76:242-252.
17. 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.
18. Lago P, Bettiol T, Salvadori S, et al. Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: a randomized controlled trial. Eur J Pediatr 2002;161:202-207.
19. Su PH, Chen JY, Su CM, et al. Comparison of ibuprofen and indomethacin therapy for patent ductus arteriosus in preterm infants. Pediatr Int 2003;45:665-670.
20. Aranda, JV, Thomas, R. Intravenous ibuprofen for preterm newborns. NeoReviews 2005;6:c516-523.
21. Aranda JV, Thomas R. Systematic review: intravenous ibuprofen in preterm newborns. Semin Perinatol 2006;30:114-120.
22. Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of a patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2003;(2):CD003481.
23. 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.
24. DeCarolis MP, Romagnoli C, Polimeni V, et al. Prophylactic ibuprofen therapy of patent ductus arteriosus in preterm infants. Eur J Pediatr 2000:150:364-368.
25. 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.
26. 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.
27. 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.
28. Gourney 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.
29. Coceani F, White E, Bodach E, et al. Age dependent changes in the response of the lamb ductus arteriosus to oxygen and ibuprofen. Can J Physiol Pharmacol 1979:57:825-831.

30. Romagnoli C, DeCarolis MP, Papacci P, et al. Effects of prophylactic ibuprofen on cerebral and renal hemodynamics in very preterm neonates. Clin Pharmacol Ther 2000;67:676-683.
31. Mosca F, Bray M, Colnaghi MR, et al. Cerebral vasoreactivity to arterial carbon dioxide tension in preterm infants: the effect of ibuprofen. J Pediatr 1999;135:644-646.
32. Austin NC, Pairaudeau PW, Haames TK, et al. Regional blood flow velocity changes after indomethacin infusion in preterm infants. Arch Dis Child 1992;67:851-854.
33. Van Bel F, Van de Bor M, Stijnen T, et al. Cerebral blood flow velocity changes in preterm infants after a single dose of indomethacin: duration of its effects. Pediatrics 1989;84:802-807.
34. Plavka R, Svihovec P, Borek I, et al. Ibuprofen vs. indomethacin in the treatment of patent ductus arteriosus in very premature neonates. Pediatri Res 2001;49:375A.
35. 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.
36. Chemtob, S. Beharry K, Barna T, et al. Differences in the effects in the newborn piglet of various nonsteroidal anti-inflammatory drugs on cerebral blood flow but not on cerebrovascular prostaglandins. Pediatr Res 1991;30:106-111.
37. Coombs RC, Morgan ME, Durbin GM, et al. Gut flow blood velocities in the newborn: effect of patent ductus arteriosus and parenteral indomethacin. Arch Dis Child 1990; 65:1067-1071.
38. Van Bel F, Van Zoeren D, Schipper J, et al. Effect of indomethacin on superior mesenteric artery blood flow velocity in preterm infants. J Pediatr 1990;116:965-970.
39. Van Bel F, Guit GL, Schipper J, et al. Indomethacin-induced changes in renal blood flow velocity waveform in premature infants investigated with color Doppler imaging. J Pediatr 1991;118:621-681.
40. Chemtob S, Laudignon N, Beharry K, et al. Effects of prostaglandins and indomethacin on cerebral blood flow and cerebral oxygen consumption of conscious newborn piglets. Dev Pharmacol Ther 1990;14:1-14.
41. 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.
42. Patel J, Marks KA, Roberts I, et al. Ibuprofen treatment of patent ductus arteriosus. Lancet 1995;346:255.
43. McCormick DC, Edwards AD, Brown GC, et al. Effect of indomethacin on cerebral oxidized cytochrome oxidase in preterm infants. Pediatr Res 1993;33:603-608.
44. Ment LR, Oh W, Ehrenkranz RA, et.al. Low dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. Pediatrics;1994:93:543-550.
45. Banstra ES, Montalvo BM, Goldberg RN, et al. Prophylactic indomethacin for prevention of intraventricular hemorrhage in premature infants. Pediatrics 1988;82:533-542.
46. Bada HS, Green RS, Pourcyrous M, et al. Indomethacin reduced the risks of severe intraventricular hemorrhage. J Pediatr 1989;115:631-637.
47. Hanigan W, Kennedy G, Roemisch F, et al. Administration of indomethacin for the prevention of periventricular-intraventricular hemorrhage in high-risk neonates. J Pediatr 1988;112:941-947.
48. Merritt TA , White CL, Coen RW, et al. Preschool assessment of infants with patient ductus arteriosus: comparison of ligation and indomethacin therapy. Am J Dis Child 1982;136:507-512.
49. Ohlsson A. Back to the drawing board. Pediatr Res 2000;47:4.
50. Dani C, Bertini G, Pessati M, et al. Prophylactic ibuprofen for the prevention of intraventricular hemorrhage among preterm infants: a multicenter, randomized study. Pediatrics 2005;115:1529-1535.

51. Green TP, Thompson TR, Johnson DE. Furosemide promotes patent ductus arteriosus in preterm infants with respiratory distress syndrome. N Engl J Med 1983;308:743-748.
52. Bohnhorst B, Muller, S, Dordelmann M, et al. Early feeding after necrotizing enterocolitis in preterm infants. J Pediatr 2003;143:484-487.
53. Fuji AM, Brown E, Mirochnick M, et al. Neonatal necrotizing enterocolitis with intestinal perforation in extremely premature infants receiving early indomethacin treatment for patent ductus arteriosus. J Perinatol 2002;22:535-540.
54. Dollberg S, Lusky A, Reichman B. Patent ductus arteriosus, indomethacin and necrotizing enterocolitis in very low birth weight infants: a population-based study. J Pediatr Gastroenterol Nutr 2005;40:184-188.
55. Nagaraj HS, Sandhu AS, Cook LN, et al. Gastrointestinal perforation following indomethacin therapy in very low birthweight infants. J Pediatr Surg 1981;16:1003-1007.
56. Grosfeld JL, Cheu H. Schlatter M, et al. Changing trends in necrotizing enterocolitis. Experience with 302 cases in two decades. Ann Surg 1991;214:300-307.
57. Cronen PW, Nagaraj HS, Janik JJ, et al. The effect of indomethacin on mesenteric circulation in mongrel dogs. J Pediatr Surg 1982;17;474-478.
58. Grosfeld JL, Chaet M, Molinari F, et al. Increased risk of necrotizing enterocolitis in premature infants with patent ductus arteriosus treated with indomethacin. Ann Surg 1996;224:350-357
59. 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
60. Knight DB. The treatment of patent ductus arteriosus in preterm infants: a review and overview of randomized trials. Semin Neonatol 2001;6:63-73.
61. Clyman, RI. Recommendations for the postnatal use of indomethacin: an analysis of four separate treatment strategies. J Pediatr 1996;128:601-607.
62. Cooke L, Steer P, Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev 2003;(2):CD00374.
63. Shennan AT, Dunn, MS, Ohlsson A. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82:527-532.
64. Mosca F, Bray M, Stucchi I, et al. Pulmonary hypertension after ibuprofen prophylaxis in very preterm infants. Lancet 2002;360:1023-1024.
65. 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.
66. Ovation Pharmaceuticals. Neoprofen (ibuprofen lysine) package insert. Deerfield, IL; April 2006.
67. Schafer AI. Effects of nonsteroidal antiinflammatory therapy on platelets. Am J Med 1999;106:25S-36S.
68. Cronberg S, Wallmark E, Soderberg I. Effect of platelet aggregation on oral administration of 10 non-steroidal analgesics to humans. Scand J Haematol 1984;33:155-159.
69. Aranda JV, Varvarigou A, Beharry K, et al. Pharmacokinetics and protein binding of intravenous ibuprofen in the premature newborn infant. Acta Paediatr 1997;86:289-293.
70. Wennberg RP, Ahlfors CE, Bhutani VK, et al. Toward understanding kernicterus: a challenge to improve the management of jaundiced newborns. Pediatrics 2006;117:474-485.
71. Personal communication: Aranda JV. April 2007
72. Ahlfors CE. Effect of ibuprofen on bilirubin-albumin binding. J Pediatr 2004;144:386-388.
73. Cooper-Peel C, Brodersen R, Robertson A. Does ibuprofen affect bilirubin-albumin binding in the newborn infant serum? Pharmacol Toxicol 1996;79:297-299.
74. Van Overmeire B, Vanhagendoren S, Schepens PJ, et al. The influence of ibuprofen-lysine on unbound bilirubin plasma levels in preterm neonates. Pediatr Res 2004;55:474A.