



# Systematic Review: Intravenous Ibuprofen in Preterm Newborns

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Ibuprofen, a nonsteroidal antiinflammatory drug, widely used as antipyretic, antiinflammatory, and analgesic agent and for therapy of arthritis, exerts a dose-dependent constriction of the ductus arteriosus in newborn lambs. Two intravenous preparations, namely ibuprofen lysine and ibuprofen-THAM, have been studied in preterm newborns with patent ductus arteriosus. Clinical trials have compared IV ibuprofen to placebo, or to indomethacin. Pharmacodynamic effects of this drug before and after its administration have also been evaluated. Compared with placebo, IV ibuprofen effectively closed PDA with minimal effect on renal function. One study using intravenous ibuprofen-THAM showed decreased renal function and increased risk of NEC and PPHN. Compared with indomethacin, IV ibuprofen lysine exerted similar efficacy (75% to 93% closure). However, indomethacin increased abnormal renal function and decreased mesenteric and cerebral blood flow and bio-energetics. Two clinical trials showed that ibuprofen did not reduce the incidence of intraventricular hemorrhage compared with placebo. The drug has prolonged elimination (plasma half-life = ca 23 hours), suggesting that once daily dosing is appropriate. Dose finding studies indicate that a starting dose of 10 mg/kg followed by 5 mg/kg/d for 2 more days provides optimal efficacy with the least adverse effects. Neonatal data on ibuprofen and indomethacin indicate that, on the first day of life when IVH prevention is desired, indomethacin and not ibuprofen should be used since ibuprofen has no effect on IVH risk. On or after the second day of postnatal life, when early or therapeutic PDA closure is needed, ibuprofen and not indomethacin is probably the first choice due to its better adverse event profile. *Semin Perinatol* 30:114-120 © 2006 Elsevier Inc. All rights reserved.

**KEYWORDS** patent ductus arteriosus, ibuprofen, indomethacin, nonsteroidal antiinflammatory drugs, NSAIDs, premature newborn infant

Ibuprofen, a nonsteroidal antiinflammatory drug, is a widely used antipyretic, antiinflammatory, and analgesic agent and is also used for therapy of arthritis. In 1979, Cocceani and coworkers showed a dose-dependent constriction of the ductus arteriosus from newborn lambs.<sup>1</sup> Its current use in the newborn was stimulated by the demonstration that it improves the cerebral blood flow autoregulation in newborn animals<sup>2</sup> and may potentially offer some degree of neuroprotection. In contrast to indomethacin, ibuprofen did not decrease and impair regional blood flow to the brain in newborn infants and animals.<sup>3</sup>

Since ibuprofen may also close the patent ductus arteriosus in newborns, as has been shown in newborn lambs,<sup>1</sup> a pilot study was performed which suggested that, compared with placebo, intravenous ibuprofen closed the patent ductus arteriosus and shortened the hospital stay in preterm newborns with minimal renal adverse effects.<sup>4</sup> The development of two intravenous formulations of ibuprofen (ibuprofen-lysine and ibuprofen-THAM)<sup>4-6</sup> permitted the evaluation of this drug in preterm newborns. To date, data on efficacy, safety, dose finding, pharmacokinetics, and pharmacodynamics in the newborn indicate that this drug is effective in medically closing ductus arteriosus in preterm neonates. Data on safety are dependent on the formulation studied.<sup>5-8</sup> This review examines the published data on ibuprofen up to July 2005 and concludes that ibuprofen lysine is a safe and effective drug for PDA closure in newborns.

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Table 1 Intravenous Dose Schedule

Study	Method	n	Ibuprofen Dose (mg/kg)	Indomethacin Dose (mg/kg)
Patel et al (1995) <sup>12</sup>	Double Blind	33	Two groups:	0.1
Mosca et al (1997) <sup>17</sup>	Open	16	10 × 5 × 5	0.2 × 0.1 × 0.1 24-h intervals
Van Overmeire et al (1997) <sup>14</sup>	Open	40	10 × 5 × 5	0.2 × 0.1 × 0.1 12-h intervals
Pezzati et al (1999) <sup>18</sup>	Open	17	10 × 5 × 5	0.2 × 0.1 × 0.1 12-h intervals
Patel et al (2000) <sup>13</sup>	Double Blind	33	10 × 5 × 5	0.2–0.25 12-h intervals
Van Overmeire et al (2000) <sup>15</sup>	Open	148	10 × 5 × 5	0.2 × 0.1 × 0.1 12-h intervals
Lago et al (2002) <sup>16</sup>	Open	175	10 × 5 × 5	0.2 × 0.2 × 0.2 12-h intervals
Plavka et al (2001) <sup>19</sup>	Open	41	8 × 8 × 8	0.2 × 0.2 × 0.2 24-h intervals
Su et al (2003) <sup>20</sup>	Open	63	10 × 5 × 5	0.2 × 0.2 × 0.2 12-h intervals

## Clinical Studies

Clinical trials have compared IV Ibuprofen to placebo, or to indomethacin, or evaluated the pharmacodynamic effects of this drug before and after its administration. Compared with placebo, IV ibuprofen lysine decreased PDA with minimal effect on renal function.<sup>4,7,8</sup> One study using another formulation of IV ibuprofen (ibuprofen-THAM) showed decreased renal function and increased risk of NEC, and PPHN.<sup>5,6</sup> Compared with indomethacin, IV ibuprofen exerted similar efficacy (75% to 93% closure). However, indomethacin increased abnormal renal function and decreased mesenteric and cerebral blood flow and bio-energetics (see below).

### Ibuprofen–Lysine or Ibuprofen-THAM versus Placebo

We studied 34 preterm neonates<sup>4</sup> consecutively assigned within 3 hours of age to treatment with either one dose of ibuprofen-lysine (10 mg/kg intravenously) followed by 5 mg/kg per dose intravenously at 24 and 48 hours of age, one dose of ibuprofen lysine (10 mg/kg intravenously), or saline. Ibuprofen treatment significantly reduced plasma levels of prostaglandins, reduced the incidence of PDA without causing notable early adverse drug reactions in this phase I trial, and was associated with better respiratory outcome and earlier discharge from the hospital. Similar findings were noted by De Carolis and coworkers,<sup>7</sup> who compared the efficacy and side effects of ibuprofen-lysine in the prophylaxis of PDA in 46 very preterm neonates less than 31 weeks gestation. A large randomized multicenter trial evaluated the efficacy of early ibuprofen-lysine (within 6 hours after birth) in reducing intraventricular hemorrhage (IVH) and PDA. A total of 415 low birth weight infants (gestational age <31 weeks) were randomly allocated to ibuprofen-lysine (10 mg/kg then two doses of 5 mg/kg after 24 and 48 hours) or placebo intravenously.<sup>8</sup> They found that ibuprofen-lysine prophylaxis in preterm infants did not reduce the frequency of intraventricular hemorrhage (17/205 or 8% versus 18/210, 9% placebo), but increased closure patent ductus arteriosus (84% versus 60% placebo). No important differences in other outcomes or side effects were noted; however, urine production was significantly lower on day 1, and concentration of creatinine in serum was significantly higher on day 3 after ibuprofen. In addition, no significant difference in the change in cerebral blood volume, change in cerebral blood

flow, or tissue oxygenation index measured by near infrared spectroscopy was found between ibuprofen- or placebo-treated infants.<sup>9</sup>

More recently, a phase III confirmatory trial on IV ibuprofen-lysine ( $n = 68$ ) versus placebo ( $n = 68$ ) showed significant reduction in PDA requiring intervention with indomethacin or surgery without deleterious renal and other adverse outcomes.<sup>10</sup>

In contrast to these studies on ibuprofen-lysine, a placebo randomized controlled trial on the efficacy and safety of another formulation of the drug, ibuprofen-THAM,<sup>5</sup> showed efficacy but increased risk of necrotising enterocolitis. In this study, infants younger than 28 weeks of gestation were randomly assigned to receive three doses of either ibuprofen-THAM or placebo within 6 hours of birth. This trial was stopped prematurely after 135 enrollments because of 3 cases of severe pulmonary hypertension in the prophylactic group. Sixty-five infants received prophylactic ibuprofen and 66 received placebo. Data from this aborted trial showed that prophylaxis reduced the need for surgical ligation from 6/65 (9%) to 0 ( $P = 0.03$ ) and tendency for a decreased rate of severe intraventricular hemorrhage from 15 (23%) to 7 (11%) ( $P = 0.10$ ). This observation partly confirmed earlier findings<sup>11</sup> that prophylactic treatment with ibuprofen reduces PDA occurrence in preterm infants with iRDS at 3 days of life in comparison with rescue treatment. However, survival was not improved (47 [71%] placebo versus 47 [72%] treatment,  $P = 1.00$ ), because of high frequency of adverse respiratory, renal, and digestive events. These findings strongly suggest a different safety profile for the 2 ibuprofen preparations.

### Ibuprofen versus Indomethacin

Several studies comparing the efficacy and safety of IV ibuprofen and indomethacin have been published. Table 1 shows the design, number of subjects, and dosage used in these trials. A small pilot trial<sup>12</sup> extended to a larger trial showed similar efficacy of ibuprofen-lysine and indomethacin on PDA closure<sup>13</sup> in preterm neonates. Indomethacin significantly decreased cerebral blood flow after the first dose. In contrast, no significant changes in CBF were observed with the first dose of ibuprofen. Cerebral oxygen delivery changed significantly after the first dose in the indomethacin group but not in the ibuprofen group.

**Table 2 Serum Creatinine (mg/dL)**

Study	n	IBU (mean ± SD)	INDO (mean ± SD)
Van Overmeire et al (1997) <sup>14</sup>	40	1.02 ± 0.36	1.25 ± 0.44
Pezzati et al (1999) <sup>18</sup>	17	1.10 ± 0.20	1.25 ± 0.20
Van Overmeire et al (2000) <sup>15</sup>	148	0.92 ± 0.29	1.08 ± 0.37
Lago et al (2002) <sup>16</sup>	175	0.92 ± 0.23	1.01 ± 0.27
Su et al (2003) <sup>20</sup>	63	1.48 ± 0.27	2.03 ± 2.10

Note: Lago et al (2002) data converted from  $\mu\text{mol/l}$  to  $\text{mg}/100\text{ ml}$  by dividing by 88.4.

Van Overmeire and his collaborators have also been actively conducting clinical trials on these drugs. In 1997, they reported that ibuprofen-lysine treatment is as effective as indomethacin in closing PDA on the third day of life in preterm infants with respiratory distress syndrome and had fewer renal side effects.<sup>14</sup> This finding was further confirmed by a larger trial from these investigators.<sup>15</sup> They studied 148 infants (gestational age, 24 to 32 weeks) with respiratory distress syndrome and PDA and randomly assigned them to receive either intravenous doses of indomethacin or ibuprofen-lysine (starting on the third day of life). The rate of ductal closure was similar with the 2 treatments: ductal closure occurred in 49 of 74 infants given indomethacin (66%) and in 52 of 74 given ibuprofen (70%). The numbers of infants who needed a second pharmacologic treatment or surgical ductal ligation did not differ significantly between the two groups. Oliguria occurred in 5 infants treated with ibuprofen and in 14 treated with indomethacin. There were no significant differences with respect to other side effects or complications.

The above findings were confirmed in a prospective randomized controlled trial on ibuprofen-lysine and indomethacin by Lago and coworkers.<sup>16</sup> They randomized 175 infants (gestational age 23-34 weeks) with respiratory distress syndrome and showed that, compared with indomethacin, ibuprofen has fewer effects on renal function in terms of urine output and fluid retention, with much the same efficacy and safety in closing patent ductus arteriosus in preterm infants. Much smaller trials with basically similar findings indicated that, indeed, ibuprofen and indomethacin have comparable efficacy on ductal closure, but the renal effects of ibuprofen were less pronounced compared with indomethacin.<sup>17-20</sup> A retrospective study by Fanos and coworkers was also in accord with the published clinical trials.<sup>32</sup> Comparison of the nonductal effects, including cerebral blood flow velocity, cerebral blood volume, oxidized cytochrome oxidase, and mesenteric and renal blood flow, indicate that indomethacin decreases these physiologic functions but ibuprofen does not influence these variables.<sup>17,18</sup>

## **Ibuprofen: Pharmacodynamics (Pre- and Post-Drug Dose Studies)**

The efficacy and pharmacodynamic studies on IV ibuprofen using Doppler blood flow and near infrared spectroscopy on cerebral, renal, and/or mesenteric hemodynamics showed

that this drug has minimal effects on organ blood flow of these systems.<sup>21-23</sup> Ibuprofen also attenuated cerebral hemodynamic changes associated with withdrawal, but not infusion, from umbilical venous and arterial catheters,<sup>53</sup> suggesting improved autoregulation at lower perfusion pressures.

## **Oral Ibuprofen**

Three clinical trials on the use of oral ibuprofen compared with IV indomethacin for PDA closure have suggested efficacy of oral ibuprofen for this indication. All studies have small sample sizes and definitive conclusions cannot be made.<sup>24,25</sup> A nonrandomized controlled trial also suggested efficacy of oral ibuprofen. The trial conducted in Israel<sup>26</sup> gave oral ibuprofen suspension 10 mg/kg/body weight for the first dose, followed at 24-hour intervals by 2 additional doses of 5 mg/kg each. Ductal closure was achieved in all newborns except for one (95.5%), in whom clinically nonsignificant ductal shunting persisted. No infant required surgical ligation of the ductus. Closure of the PDA in 11/13 infants given oral ibuprofen was also reported in a small study from India.<sup>27</sup> Small clinical, nonrandomized trials should no longer be done nor should be reported. Rigorously designed and appropriately powered clinical trials on oral ibuprofen that address issues of safety and efficacy in the preterm population are yet to be performed.

## **Meta-Analyses**

Three meta-analyses have examined the efficacy and safety of intravenous ibuprofen compared with indomethacin, placebo, or other drugs.<sup>28-30</sup> All three meta-analyses concluded that the efficacy on PDA closure of ibuprofen and indomethacin was not different. However, the interpretation of the adverse effects, particularly on the renal and pulmonary effects, differed. Ohlsson and coworkers found no statistically significant difference in the effectiveness of ibuprofen compared with indomethacin in closing the PDA. Although ibuprofen has lower risk of oliguria, the drug may increase the risk for chronic lung disease, and pulmonary hypertension has been observed in three infants after prophylactic use of ibuprofen. They concluded that ibuprofen does not appear to confer a net benefit over indomethacin for the treatment of a PDA and that indomethacin should remain the drug of choice for the treatment of a PDA. Thomas and coworkers concluded that ibuprofen and indomethacin have similar efficacy in patent ductus arteriosus closure, but preterm infants treated with ibuprofen experience lower serum creatinine values, higher urine output (Tables 2 and 3), and less unde-

**Table 3** Urine Output (ml/kg/min)

Study	n	IBU (mean ± SD)	INDO (mean ± SD)
Van Overmeire et al (1997) <sup>14</sup>	40	3.20 ± 1.28	1.80 ± 0.72
Pezzati et al (1999) <sup>18</sup>	17	2.80 ± 0.40	1.60 ± 0.40
Van Overmeire et al (2000) <sup>15</sup>	148	2.95 ± 1.23	2.17 ± 0.87
Lago et al (2002) <sup>16</sup>	175	3.50 ± 1.20	2.80 ± 1.20
Su et al (2003) <sup>20</sup>	63	3.60 ± 1.30	2.80 ± 1.10

sirable decreased organ blood flow and vasoconstrictive adverse effects. In view of equal efficacy but with less toxicity, this suggests a slight therapeutic superiority in favor of ibuprofen.

### Efficacy in Intraventricular Hemorrhage

Ibuprofen enhances cerebral blood flow autoregulation and may protect neuralgic functions after oxidative stress in experimental animals.<sup>2,31</sup> Studies in animal models<sup>2</sup> and in newborn infants demonstrated that ibuprofen was effective in closing PDA without reducing cerebral blood flow<sup>12,13,21</sup> or affecting the cerebral vasoreactivity to carbon dioxide, intestinal blood flow, or renal hemodynamics.<sup>18</sup> These observations suggested that ibuprofen may also influence the development of IVH. However, two recent randomized, double blind placebo controlled trials indicate that ibuprofen is not effective in preventing IVH.<sup>8,33</sup> Van Overmeire and coworkers<sup>8</sup> studied 415 preterm newborns <31 weeks gestation given either ibuprofen or placebo within 6 hours after birth. Although there was a decrease in PDA by the drug, there was no significant effect of ibuprofen on IVH with 17/205 (8%) of infants in the ibuprofen group, and 18/210 (9%) in the placebo group developed severe intraventricular hemorrhage. Similarly, Dani and coworkers<sup>33</sup> randomized 155 neonates <28 weeks gestation to receive ibuprofen or placebo within 6 hours after birth. Again, no effect on IVH was observed with 16/77 (21%) in the ibuprofen group and 13/78 (17%) developing Grade 2 to 4 IVH. These data indicate that ibuprofen is not indicated for the prevention of IVH.

### Dose Finding

The initial dosing guidelines consisting of 10 mg/kg loading dose followed by 5 mg/kg/d every 24 hours twice (total of 3 doses in 3 days) were based on the pharmacokinetic data by Aranda and coworkers.<sup>34</sup> This dosing regimen was subjected to further investigation by Desfrere and coworkers,<sup>35</sup> who determined the minimum effective dose regimen (MEDR) of IBU (one course) required to close ductus arteriosus in preterm infants. A double-blind dose-finding study was conducted in 40 neonates <29 weeks gestation using the continual reassessment Bayesian sequential design. Four different dose regimens were tested: loading doses of 5, 10, 15, or 20 mg/kg, followed by two doses (1/2 loading dose) at 24-hour intervals. Efficacy was evaluated by echocardiography 24 hours after the third infusion. This study confirmed that the currently recommended dose regimen (10-5-5 mg/kg) of IBU developed by Aranda and coworkers<sup>4,34</sup> is associated with a high closure rate (80%) and few adverse effects in

premature infants with a PMA of 27 to 29 weeks. A higher dose regimen (20-10-10 mg/kg) might achieve a greater closure rate but must be balanced with the tolerability and safety.<sup>35</sup>

### Pharmacokinetics, Metabolism, and Disposition

The pharmacokinetics of ibuprofen in adults has been reviewed.<sup>36</sup> Ibuprofen is extensively metabolized to two major metabolites: 2-[4-(2-hydroxy-2-methyl propyl) phenyl] propionic acid (2-hydroxy ibuprofen) and 2-[3-(2-carboxypropyl) phenyl]propionic acid (carboxy ibuprofen). Recent evidence suggests that CYP 2C9 is the major CYP mediating the 2- and 3-hydroxylations of R- and S-ibuprofen in the liver of Caucasians. Other CYPs, particularly CYP 2C8, may play a role in these biotransformations and hence the relative expression of CYP 2C9 and 2C8 may contribute to variability in the clearance of ibuprofen enantiomers. The hydroxy and carboxy metabolites of ibuprofen have no apparent pharmacologic activity. A major metabolic pathway of ibuprofen is conjugation with glucuronic acid to yield acyl glucuronides. Ibuprofen is also metabolized to ibuprofen acylglucuronide. All known phase 1 metabolites of ibuprofen form  $\beta$ -1-O-acylglucuronides at the carboxylic group of the propionic side chain. CYP 2C9 has been identified as the most important catalyst for formation of all the oxidative metabolites of R(-) and S(+)-ibuprofen.

The pharmacokinetics properties of a single intravenous dose of ibuprofen lysine was first described by Aranda and coworkers<sup>34</sup> in 21 preterm neonates with gestational age ranging from 22 to 31 weeks. All infants were less than 1 day old. The ibuprofen's apparent volume of distribution (AVd) was  $62.1 \pm 3.9$  mL/kg, plasma t<sub>1/2</sub> beta was  $30.5 \pm 4.2$  hours, elimination rate constant (K<sub>el</sub>) was  $0.032 \pm 0.004$  hours<sup>-1</sup>, plasma clearance was  $2.06 \pm 0.33$  mL/kg/h. Gestational age and birth weight were not related to drug elimination. Van Overmeire studied 27 preterm newborn infants at 3 and 5 days of age.<sup>37</sup> Ibuprofen pharmacokinetics followed a 2-compartment open model. Between the first and third doses (day 3 and day 5), there was a significant decrease of the volume of distribution of the central compartment (Vd(c)) (0.244 versus 0.171 L/kg;  $P = 0.03$ ) and area under the plasma concentration-time curve (524 versus 447 mg h/L;  $P = 0.01$ ). The decrease in Vd(c) was most pronounced in patients with a closing ductus. Total body clearance and plasma half-life did not change significantly.

Ibuprofen is a chiral drug with R and S enantiomers and a unidirectional conversion of the R to the S enantiomer. A population PK study on ibuprofen THAM enantiomers in 62 preterm neonates was described by Gregoire and coworkers.<sup>38</sup> The plasma half lives of R- and S-ibuprofen were about 10 hours and 25.5 hours, respectively. The mean clearance of R-ibuprofen (CLR = 12.7 mL/h) was about 2.5-fold higher than for S-ibuprofen (CLS = 5.0 mL/h) and increased significantly with gestational age. The mean estimation of R-ibuprofen clearance was found to be higher than for S-ibuprofen, and the clearance of both enantiomers increased with gestational age.

The pharmacokinetics of an oral dose of ibuprofen in preterm newborns was studied in 20 premature infants born at 26 to 32 weeks gestation given a single oral dose of 10 mg/kg ibuprofen by Sharma and coworkers.<sup>39</sup> The peak plasma concentrations of ibuprofen ranged from 4.9 to 65.6 microgram/L and were lower compared with those achieved with an IV dosing. The plasma half life ranged from 3 to 77 hours (mean = 15.7 hours). These data suggest that much higher oral dose is probably required to generate similar plasma concentrations obtained from an IV route.

## Adverse Effects and Potential Drug-Drug Interactions

Ibuprofen, like all NSAIDs, exerts many pharmacologic effects resulting in adverse events leading to gastrointestinal and hematologic side effects. Some potential drug interactions are also noted below.

### Gastrointestinal

In adults, NSAID including ibuprofen is associated with gastrointestinal adverse effects including peptic ulcer and bleeding.<sup>40</sup> Thus far, IV ibuprofen lysine has been reported to be safe. In contrast, ibuprofen-THAM has been associated with increased risk for necrotizing enterocolitis.<sup>5</sup> Spontaneous intestinal perforation after oral ibuprofen treatment of patent ductus arteriosus in two very-low-birth weight infants was also recently reported.<sup>41</sup> These intestinal perforations resolved with penrose drains only. The gastrointestinal complications would be an important issue particularly with the oral route.

### Cortisone

Postnatal steroid therapy is associated with increased risk of gastrointestinal perforation.<sup>42-45</sup> The NSAIDs have the potential of interacting with steroids to increase further the risk of GI perforation. Pertoniemi and coworkers<sup>45</sup> had to stop a randomized placebo controlled trial on hydrocortisone in preterm newborns because of GI perforation in the hydrocortisone group only (4/25 versus 0/26,  $P = 0.05$ ). Three of the 4 infants with perforation also received either indomethacin or ibuprofen.

## Bilirubin

Ibuprofen is 99% protein bound and it has been suggested that the drug may exert a bilirubin–drug–protein interaction.<sup>46</sup> In vitro, reverse displacement studies show that free bilirubin is increased by a factor of 4 at concentrations equivalent to those achieved in newborns after IV ibuprofen. None (10 studies) reported bilirubin encephalopathy. However, in vitro bilirubin–albumin–ibuprofen displacement studies by salicylate saturation index showed that ibuprofen does not displace bilirubin from albumin (bili: albumin molar ratios 0.5 to 1.5).<sup>47,48</sup> In addition, horseradish peroxidase (measure of free bilirubin) assay of spiked newborn cord plasma shows free bilirubin at bilirubin albumin molar ratios 0.5 to 1.5 and bilirubin at 10 mg/dL.<sup>48,49</sup> This in vitro observation was further tested in 15 preterm neonates whose free or unbound bilirubin were measured in preterm neonates ( $n = 15$ ) before and after ibuprofen administration. No change in free bilirubin before and after ibuprofen infusion (10-5-5 mg/kg/dose) (1.07  $\mu\text{g/dL}$  versus 1.00  $\mu\text{g/dL}$ ,  $p = \text{NS}$ ) was noted.<sup>50</sup> These observations taken together with published efficacy and safety data suggest that ibuprofen at the doses used, does not produce significant bilirubin–drug–albumin interaction.

## PPHN

Three neonates developed pulmonary hypertension in babies given ibuprofen-THAM in the French collaborative trial.<sup>5</sup> All responded to inhaled NO. PPHN as an adverse event has not been reported with IV ibuprofen-lysine.<sup>8,51</sup> This adverse effect, although searched for, has not been described with other trials on ibuprofen.

## Hematologic

NSAIDs inhibits platelet adhesiveness leading to bleeding disorder. As part of the safety evaluation of this drug in published randomized clinical trials, IV ibuprofen has not been associated with any bleeding disorder. Dani and coworkers observed no differences in serial platelet function and number between placebo and drug.<sup>33</sup>

## Aminoglycosides Interaction and Other Renal Effects

Retrospective calculations of the pharmacokinetics of amikacin in 72 preterm newborns <31 weeks gestation who received either placebo or ibuprofen showed that the median serum half-life (16.4 versus 12.4 hour) of amikacin was significantly longer ( $P < 0.02$ ), and the clearance (0.36 versus 0.6 mL/kg/min;  $P < 0.005$ ) of amikacin was significantly lower in infants who received ibuprofen-lysine.<sup>52</sup> The renal effects of ibuprofen in the human newborn appears to be less compared with neonatal experimental animals. In newborn rabbits, ibuprofen-lysine exerted acute renal effects similar to those noted with indomethacin.<sup>54-56</sup>

## Therapeutic Strategy for Ibuprofen and Indomethacin Use in Newborns

Data described above indicate that ibuprofen has no effect on IVH prevention. Thus, when NSAID is indicated at age 1 day where IVH prevention is timely, indomethacin but not ibuprofen should be used. After days 2 and 3, when early therapy of pharmacologic closure of a hemodynamically significant PDA is desired, ibuprofen should be the first choice due to its better safety profile.

In summary, clinical trials have compared IV ibuprofen to placebo, or to indomethacin, and have shown efficacy of this drug for ductal closure of patent ductus arteriosus. IV ibuprofen decreased PDA without little effect on renal function.<sup>4,7,8</sup> One study using another formulation of IV ibuprofen (ibuprofen-THAM) showed decreased renal function and increased risk of NEC, and PPHN.<sup>5,6</sup> Compared with indomethacin, IV ibuprofen exerted similar efficacy (75% to 93% closure). However, indomethacin increased abnormal renal function and decreased mesenteric and cerebral blood flow and bio-energetics (see below). Thus, it appears that enough data are now available to support the use of ibuprofen lysine in the management of PDA in the newborn. Further safety evaluation of ibuprofen-THAM appears warranted. A head-on comparison of the two intravenous ibuprofen preparations is also needed.

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