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REVIEW ARTICLE

Pharmacologic, Pharmacodynamic, and Pharmacokinetic Considerations with Intravenous Ibuprofen Lysine

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Patent ductus arteriosus (PDA) is a common complication in preterm infants. An intravenous (IV) cyclooxygenase (COX) inhibitor is the pharmacotherapy of choice. Concerns over adverse effects associated with the traditional treatment, IV indomethacin, have led to the investigation of other COX inhibitors to assist closure of PDA. IV ibuprofen lysine is a COX inhibitor that demonstrates similar efficacy to indomethacin with few adverse effects. In addition, IV ibuprofen lysine does not cause reductions in cerebral, renal, and mesenteric blood flow that can be seen with indomethacin, and thus ibuprofen therapy is not associated with reduced renal function. Ibuprofen is primarily metabolized by cytochrome P450 (CYP) 2C9. The immaturity of neonatal biotransformation pathways has a pronounced effect on the pharmacokinetic parameters of ibuprofen, particularly because CYP2C9 enzyme activity is known to be very low at birth and to increase rapidly over the first several days of life. Ibuprofen is highly bound to albumin, raising concern that ibuprofen may displace bilirubin and subsequently increase free bilirubin concentrations. However, the ibuprofen concentrations achieved with approved dosing with IV ibuprofen lysine are lower than those expected to result in displacement of bilirubin and related adverse effects. Factors such as gestational age and CYP2C9 polymorphism may affect ibuprofen metabolism and therefore optimal dosing, but further clinical investigation is needed in these areas. Other areas for future investigation include prolonged dosing regimens, prophylactic administration, and alternate indications. At the approved dose, IV ibuprofen lysine is a safe, effective pharmacologic agent to promote closure of PDAs in preterm infants.

KEYWORDS cyclooxygenase inhibitor, ibuprofen, indomethacin, nonsteroidal anti-inflammatory drugs, patent ductus arteriosus

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INTRODUCTION

Patent ductus arteriosus (PDA) is a common complication in preterm infants that increases the risk of bronchopulmonary dysplasia development, intraventricular hemorrhage (IVH), necrotizing enterocolitis, and death.[1,2] PDA entails a dynamic process with disease-specific progression during postnatal development that is influenced by prostaglandins and nitric oxide. An intravenous (IV) cyclooxygenase (COX) inhibitor is the pharmacologic treatment of choice to promote closure of the PDA. While the exact mechanism of action of the COX inhibitors for PDA closure is unknown, it is believed that they inhibit the synthesis

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of prostaglandins that maintain the in utero patency of the ductus.[3]

ABBREVIATIONS CBF, cerebral blood flow; CBV, cerebral blood volume; C_{max}, peak plasma concentration; COD, cerebral oxygen delivery; COX, cyclooxygenase; CYP, cytochrome P450; IC_{50}, 50% inhibitory concentration; IV, intravenous; IVH: intraventricular hemorrhage; NNT, number needed to treat; NSAIDs, nonsteroidal anti-inflammatory drugs; PDA, patent ductus arteriosus; RR, typical relative risk; T_{max}, time to attain peak plasma concentration

Intravenous indomethacin (Indocin IV; Ovation Pharmaceuticals, Deerfield, IL) has been the traditional pharmacotherapy of choice to assist closure of the PDA. Although IV indomethacin has proven an effective treatment, its use may be associated with complications such as decreased cerebral, mesenteric, and renal blood flow; gastrointestinal perforation or hemorrhage; and altered platelet function, as well as common side effects such as oliguria, anuria, and transient renal failure.[1,4] These complications have been the impetus for the administration and examination of other COX inhibitors in an effort to find an effective pharmacologic treatment for PDA with fewer adverse consequences. One such COX inhibitor of interest is ibuprofen.

IV ibuprofen lysine (NeoProfen; Ovation Pharmaceuticals, Deerfield, IL) is a new product that is indicated for the closure of clinically significant PDA in premature infants weighing between 500 and 1,500 g who are no more than 32 weeks gestational age when usual medical management (e.g., fluid restriction, diuretics, respiratory support, etc.) is ineffective.[5] Ibuprofen is a COX inhibitor that has undergone extensive clinical study and enjoyed widespread clinical use as an antipyretic and analgesic in oral formulations.[6,7] The commercial release of this new IV formulation gives cause for review of these COX-inhibiting pharmacological agents used for the treatment of PDA.

The availability of a new, potentially safer pharmacologic treatment option for PDA is an exciting prospect. It is important that practitioners understand the clinical effects, dosing, metabolism, and safety profile of IV ibuprofen lysine. Therefore, the purpose of this article is to review the pharmacology of COX inhibitors for the treatment of PDA, to review the pharmacokinetic and pharmacodynamic characteristics of IV ibuprofen lysine, to examine special considerations for its dosing, and to explore new directions and generate hypotheses for future clinical investigation.

PHARMACOLOGY OVERVIEW

COX inhibitors are thought to encourage closure of a PDA in preterm infants at least in part by inhibiting the synthesis of prostaglandins that maintain ductus patency.[3,4] The nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit COX-mediated transformation of arachidonic acid to thromboxane and the various prostaglandins.[8] The COX-1 isoenzyme is thought to play a role in constitutive homeostasis, including the basal physiologic processes in the kidneys.[9] COX-2 is thought to be primarily induced and activated during inflammation.

The approved IV ibuprofen preparation exists as a racemic mixture of S(+) and R(–) enantiomers with the S(+) enantiomer being primarily responsible for COX inhibition.[6] Although both indomethacin and ibuprofen inhibit COX-1 and COX-2, indomethacin is a more potent inhibitor of COX-1 and COX-2 than ibuprofen.[9] In addition, indomethacin is more selective towards COX-1 inhibition. While the ibuprofen 50% inhibitory concentrations (IC_{50}) are about equal for COX-1 and COX-2, indomethacin IC_{50} is about 10-fold lower for COX-1 than for COX-2. Inhibition of COX-1 can result in adverse effects such as gastrointestinal irritation and damage, platelet dysfunction and bronchospasm.[10] Ibuprofen inhibits both COX-1 and COX-2 enzymes, but its COX-1 inhibition is less than that of indomethacin. While adverse effects due to COX-1 inhibition can occur with ibuprofen, it may offer safety advantages in infants at risk for such side effects.[11-17] Several studies that examine cerebral, renal, and mesenteric perfusion reinforce the safety profile of IV ibuprofen compared to IV indomethacin.

Mosca et al. used near-infrared spectroscopy and Doppler ultrasonography to evaluate the impact of IV ibuprofen lysine (10 mg/kg; n = 8) on cerebral perfusion and oxygenation and compare these effects to IV indomethacin (0.2 mg/kg; n = 8) in preterm infants with PDA.[18] Both drugs were administered as rapid infusions over 1 minute. The authors found that ibuprofen lysine caused no significant reduc-

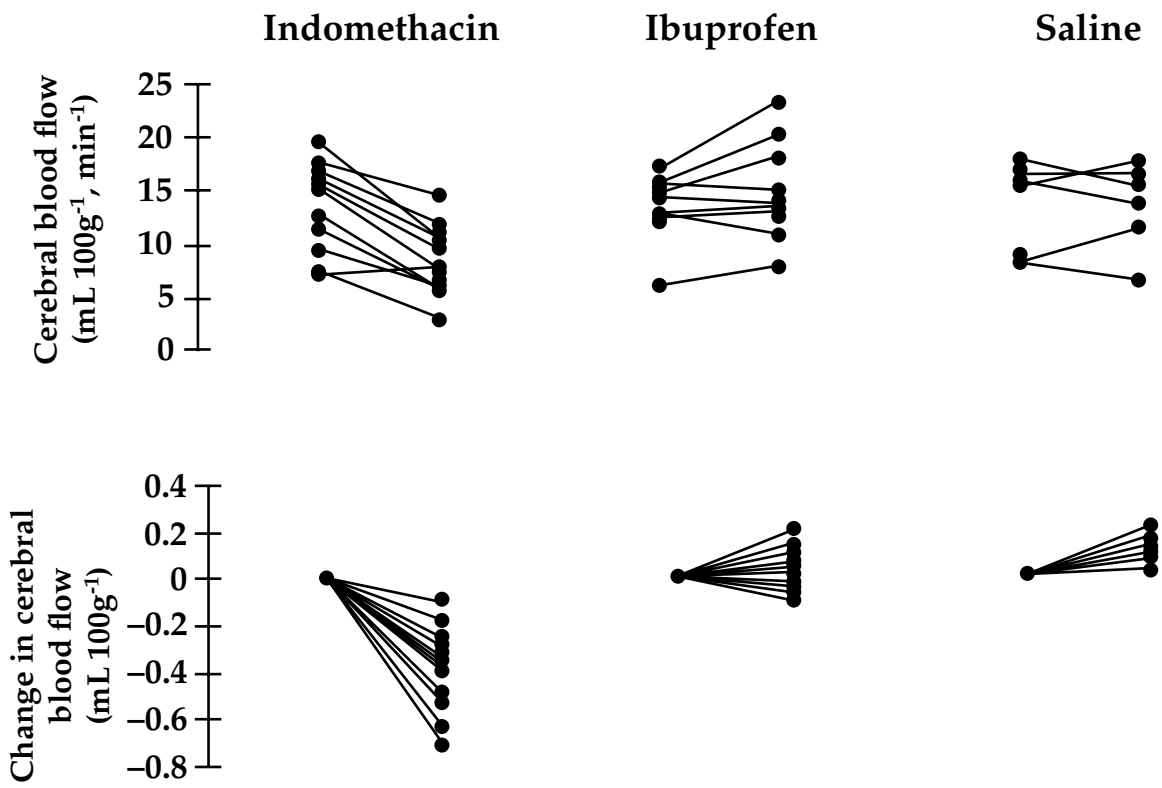

Figure 1. Individual mean values for cerebral blood flow and changes in cerebral blood volume before and after the first doses of IV indomethacin, IV ibuprofen and saline. Change in cerebral blood volume with treatment has been related to an arbitrary zero. Reprinted from reference 2 with permission of Lippincott Williams & Wilkins.

tion of cerebral blood volume (CBV) or cerebral blood flow (CBF) compared to baseline. However, indomethacin caused a significant reduction in post-treament CBV compared to ibuprofen lysine (1.9 ± 0.3 mL/100 g vs. 3.1 ± 0.4 mL/100 g; P < .05), and the changes in CBV were consistently significantly different at all time points (P = .022). The researchers also found that CBF velocity, as measured by Doppler, fell significantly after administration of indomethacin, whereas ibuprofen caused no significant reduction in CBF compared to baseline and CBF was significantly greater following ibuprofen than indomethacin.

Patel et al. also found differences between IV ibuprofen and IV indomethacin in their effects on CBF in a randomized, double-blind, controlled trial treating infants for a hemodynamically significant PDA (Figure 1).[2] Trial infants were randomly assigned to receive 3 IV doses of either indomethacin (0.20-0.25 mg/kg every 12 hours; n = 15) or ibuprofen (5-10 mg/kg every 24 hours; n = 18) administered over 15 minutes with a dose of saline to maintain blinding of the treatment scheme. The group mean values for CBF (mL/100 g·min) before and after the first dose of indomethacin were 13.6 ± 4.1 and 8.3 ± 3.1 respectively (P < .001); there was no significant change in CBF after the first dose of ibuprofen (13.3 ± 3.2 vs. 14.9 ± 4.7). There was also a significant difference in the median value for change in CBV after the first dose in the indomethacin group compared to the ibuprofen group (–0.4 [interquartile range –0.3 to –0.6] vs. 0.0 [0.1 to –0.1]; P < .001). Cerebral oxygen delivery (COD) changed significantly after the first dose in the indomethacin group but not in the ibuprofen group. The investigators also found significant reductions in CBF, CBV, and COD after the 24-hour dose of indomethacin. No changes in CBF, CBV, or COD were observed with the repeated ibuprofen doses. These results are of interest because stabilization of CBF might lead to reduce the risk of IVH in preterm infants.[2] However, studies to date, including a placebo-controlled study of prophylactic IV ibuprofen in 155 premature infants, have failed to showed a reduction in IVH with ibuprofen.[19]

The results of the study by Patel et al. were supported by the findings of Romagnoli et al., who examined the effects of prophylactic IV ibuprofen lysine (10 mg/kg followed by 5 mg/kg at 24 and 48 hours) on 17 preterm neonates of gestational age 30 weeks or less.[2,20] Using the results of Doppler ultrasonography, the researchers determined that ibuprofen did not exert any direct pharmacologic effect on cerebral or renal blood flow velocities (Figure 2). Overall, positive hemodynamic changes were observed in infants with echocardiographically confirmed PDA, such as significant increases in diastolic and mean blood velocities in the anterior cerebral artery and the renal artery ($P < .0001$), which were attributed to closure of the ductus induced by ibuprofen.

These favorable outcomes for renal blood flow were supported by the results of a study performed by Pezzati et al., who also examined the effects of IV ibuprofen and IV indomethacin on mesenteric blood flow.[16] The authors measured mesenteric and renal blood flow velocities using Doppler ultrasonography in 17 preterm infants who received either 0.2 mg/kg IV indomethacin ($n = 8$) or 10 mg/kg IV ibuprofen ($n = 9$) infused over 15 minutes. They found that urine output and serum creatinine were unchanged by IV ibuprofen but were significantly affected by IV indomethacin, with urine output taking 7 days to return to pretreatment levels. IV ibuprofen did not alter blood flow 30 minutes after treatment, and blood flow actually increased 120 minutes after treatment. The researchers found that IV indomethacin caused a significant reduction in mesenteric and renal blood flow velocity 30 minutes after drug administration that did not return to pretreatment values by 120 minutes. Differences between the 2 treatment groups in mesenteric and renal blood flow velocity changes were significant.

In total, these observations provide clinical evidence that IV ibuprofen lysine does not cause a reduction in renal, cerebral, or mesenteric blood flow; this may lead to a lower incidence of adverse effects.

DOSING AND PHARMACODYNAMICS

The dosing of IV ibuprofen lysine for the treatment of PDA is driven by the known pharmacokinetic and pharmacodynamic properties of ibuprofen in this population. IV ibuprofen lysine is administered as a course of 3 doses given intravenously; an initial dose of 10 mg/kg birth weight is followed by 2 doses of 5 mg/kg birth weight each, at 24 and 48 hours after the first dose.[5] If anuria or marked oliguria (urinary output <0.6 mL/kg/hr) is evident at the scheduled time of the second or third doses, no additional dose should be given until laboratory studies indicate that renal function has returned to normal. If the ductus closes or is significantly reduced in size after completion of the first course of IV ibuprofen lysine, no further doses are necessary. If during continued medical management the ductus arteriosus fails to close or reopens, then a second course of IV ibuprofen lysine, alternative pharmacological therapy, or surgery may be necessary.

Desfrere and colleagues conducted a dose-finding trial of ibuprofen for PDA using a different ibuprofen formulation that has been studied in Europe, ibuprofen trometamol.[21] The study design employed a continual reassessment method to arrive at an effective dose. The researchers examined 4 dose regimens using IV ibuprofen trometamol and evaluated efficacy using echocardiography 24 hours after the third dosing infusion. The authors confirmed that the currently recommended dose regimen (10, 5, and 5 mg/kg at 0, 24, and 48 hours, respectively) of ibuprofen was associated with a high closure rate (80%) and few adverse effects, but that failure rate was much higher with infants born at a postmenstrual age of less than 27 weeks. They postulated that the approved dose was appropriate for infants born at 27-29 weeks gestation, but a higher dose regimen (20, 10, 10 mg/kg) might be needed to achieve a similar closure rate in less mature infants (less than 27 weeks postmenstrual age). However, the tolerability and safety of a higher dose in less mature infants should be thoroughly assessed in larger studies before consideration of the clinical use of these doses.

While clinical pharmacodynamics research of NSAIDs including ibuprofen for the treatment of PDA is limited, inferences can be drawn from available data and research for other indications. Ibuprofen exerts antipyretic effects in children at concentrations of 10 μg/mL.[22] These clinical effects occur at concentrations about 4 to 5 times the in vitro ibuprofen IC_{50} of COX-1

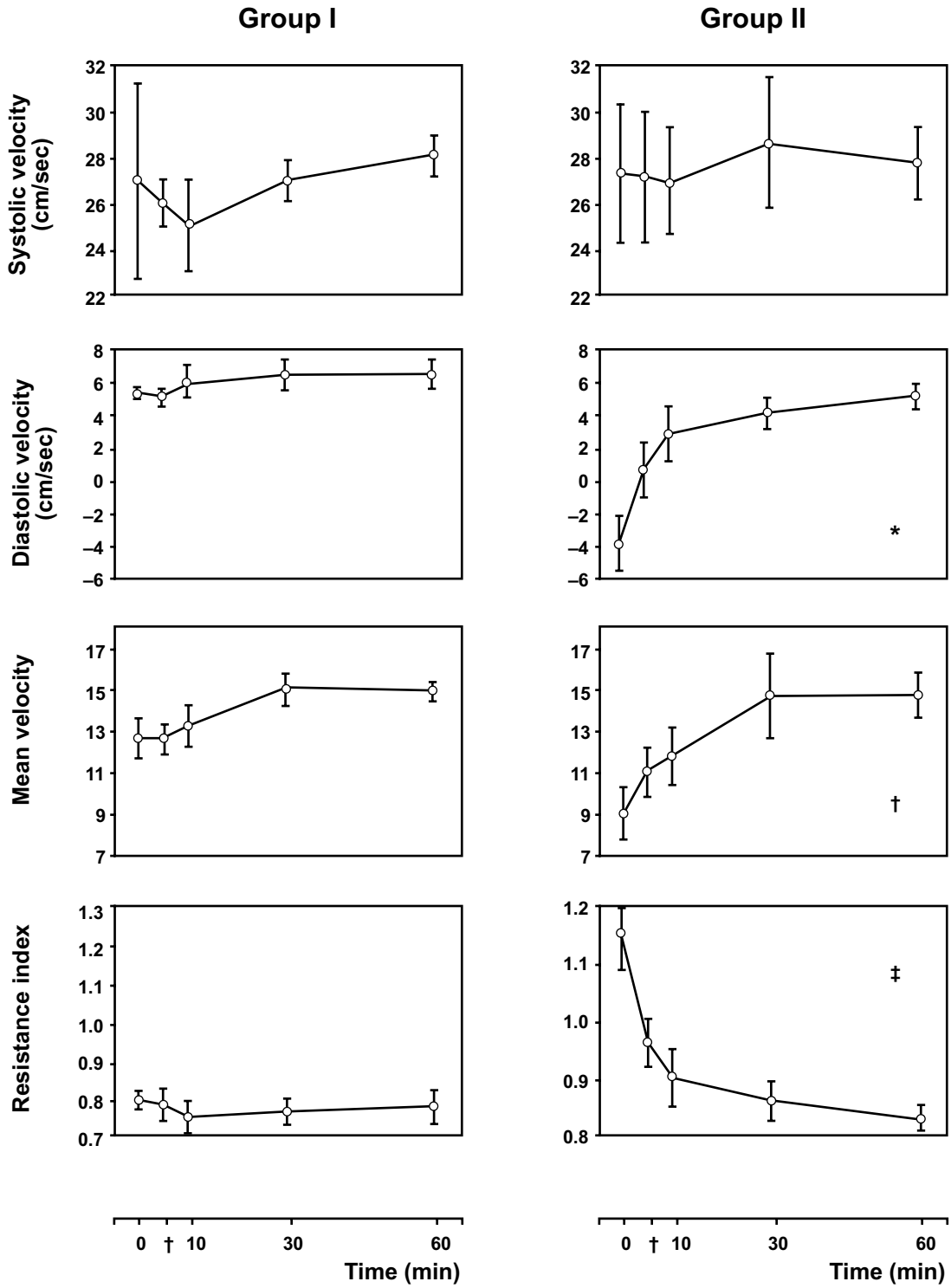

Figure 2. Renal Doppler blood velocity and resistance before, during, and 10, 30, and 60 minutes after IV ibuprofen lysine administration. Time 0 refers to preinjection values; the arrow indicates drug infusion. Left panel, Group 1 (without PDA, n = 4). Right panel, Group 2 (with PDA, n = 13). Values are given as mean ± standard margin of error (range). * = P < .0001; † = P < .004; ‡ = P < .001 compared with preinfusion values (by analysis of variance for repeated measures). Reprinted with permission from Macmillan Publishers Ltd: Clinical Pharmacology & Therapeutics, copyright 2000.

and COX-2 activity, which are roughly 2-2.5 μg/mL. In vitro, indomethacin COX-1 inhibition is more than 10 times greater than its COX-2 inhibition (IC_{50} ~15 ng/mL vs. ~200 ng/mL) and time-dependent. As the level of COX-1 inhibition may be indicative of adverse effects, it follows that the lower level of COX-1 inhibition of ibuprofen lysine should lead to a lower incidence of these adverse effects.

PHARMACOKINETICS

IV ibuprofen lysine is indicated for use in premature infants weighing between 500 and 1,500 g who are no more than 32 weeks gestational age. Metabolic pathways are not fully developed in this specialized population. Therefore, a pharmacokinetic review of ibuprofen, including known information on oral and IV administration, is warranted.

The pharmacokinetic properties of ibuprofen in adults have been extensively studied and reviewed.[6,7] In adults, oral ibuprofen is rapidly and extensively absorbed, and its bioavailability is near 100%. The drug is eliminated primarily by metabolism in the liver, via cytochrome P450 (CYP) 2C9 and 2C8.[6,23] CYP 2C9 predominately mediates the 2- and 3-hydroxylations of R-(–) and S-(+) ibuprofen and accounts for the majority of ibuprofen metabolism. In adults, the relative elimination and clearances of these 2 enantiomers are similar despite unidirectional chiral inversion from R-(–) ibuprofen to S-(+)-ibuprofen due to rapid metabolism of both enantiomers. Ibuprofen also undergoes conjugation with glucuronic acid to yield acyl glucuronides; this metabolic pathway accounts for approximately one-fifth of the dose.[23] Renal elimination of unchanged ibuprofen accounts for only 10-15% of a dose and occurs primarily by glomerular filtration and tubular secretion, with tubular reabsorption playing a minor role.[6]

All of these pathways have greatly reduced activity in premature infants. The activity of CYP 2C9 (and 2C8) is known to be very low at birth (<5%) in both term and preterm infants when assessed by liver enzyme content or inferred by altered pharmacokinetics of known CYP 2C9 substrates such as indomethacin or tolbutamide.[24,25] There is a rapid surge in acquisition of CYP 2C9 activity in the first few days of life, but the pattern of further acquisition of this enzyme remains poorly defined in infants.[26] The markedly reduced CYP 2C9 activity likely leads to increases in the contributions of other metabolic pathways in preterm infants, although these other pathways also have limited function in newborn infants. Nephrogenesis is completed between the 28th and 36th gestational week. At birth, the glomerular filtration rate is low: only about 30% of the rate in adults, with additional impairments in premature infants.[27,28] Glucuronidation activity is reduced in infants but can double within the first weeks of life for some of the UDP-Glucuronosyltransferase (UGT) isoforms.[29] The summed metabolic and elimination disposition of ibuprofen in infants, including a low glucuronic conjugation capacity, reduced renal elimination of ibuprofen,[3] and the low activity of CYP 2C9 at birth, can have a profound effect on ibuprofen dosing requirements and response.

Oral Ibuprofen

Oral ibuprofen has been studied as a single 10 mg/kg dose administered with milk or as a suspension in 20 premature newborns with a gestational age of 30.45 ± 0.33 weeks and a birth weight of 1262.5 ± 55.4 g.[30] The authors noted large interindividual variability for plasma concentration, elimination half-life (15.72 ± 3.76 hours), and area under the plasma concentration-time curve (402.60 ± 79.67 μg•hr/mL). Mean peak plasma concentration (C_{max}) and time to attain peak plasma concentration (T_{max}) were 20.09 μg/mL and 3.0 hours, respectively. While oral therapy with ibuprofen for PDA closure is not recommended due to concern for the potential of increased gastrointestinal toxicities, the study demonstrated that ibuprofen dosage for oral administration requires no modification to achieve comparable plasma concentrations following IV administration.[30]

IV Ibuprofen Lysine

The introduction of the new IV ibuprofen lysine product has generated much clinical interest, including several pharmacokinetic analyses. A study of 21 premature infants, 22-31 weeks gestational age, who received IV ibuprofen lysine as a 10 mg/kg bolus within the first 3 hours of birth reported the apparent

volume of distribution as 62.1 mL/kg and the plasma half-life as 30.5 hours.[31] The authors concluded that ibuprofen elimination is prolonged in neonates and that protein binding in neonates is marginally lower compared to adults and older children. They added that the decrease in protein binding should be taken into account when using IV ibuprofen lysine in newborn infants because, for a given plasma ibuprofen concentration, more free or unbound drug is present in the newborn; therefore, a more intense pharmacologic effect relative to adults should be expected.[31]

A pharmacokinetic study of 27 premature infants with PDA, gestational age 28.6 ± 1.9 weeks, who received a 15 minute infusion of 10, 5, and 5 mg/kg of IV ibuprofen lysine on postnatal days 3, 4, and 5 respectively, indicated that there was a significant decrease in the volume of distribution and area under the curve as time progressed.[32] The authors found a large interpatient variability in the kinetics of these infants and postulated that the presence of a hemodynamically significant PDA may alter drug disposition by causing hypoperfusion of drug-eliminating organs (liver and kidney), introducing fluid overload, or inducing systemic hypoxia and acidosis. Closure of the ductus may have improved these physiologic effects and resulted in an abrupt decrease in the volume of distribution,[32] although another study in 52 infants with PDA indicated that on the last dose of ibuprofen there was no statistical difference in the volume of distribution between those with a closed, or closing, ductus and those with an open ductus.[3] Van Overmeire and colleagues noted that these findings may have implications regarding the treatment schedule.[32]

A randomized, double-blind, multicenter study for the early treatment of PDA evaluated treatment with IV ibuprofen lysine or placebo in low birth weight infants (500-1,000 g; n=136), gestational age 23-30 weeks, at less than 72 hours of life with nonsymptomatic PDA but ductal shunting documented by echocardiography.[5,33] The infants received 3 doses of either IV ibuprofen lysine (10 mg/kg followed by 2 doses of 5 mg/kg at 24 and 48 hours, administered over 10-15 minutes) or placebo. The mean age and birth weight at first dose was 37.5 hours (4.6-73 h) and 798 g (530-1,015 g), respectively. Serum creatinine did not increase with IV ibuprofen lysine therapy. The observed range of ibuprofen plasma concentrations (10-50 μg/mL) was consistent with other studies of premature infants with PDA. Mean ibuprofen concentrations were 34.71 mg/L at 1 hour after the first dose, 24.19 mg/L immediately before the second dose, and 27.32 mg/L immediately before the third dose.

A population pharmacokinetic analysis was performed to estimate pharmacokinetic parameters in this study.[34] Ibuprofen clearance was approximately 10% of that reported in adults, and it increased with postnatal age (0.48 mL/hr/kg per day of age) but was not affected by gestational age. Estimated pharmacokinetic parameters and intersubject variability for clearance at birth and volume of distribution were 2.96 mL/hr/kg (coefficient of variation [CV] 55%) and 3,210 mL/kg (CV 14%), respectively, with a calculated half-life of 74.9 hours. Clearance exhibited more than a 10-fold range, and the median clearance increased by 52% during the 5 days of pharmacokinetic sampling. The model predicted maintenance of unbound serum ibuprofen concentrations above the IC_{50} for COX in greater than 99% of infants for 72 hours and 58% of infants for 168 hours. The authors concluded that while ibuprofen elimination was markedly reduced at birth, it increased dramatically during the first week of life. Three doses of ibuprofen lysine maintained serum concentrations at levels expected to exert COX inhibition during the first week of life to promote closure of PDA in preterm infants.

The stereo-specific ibuprofen pharmacokinetics have been characterized in premature infants following administration of ibuprofen trometamol, a formulation not approved for use in the United States, but has been studied in Europe.[4] While prior studies in adults have found the pharmacokinetics of the 2 ibuprofen enantiomers to be similar, in infants concentrations of the S(+)-ibuprofen were several fold higher than the R(–)-ibuprofen concentrations. This difference persisted for at least 48 hours and likely represents a higher relative contribution of the unidirectional chiral inversion, R(–) to S(+) enantiomer, in the setting of greatly impaired CYP2C9 activity.

Overall, the pharmacokinetic studies completed to date with ibuprofen in premature infants

indicate that the clearance appears to increase and half-life decreases with postnatal age, and overall the half-life during the first few days of life is generally more than 10 times longer than for adults.[5,33,34] It is important for the practitioner to take these pharmacokinetic implications into consideration when monitoring dose and response in this specialized population.

Binding Interactions

There has been some concern over the possible displacement of protein-bound bilirubin by ibuprofen. Ibuprofen exhibits extensive albumin binding (greater than 98%), which is stereoselective and nonlinear. Ibuprofen, like other highly protein-bound drugs, can displace bilirubin from its binding site on albumin, increasing free bilirubin levels. However, this interaction is concentration-dependent, and studies in premature infants indicate that bilirubin can be displaced at ibuprofen concentrations of 100 mg/L, but not at 50 mg/L or below.[35,36] Although significant pharmacokinetic interpatient variability exists in this population, studies indicate that, in the intended population with the approved dose and infusion time, plasma levels of IV ibuprofen lysine do not exceed 100 mg/L and rarely exceed 50 mg/L.[5] Desfrere and colleagues evaluated the time course of unbound bilirubin concentrations, as determined by the peroxidase-diazo method, in 23 premature infants (27.2 ± 1.8 weeks gestational age) receiving standard doses of IV ibuprofen lysine.[37] The mean baseline total and unbound bilirubin concentrations were 5.9 ± 1.7 and 1.4 ± 0.7 μg/dL, respectively. Unbound bilirubin concentrations did not change during the 72 hours of evaluation (range of mean concentrations 1.3-1.5 μg/dL). These results indicate that appreciable bilirubin binding displacement does not occur with standard ibuprofen dosing in infants with bilirubin concentrations less than 10 μg/dL.[37]

Evaluations of the potential impact of COX inhibitors on bilirubin and the incidence of hyperbilirubinemia are somewhat conflicting, but neither IV ibuprofen lysine nor indomethacin appears to increase bilirubin concentrations. In a pooled analysis,[4,5,33,38] hyperbilirubinemia was reported for a statistically significantly lower percentage of infants receiving IV ibuprofen than those receiving placebo or no treatment (51% vs. 60%, P = .002); however, a lower percentage of infants in the IV indomethacin comparator group (16%) experienced this event compared with infants receiving IV ibuprofen lysine or placebo/no treatment (P = .001). In the Van Overmeire study, the incidence rates for hyperbilirubinemia were relatively low and similar for IV ibuprofen and IV indomethacin (20% vs. 16%).[4] In contrast, overall incidence rates for hyperbilirubinemia reported in a later study by Van Overmeire et al. were substantially higher than in the earlier study, but were similar between the IV ibuprofen group and the placebo group (73% vs. 78%).[38] The absence of an indomethacin group in the later study[38] created an artificially lower incidence rate for indomethacin when the study results are combined. Furthermore, a higher incident rate was reported in the later study,[38] probably because adverse event collection was initiated earlier than in the previous study (6 hours vs. 2-3 days after birth) before a baseline could be established for bilirubin in those infants. There was no difference in the incidence of jaundice in the 3 groups, and only 1 infant received a transfusion to treat elevated serum bilirubin.[38] In the Aranda placebo-controlled clinical trial, the rate of "significant but not serious treatment emergent adverse events related to hyperbilirubinemia" was not statistically significantly different between treatment groups (15.9% vs. 14.9%).[33]

The lack of a clinically important difference in adverse events related to increased bilirubin between the IV ibuprofen lysine and placebo/no-treatment groups, and the rarity of intervention to treat elevated bilirubin, suggests that IV ibuprofen lysine injection at the proposed dose and indication is not associated with clinically important hyperbilirubinemia. Nonetheless, since all highly protein-bound drugs, including ibuprofen, have the potential to displace bilirubin, clinicians should be alert to this possibility, particularly in infants receiving other highly bound drugs that can displace bilirubin or in infants with pre-existing hyperbilirubinemia.

SPECIAL PHARMACOKINETIC AND DOSING CONSIDERATIONS

As CYP2C9 is the primary metabolic path-

way of elimination for ibuprofen, it follows that polymorphisms of CYP2C9 may alter its rate of elimination. While no study has specifically examined the effects of CYP2C9 polymorphism on the effects of ibuprofen elimination in infants with PDA, Christesen et al. note that initially prolonged tolbutamide (a CYP2C9 substrate) half-lives and zero-order kinetics suggest immaturity of hepatic elimination during the first 2 days of postnatal life.[24] It is important to consider that polymorphisms in the CYP2C9 metabolic pathway may affect elimination and therefore serum concentration of ibuprofen, and this is certainly an area for future clinical investigation.

Furthermore, the efficacy of COX inhibitors in closing PDA has been correlated to gestational age. Infants of lower gestational age (less than 28 weeks) have been reported to be significantly less responsive to pharmacologic treatment (60% vs. 81%) and to undergo surgical ligation more frequently (23% vs. 4%).[11,39] Incidence and treatment rates of PDA vary depending on birth weight and source of data.

While evidence regarding the effect of age and birth weight on ibuprofen pharmacodynamics for the treatment of PDA is lacking, certain inferences can be drawn from existing data on other NSAIDs, particularly indomethacin. Shaffer et al. examined PDA closure rates and toxicity rates in neonates that received IV indomethacin according to an individualized pharmacokinetic/pharmacodynamic dosing approach.[40] The authors noted no significant differences in response rates based on treatment weight or postnatal age. However, significant differences were found between neonates categorized for postnatal age less than 10 days vs. those 10 days or older in total days of therapy, total number of doses required to close a PDA, critical indomethacin dose, critical indomethacin concentration, and critical dose/critical concentration ratio. The researchers postulated that the poor PDA closure rates with indomethacin for neonates more than 10 days postnatal age were the result of pharmacokinetic differences in older infants and that individualized pharmacokinetic/pharmacodynamic dosing achieved higher closure rates than standard dosing practices. Considering that ibuprofen is similar to indomethacin in pharmacokinetics, mechanism of action for closure of PDA, and metabolism by CYP2C9, this pharmacokinetic/pharmacodynamic method of dosing is worthy of clinical investigation for ibuprofen.

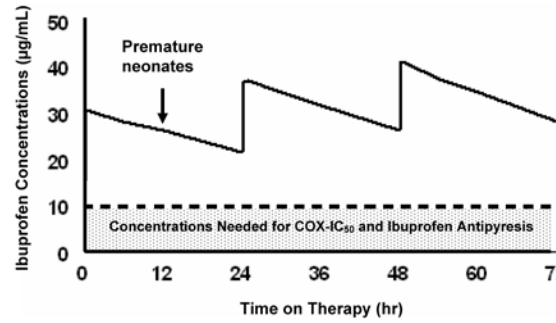

Figure 3. Predicted serum ibuprofen concentrations in premature neonate following IV administration of ibuprofen lysine at the approved dose of 10 mg/kg × 1, 5 mg/kg × 2. Predicted concentrations are based on a population pharmacokinetic model in a "typical" premature infant.[34] While concentrations needed for PDA closure have not been determined, the concentrations throughout the first 5 days exceed the ibuprofen COX-IC_{50} and ibuprofen concentrations needed for antipyretic effect.

At the current time, the concentration of ibuprofen necessary to achieve PDA closure has not been established. However, based on the typical predicted concentrations from a population analysis of ibuprofen in infants with PDA, the plasma concentration profile exceeds the concentration necessary to achieve antipyretic effects (10 µg/mL) and also exceeds the in vitro IC_{50} for at least 5 days (Figure 3).[34]

While the risk for renal dysfunction following IV ibuprofen lysine administration is less than that of indomethacin, acute renal failure can occur, and renal function must be monitored with ibuprofen therapy. Serum creatinine, blood urea nitrogen and urine output should be evaluated before and during therapy, with potential interruption of therapy for significant changes in serum creatinine or urine output. Signs of potential bleeding and platelets should also be assessed before and during therapy due to the antiplatelet effects of ibuprofen. Alternative therapy should be considered if bleeding or thrombocytopenia exists or develops.

FUTURE DIRECTIONS

While a growing body of knowledge is emerging regarding the use of IV ibuprofen lysine for

the closure of PDA, clearly further clinical studies are necessary to define the optimal role of this medication in therapy. While dose-finding studies have been conducted and the manufacturer provides dosage recommendations,[5] there is clearly room for further investigation of alternate dosing regimens. The use of prolonged dosing regimens is one avenue for future research. Surgery may be necessary in cases in which the infant remains unresponsive to therapy, but prolonged dosing regimens for PDA closure have been described for IV indomethacin and may be appropriate for investigation with IV ibuprofen lysine. Three trials[41-43] that tested day 6 of therapy with IV indomethacin demonstrated that the prolonged dose produces a more consistent ductal closure, but 2 other trials,[44,45] one of which tested a 7-day regimen,[44] both conclude that prolonged dosing with IV indomethacin does not offer a better choice over the standard 3-dose course. Clearly this is an area for future clinical interest in regard to IV ibuprofen lysine.

Another area for further investigation involves the prophylactic use of IV ibuprofen lysine to prevent prolonged PDA in infants that are at high risk of complications. Studies that evaluated ibuprofen for the prevention of PDA were reviewed in a meta-analysis that demonstrated a day-3 closure rate of 84% for ibuprofen and 55% for placebo.[46] Further analyses of these data discovered statistically significant differences in the incidence of PDA on day 3 in the ibuprofen group ($P < .00001$, typical relative risk [RR] = 0.37, number needed to treat [NNT] = 3), rescue treatment with COX inhibitors ($P < .00001$, RR = 0.17, NNT = 4), and surgical ligation ($P = .02$, RR = 0.34, NNT = 25).[47] The authors concluded that prophylactic ibuprofen reduces the incidence of PDA, the need for rescue therapy, and surgical closure in the population reviewed. Nonetheless, with the high spontaneous rate of closure (60%) observed in the target infant population, they advised against the routine use of IV ibuprofen for prophylaxis.[47] However, considering the risks of unresolved PDA, and the fact that spontaneous ductus closure is less common in preterm infants, this may be an area for more focused clinical investigation, particularly among patients who are at high risk for complications due to other concomitant conditions.

Finally, in addition to closure of PDA, there may be other potential uses for IV ibuprofen lysine in this patient population. Limited data on the use of ibuprofen for cystic fibrosis[48,49] and for the prevention of bronchopulmonary dysplasia[50] warrant further examination. Other indications for ibuprofen in adults and children include fever reduction, pain relief, and relief of the signs and symptoms of several types of arthritis. Although the use of IV ibuprofen lysine for some of these indications may prove applicable to the neonatal population, they would each require their own dosage and efficacy studies and therefore further clinical investigation.

CONCLUSIONS AND RECOMMENDATIONS

As shown in many clinical trials, IV ibuprofen lysine is a safe and effective method for pharmacological closure of PDA. Ibuprofen, a COX inhibitor with mixed COX-1 and COX-2 activity, does not typically cause detrimental changes in cerebral, renal, and mesenteric blood flow at approved doses. The pharmacologic profile for IV ibuprofen lysine has led to reduced renal toxicity compared to IV indomethacin. There are no demonstrable differences between these drugs in relative efficacy for the closure of PDA; thus, therapy selection may be influenced by the favorable renal profile demonstrated by IV ibuprofen lysine. The review of pharmacokinetics presented herein may assist with dosing considerations in the affected population, particularly considering the immaturity of metabolic pathways in the preterm neonate. While dose-finding studies for IV ibuprofen endorse the regimen recommended by the manufacturer,[5] other dosing regimens may be appropriate based on special cases such as CYP2C9 polymorphism and certainly warrant future research. Other areas for further clinical investigation include prolonged ibuprofen dosing, prophylactic dosing, and dosing for other indications.

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