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Evidence-Based Use of Indomethacin and Ibuprofen in the Neonatal Intensive Care Unit

Palmer G. Johnston, MD^a, Maria Gillam-Krakauer, MD^a, M. Paige Fuller, PharmD, BCPS^b, and Jeff Reese, MD^{a,c,*}

^aNeonatal-Perinatal Medicine, Division of Neonatology, Department of Pediatrics, Vanderbilt University Medical Center, 2200 Children's Way, Doctor's Office Tower 11111, Nashville, TN 37232-9544, USA

^bDepartment of Pharmacy, Monroe Carell Jr. Children's Hospital at Vanderbilt, 2200 Children's Way, Room 4508, Nashville, TN 37232, USA

^cDepartment of Cell and Developmental Biology, Vanderbilt University Medical Center, U-3218 MRB III Building, Nashville, TN 37232-8240, USA

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Pioneers in the care of premature infants recognized that a patent ductus arteriosus (PDA) could result in symptomatic hemodynamic changes with left-to-right circulatory shunt, and increased incidence of pulmonary hemorrhage,¹ parenchymal lung disease, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and death.² The prevalence of hemodynamically significant PDA (hsPDA) is inversely related to maturity. Although it affects 42% to 60% of infants born weighing less than 1000 g, the incidence decreases to 5% in infants weighing 1500 to 1750 g at birth.^{3,4} From 1939 to 1976, the primary treatment of a symptomatic PDA was surgical ligation. In 1969, Arcilla and colleagues⁵ reported a case of an infant born with heart failure from suspected in utero ductus closure following maternal treatment with salicylates late in pregnancy. Subsequent animal studies examining the relationship between the ductus arteriosus and prostaglandins led to clinical studies in neonates showing the effectiveness of prostaglandin synthesis inhibitors as a treatment for PDA.^{6,7}

In the same 1976 issue of the *New England Journal of Medicine*, both Friedman and colleagues⁶ and Heymann and colleagues⁷ presented the cases of 6 and 18 premature infants, respectively, each with a large PDA, most of which were successfully closed with a single dose of rectal or enteral indomethacin. These reports were the first clinical trials of indomethacin use in human premature infants. Although Coceani and colleagues^{8,9} studied the effects of ibuprofen on ductus patency in a lamb model in the late 1970s, it would take another 2 decades for clinical studies evaluating the effectiveness of ibuprofen for ductus closure to be published.^{10–12}

PHARMACOLOGY OF INDOMETHACIN AND IBUPROFEN

Within the body, synthesis of prostaglandins occurs when arachidonic acid is freed from lipid storage by phospholipase A₂. Subsequently, cyclooxygenase (COX) converts arachidonic acid to PGG₂ and PGH₂. PGH₂ is the precursor to multiple types of prostaglandins, including PGE₂, PGD₂, PGF_{2α}, and PGI₂ and thromboxane.¹³ Prostaglandins are known to play a critical role in the pathophysiology of PDA, thus, inhibiting the production of these vasoactive substances has been the goal of pharmacologic approaches for many years.¹⁴ Two particular prostaglandin inhibitors, indomethacin and ibuprofen, have been the most studied for the prophylaxis and treatment of PDA because of their ability to enter the COX hydrophobic channel, competing with arachidonic acid for binding at the catalytic site and blocking the production of prostaglandins.^{15,16}

Indomethacin

Although both are classified as nonsteroidal antiinflammatory drugs (NSAIDs), indomethacin and ibuprofen have different kinetics and pharmacologic properties. Indomethacin first became available in 1963¹⁷ and belongs to a group of drugs called indoleacetic acids. Synthetically derived from arylacetic acid,¹⁸ indomethacin inhibits COX in a competitive, time-dependent, slowly reversible manner.^{15,16,18} Indomethacin nonselectively inhibits COX enzymes, resulting in decreased synthesis of all prostaglandin types. The nonselective mechanism of COX inhibition is responsible for the various unwanted side effects that can occur with administration.¹⁴ From 1976 until 2004, indomethacin was the standard medication for the pharmacologic closure of PDA until the arrival of intravenous (IV) formulations of ibuprofen on the market (Fig. 1).

Ibuprofen

Ibuprofen was the first drug in the propionic class to become used routinely by the general public in its oral form.¹⁷ It is a chiral compound derived from arylpropionic acid.¹⁸ Ibuprofen exerts its effect in a simple, competitive, rapidly reversible manner.^{15,16,18} Like indomethacin, ibuprofen inhibits COX in a nonselective manner.^{14,17} In 2006, ibuprofen lysine, an IV formulation, became available in the United States for the treatment of PDA (see Fig. 1).

Two Cyclooxygenases

In 1991, a second COX enzyme (COX-2) was discovered, which led researchers to study why 2 isoforms, COX-1 and COX-2, exist.¹⁹ Studies in mice suggest that COX-2 has a more important role in the closure of the DA, whereas COX-1 plays a more compensatory function.^{19–22} Results in the human ductus are less clear; COX-1 expression is greater than COX-2,²³ but selective COX-2 inhibitors can constrict the fetal ductus.²⁴ The catalytic channel of COX-2 is larger and more accommodating based on the size, charge, and chemical environment versus COX-1 (Fig. 2).^{15,25,26} All classical NSAIDs (those before 1995) inhibit both COX-1 and COX-2 but in general bind more tightly to COX-1.¹⁵ Indomethacin is more specific for COX-1, thus, resulting in overall greater systemic, nonselective vasoconstriction,²⁷ although ibuprofen is also somewhat more selective for COX-1 than COX-2 (Fig. 3).^{18,28} Indomethacin and other NSAIDs may also have effects on noncyclooxygenase pathways that augment ductus constriction or add to their deleterious side effects.^{17,29–32}

TREATMENT OF hsPDA

Efficacy when Treatment is Indicated

NSAIDs are an effective measure to induce PDA closure. Following the initial reports of Friedman and Heymann in the mid-1970s, many studies were published in the early 1980s showing a significant decrease in the presence of PDA after infants were treated with indomethacin compared with control. Rates of initial ductus closure in infants born weighing less than 1750 g range from 60% to 86% after a treatment course of indomethacin.^{7,33–39} By comparison, spontaneous closure occurs in just 35% of infants weighing less than 1750 g³³ and is more likely to occur in infants greater than 29 weeks' gestation and 1000 g at birth.^{4,40}

Ibuprofen and indomethacin have similar efficacy for primary closure of a PDA. Rates of closure after an initial 3-dose course of ibuprofen range from 66% to 73%.^{34,35,39,41} In a randomized controlled trial comparing treatment of PDA with ibuprofen or indomethacin in the first 48 to 72 hours of age, Lago and colleagues³⁴ reported successful closure after 3 doses of medication in 69% of infants given indomethacin compared with 73% who were given ibuprofen. Between 44% and 48% of infants required 3 additional doses of the same medication, resulting in an overall closure rate of 82% for indomethacin and 86% for ibuprofen (*P* values not significant).

The overall rate of ductus reopening after successful treatment with either indomethacin or ibuprofen is around 21% to 26%.^{33,34,42} Infants born at less than or equal to 26 weeks' gestation have a significantly increased risk of ductus reopening compared with infants born at older gestational ages (37% vs 11%, *P* < .03).⁴² Treatment failure has been found to be more common in infants with (1) residual flow through the ductus lumen, (2) absence of antenatal steroids, (3) increased severity of respiratory distress syndrome (RDS), (4) exposure to antenatal indomethacin, and (5) chorioamnionitis.^{42–49}

Decreased Need for Surgical Ligation

In most studies, treatment of a PDA with indomethacin has been shown to decrease the need for surgical ligation.^{7,33,36,50} Mahony and colleagues⁵⁰ found a significant decrease (*P* < .005) in the need for surgical ligation of the PDA in infants with less than a 1000-g birth weight who received indomethacin compared with control. One of the first published studies comparing indomethacin versus aspirin for the treatment of PDA by Heymann and colleagues⁷ enrolled 18 infants and found that no patients who received indomethacin treatment required surgical ligation of the PDA. Another early study of 59 infants by Merritt and colleagues³⁶ in 1978 compared indomethacin treatment with primary surgical ligation. Only 4 of 35 (11%) infants in the indomethacin group needed surgical ligation of their ductus secondary to symptoms of heart failure after treatment with indomethacin. Delaying treatment with indomethacin during a brief course of supportive care does not seem to significantly increase the need for later surgical ligation.³³

In one of only a few studies that examined ibuprofen compared with placebo for the treatment of PDA, Aranda and colleagues⁵¹ (2009) reported a multicenter, double-blinded, randomized, controlled trial in 136 infants who had a hsPDA diagnosed before 72 hours of age. Infants were randomized to receive ibuprofen or placebo initially with indomethacin for rescue therapy and then surgical ligation if needed. Infants who received ibuprofen had a significant decrease in the need for rescue indomethacin as compared with controls (*P* = .0003). Interestingly, there was no difference between the ibuprofen group and control in the need for surgical ligation in the infants who received rescue indomethacin. Rescue indomethacin was given to all infants who failed to have duct closure before proceeding with surgical ligation.

Several randomized, placebo-controlled trials found that ibuprofen was as effective as indomethacin at decreasing the need for surgical ligation.^{11,34,41,52} A Cochrane meta-analysis evaluating the efficacy of ibuprofen for PDA closure identified 13 trials (n = 848 infants) that reported ligation as an endpoint. By meta-analysis, there was no significant difference between ibuprofen- and indomethacin-treated groups in the need for ligation.⁵³

Indomethacin

Treatment dosing—Determining the optimal dosing regimen, length of treatment, and timing of indomethacin for the management of PDA has been challenging. The response of the PDA to indomethacin depends on the size of the dose and the number of doses.⁵⁴ Furthermore, it is known that the success of indomethacin in producing PDA closure wanes with advancing postnatal age.^{27,54,55} However, the risks of PDA treatment in the youngest preterm infants should be weighed against the potential benefits. Although one standard regimen may not be optimal for each individual, evidence shows that there are advantages and disadvantages to different approaches.

Prolonged versus short course—Circulating PGE₂ concentrations return to pretreatment levels several days following the completion of an indomethacin course, which may not allow enough time for ductus remodeling in the immature infant.⁵⁴ Seyberth and colleagues⁵⁶ reported a significant reappearance of PGE₂ after 5.5 days of completed therapy with indomethacin. Thus, prolongation of the more typical 2- to 3-day course of indomethacin has been described.

A 2007 Cochrane meta-analysis sought to determine whether longer courses of indomethacin would increase the success rate of PDA closure. Five trials describing the outcomes of a total of 431 preterm infants were included in the review. On comparison of short (3 doses) versus prolonged (4 doses) treatment courses, there were no significant effects on closure, re-treatment, reopening, or ligation rates of PDA. Additionally, there was no significant effect on outcomes, such as chronic lung disease, IVH, and mortality. When examining side-effect differences, the prolonged course of indomethacin was linked to an increased possibility of developing NEC, but a decreased risk of renal dysfunction. The investigators concluded that although there is less renal impairment with a prolonged dosing approach, the risk of NEC precludes routine recommendation of prolonged courses of indomethacin.⁵⁷

Continuous infusion versus intermittent bolus—Prolonging the indomethacin infusion time from a short bolus to 20 to 30 minutes reduces the detrimental effects of indomethacin on cerebral blood flow velocity.^{14,54} Investigators subsequently hypothesized that a continuous infusion of indomethacin might also alleviate the side effects seen with bolus dosing. In 1995, Hammerman and colleagues⁵⁸ published findings of 18 preterm patients: 9 that received continuous indomethacin (0.011 mg/kg/h for 36 hours) and 9 that received bolus dosing (0.2 mg/kg over 60 seconds followed by 0.1 mg/kg doses every 12 hours for 2 additional doses). Fluctuation found in the middle cerebral artery systolic and diastolic flow velocities in the continuous indomethacin group were significantly less than in the bolus group.

A similar trial by Christmann⁵⁹ evaluated 32 preterm infants comparing differences in blood flow in the cerebral vasculature. Infants in the continuous indomethacin group received the same total dose of 0.4 mg/kg over 36 hours (0.011 mg/kg/h) as in the Hammerman trial. In the bolus group (given over 30 seconds), doses were divided into 3 injections: 0.2 mg/kg at the first dose, then 0.1 mg/kg at 12 and 36 hours after the first injection. Statistically significant differences between the 2 regimens occurred at various time points during the

study regarding cerebral, renal, and mesenteric blood flow velocities.⁵⁹ The benefits of continuous indomethacin infusion are tempered by potential drawbacks with this approach: necessity for stable IV access, an infusion time of 36 hours, adequate preservatives for a prolonged infusion time, concerns regarding drug precipitation or incompatibility with other infusions, or excess fluid administration. A standard administration time of at least 20 to 30 minutes is currently favored, until continuous infusion is more thoroughly studied.

Routes of Administration—Over the years, indomethacin has been administered intravenously, intramuscularly, enterally, and rectally for the treatment of PDA.^{60,61} Enteral administration is the most studied alternative to the IV formulation. In 1979, Cooke⁶² reported an inadequate response to oral indomethacin provided at 0.2 mg/kg/dose every 12 hours for 3 doses; 5 of the 7 treated infants had no clinical response. More concerning than the potential lack of clinical response are the reports of intestinal perforations associated with enteral indomethacin. Alpan and colleagues⁶³ published a case series in 1985 in which 4 premature infants experienced localized small-bowel perforation after the administration of indomethacin via a nasogastric tube. The investigators speculated that perhaps their findings were related to a locally induced prostaglandin deficiency resulting in less cytoprotection in the gastrointestinal tract. Kuhl and Sey-berth⁶⁰ hypothesized that the gastrointestinal side effects are not a local effect caused by oral administration, but rather decreased gut perfusion caused by the PDA, coupled with the blockage of mucosal vasodilation and integrity normally provided by prostaglandins. Similar findings were reported in a single case report in a letter to the editor in 1985 and by Nagaraj⁶¹ in 1981 in which 8 of 82 infants given enteral indomethacin developed a focal perforation in various locations in the gastrointestinal tract.^{60,61,64} Inadequate and inconsistent drug absorption by the enteral route has also been a concern with this method of administration.^{65,66} Determining the optimal formulation of enteral indomethacin has also proved challenging and may affect absorption.⁶⁷ Because of the potential side-effect profile and variation in absorption of enteral indomethacin in the literature, the IV formulation is preferred over the enteral formulation at this time.

Ibuprofen

A recent Cochrane review on the use of ibuprofen for the treatment of PDA included a total of 20 trials (n = 1092) that compared ibuprofen with indomethacin, and 1 trial (n = 136) comparing ibuprofen with placebo. Among the 21 trials, 14 used the IV formulation. Of these, 12 used a dosing regimen of 10 mg/kg for the initial dose followed by 5 mg/kg doses every 24 hours for 2 days,⁵³ which is the dosing regimen outlined by the manufacturers. This regimen was determined by the dose-finding study by Aranda and colleagues⁶⁸ in 1997 and confirmed by Desfrere's group in 2005 who found this regimen provides an 80% closure rate balanced with minimal side effects.⁶⁹

Seven trials included in the Cochrane review provided ibuprofen via the enteral route. Five of these studies followed the same dosing regimen that most researchers have used in IV trials: 10 mg/kg for the initial dose followed by 5 mg/kg daily for 2 days. One study used 10 mg/kg/dose for all 3 doses given every 24 hours, whereas one study did not specify an exact dosing regimen. When comparing oral ibuprofen with IV indomethacin, the meta-analysis found no statistically significant difference in the failure to close a PDA after 3 doses, although the investigators commented that enteral ibuprofen seemed less effective than IV indomethacin. It was concluded that both the enteral and IV routes of ibuprofen seem equally effective in the closure of PDA.⁵³ There have been 2 studies that compared safety and efficacy between IV and oral ibuprofen.^{70,71} Both studies found that the oral formulation had a higher success in the PDA closure rate compared with IV, although the

Gokmen study⁷¹ comments on the trend of more immature infants in the IV group, which may have affected outcomes.

Several concerns have been raised surrounding the use of enteral ibuprofen, specifically gastrointestinal side effects with the potential for a localized COX-inhibition effect in the gut similar to oral indomethacin. There were no bowel perforations reported in either the Cherif⁷⁰ or Gokmen studies in the oral groups.^{70,71} In the Gokmen trial, 6.0% of the patients in the IV group and 3.6% of the patients in the oral group experienced NEC, whereas 3.1% of the patients in the IV group and 6.3% of the patients in the oral group were observed to have the same outcome in the Cherif study. One patient in the oral ibuprofen group was found to have a gastrointestinal hemorrhage versus none in the IV group in both trials. Gokmen and colleagues mention 19 other cases of gastrointestinal bleeding out of 191 total patients in other pooled studies and theorizes that that gastrointestinal irritation is caused by the method of administration. Neither study had the power to detect a difference in complications, thus, prompting the need for trials with larger numbers.^{70,71}

Other concerns regarding the use of enteral ibuprofen include interpatient pharmacokinetic variability, which can be caused by differences in cytochrome P450 enzyme expression and interactions with other medications that affect protein binding, elimination, or hepatic metabolism of ibuprofen. Additionally, peak plasma concentrations are reportedly not as high as those with IV, suggesting that a higher milligram-perkilogram dosing regimen might be necessary. However, the longer half-life in infants, larger AUC₂₄, and adequate absorption, all factors that contribute to more contact time with the ductus, may explain the better response rates seen in recent studies investigating enteral ibuprofen.^{70–74}

In summary, larger studies with improved design are needed that are powered to detect both closure and complication rates between oral and IV ibuprofen, as well as additional pharmacokinetic data to determine the optimal dosing scheme. More information is also needed on the osmolality of the enteral formulations being used and studied. Until more data are available, the authors cannot recommend using enteral ibuprofen in an off-label fashion for the closure of the PDA unless IV alternatives are not available.

ADVERSE EFFECTS

Gastrointestinal Effects

Untoward gastrointestinal events occur with increased frequency in infants treated with NSAIDs. These adverse effects may be greater with indomethacin than ibuprofen and depend on the mode of administration, with rectal and enteral forms having greater toxicity.^{2,75}

Spontaneous intestinal perforation—Early indomethacin exposure has been associated with spontaneous intestinal perforation (SIP), especially when given in close proximity to postnatal corticosteroids. Both Stark and colleagues⁷⁶ and Watterberg and colleagues⁷⁷ found a significant effect with indomethacin and dexamethasone both given within the first 24 hours of age and indomethacin and hydrocortisone at 48 hours of age. A randomized, placebo-controlled trial of hydrocortisone to prevent bronchopulmonary dysplasia (BPD) was prematurely terminated because of gastrointestinal perforations in the hydrocortisone group that received indomethacin or ibuprofen.⁷⁸ A retrospective study by Attridge and colleagues⁷⁹ found that one of the independent risk factors for developing SIP was the administration of IV indomethacin within the first 3 days of life (odds ratio 1.86; $P < .0001$). Patients who developed SIP were also more likely to have a significant PDA.

There are case reports of increased incidence of SIP in infants who received either enteral or IV indomethacin as prophylaxis.^{61,63,80,81} In a large prospective study, Sharma and colleagues⁸² observed that any indomethacin exposure increased the risk for SIP, with increased risk among infants treated at less than 12 hours of age. Although conflicting evidence exists,⁸² there is also concern that *antenatal* exposure to indomethacin may also pose a risk for postnatal intestinal perforation.^{47,83–85} However, no randomized control trial comparing prophylactic indomethacin to placebo (including a Cochrane meta-analysis) found a significant increase in the incidence of SIP or NEC in infants who received indomethacin for prophylaxis.⁸⁶

Necrotizing enterocolitis—Although the pathogenesis of NEC is multifactorial, there is evidence to suggest that disturbances in gut perfusion leading to ischemia may play an important role in this disease. Several studies identified a correlation between the mere presence of an hsPDA and the development of NEC or increased mortality from NEC, especially among infants with a birth weight less than 1500 g and gestational age less than 28 weeks.^{2,87–90} This correlation is thought to be secondary to the mesenteric blood flow disturbances resulting from a left-to-right circulatory shunt.

Using Doppler ultrasonography, multiple studies have shown that indomethacin decreases blood flow velocity in the superior mesenteric artery.^{59,91–95} This effect is especially pronounced when indomethacin is given by rapid bolus (duration 20 seconds), but even slow infusion (duration 30–35 minutes) is associated with significantly decreased blood flow velocity compared with continuous infusion.⁵⁹ Although compelling, these small studies provide insufficient data to support continuous dosing rather than slow infusion.^{59,91,92,94}

There are numerous studies that report NEC as an adverse outcome after treatment with indomethacin.^{61,96–100} In a retrospective analysis, Grosfeld and colleagues⁹⁷ found a significant increase in the incidence of NEC in infants with a PDA who were treated with indomethacin as compared with infants who did not have a PDA and did not receive indomethacin treatment (35% vs 13%, $P<.5$). In a larger retrospective study involving more than 18,000 infants admitted to 17 level III nurseries in Canada, Sankaran and colleagues¹⁰⁰ observed a similar association between NEC and indomethacin in infants with a birth weight less than 1500 g. In contrast, an observational population study by Dollberg and colleagues⁸⁸ did not find an increased risk of NEC with indomethacin treatment of PDA in more than 6000 very-low-birth-weight (VLBW) infants. Moreover, the Trial of Indomethacin Prophylaxis in Preterm Infants (TIPP) involving more than 1000 VLBW infants did not find a significant increase in the risk of NEC associated with the administration of indomethacin as prophylaxis for PDA.¹⁰¹ Despite the known association between indomethacin and NEC, there is no clear evidence that the incidence or severity of NEC is related to treatment with indomethacin or that a cause-effect relationship exists.^{86,102–104}

When ibuprofen was compared with indomethacin for the treatment of hsPDA in a meta-analysis of 15 studies that had NEC as an outcome, there was a decrease in the relative risk (RR) of NEC with the use of ibuprofen (RR 0.68, confidence interval [CI] 0.47–0.99).⁵³ Pezzati and colleagues⁹² compared mesenteric blood flow velocities in 17 infants using Doppler ultrasonography following bolus administration of either indomethacin or ibuprofen and found that, unlike indomethacin, ibuprofen did not significantly reduce mesenteric blood flow. No cases of NEC developed in either group.

Enteral prophylactic ibuprofen may confer a slightly increased risk of gastrointestinal bleeding when compared with control. Two different randomized, placebo-controlled trials by the same investigators enrolled a combination of 104 infants to evaluate the effectiveness

of oral ibuprofen for prophylaxis. Neither study found a significant increase in gastrointestinal bleeding in the treatment group. Bleeding only became significant when the studies were analyzed together by meta-analysis (RR = 1.99 [95% CI 1.13–3.50]).^{105–107}

Renal Effects

Adverse effects on the kidney, including increased blood urea nitrogen and creatinine, oliguria, and renal failure, have been noted following treatment with indomethacin. Indomethacin causes water retention and hyponatremia by enhancing vasopressin action and increasing renal vascular resistance and reducing renal blood flow.¹⁰⁸ Ibuprofen does not decrease renal blood flow and, in fact, is associated with increased blood flow velocity at 120 minutes.⁹²

Increased creatinine

VLBW infants with hsPDA have a statistically significant increase in serum creatinine concentration following treatment with indomethacin, but no increase occurs following treatment with the first course of ibuprofen.^{33,34,92} This effect is transient and usually disappears within 24 hours, although resolution may take up to 7 days.^{34,92} However, when infants who receive a second course of either medication are compared, there is no difference between the decrease in urine output and the increase in creatinine.^{34,109} In contrast, Katakam and colleagues¹¹⁰ did not find a significant difference in creatinine between infants treated with indomethacin or ibuprofen. Continuous infusion of indomethacin prevents the increase in creatinine induced by bolus dosing.⁵⁸

Prophylactic ibuprofen may be associated with a brief increase in creatinine levels. Van Overmeire and colleagues¹¹¹ randomized 415 infants to receive either placebo or prophylactic ibuprofen and found a transient but significant increase in serum creatinine 24 hours after the third dose of ibuprofen when compared with placebo ($P < .0001$). Gournay and colleagues¹¹² also noted a significant increase in serum creatinine 4 to 7 days after treatment in the infants who received prophylactic ibuprofen ($P < .002$). A meta-analysis of 5 trials that reported creatinine level as an outcome indicated that prophylactic use of ibuprofen compared with placebo is associated with a statistically significant increase in creatinine levels on the third day of life.¹⁰⁵

Decreased urine output—Oliguria, defined as urine output less than 1 mL/kg/h, is observed more often in infants receiving indomethacin compared with ibuprofen.^{34,39,41,52,92} When compared with placebo, infants weighing greater than 1000 g receiving indomethacin have a significant decrease in mean urine output at 24 to 48 hours after treatment.⁵⁰ Bandstra and colleagues¹¹³ reported that oliguria also occurs after prophylactic indomethacin. The infants most affected tended to have a higher birth weight (900–1300 g), but all infants had resolution of oliguria within 72 hours. Bolus indomethacin is more likely to cause oliguria at 12 and 24 hours than continuous infusion.⁵⁹

Although treatment with ibuprofen results in a lower incidence of oliguria than indomethacin, it is not completely free of negative effects on the kidney. In a 2008 study involving 119 infants randomized to ibuprofen or indomethacin for the treatment of a PDA, Su and colleagues⁴¹ found an incidence of oliguria in the ibuprofen group of 6.7%. It was still significantly lower than the rate of oliguria in the indomethacin group (15.3%, $P < .05$). A more recent study by Vieux and colleagues¹¹⁴ suggests that renal impairment after ibuprofen may not be transient. In this study, ibuprofen-treated infants did not experience the normal postnatal increase in glomerular filtration rate (GFR) on days 2 to 7, and alterations in GFR and tubular function (fractional excretion of sodium) were noted until 28 days of age. In addition, instances of acute renal failure indicate that ibuprofen treatment

still poses nephrotoxic risks for preterm infants.^{115–119} Thus, although the rate of renal complications is lower with ibuprofen than with indomethacin, they nevertheless deserve consideration.

There is no evidence to support the use of either furosemide or dopamine during treatment with indomethacin to prevent adverse effects on the kidney. Although dopamine does not impair ductus closure^{120,121} and may increase urine output,¹²⁰ it neither prevents elevation of creatinine nor decreases incidence of oliguria.^{120–122}

Hyperbilirubinemia

In vitro studies suggest that high doses of ibuprofen can displace bilirubin from albumin, thus, increasing free bilirubin levels and theoretically increasing the risk of kernicterus.¹²³ Rheinlaender and colleagues¹²⁴ reported that total bilirubin levels were significantly elevated in patients who received ibuprofen compared with indomethacin for treatment of hsPDA ($P < .01$). However, even with the increase in bilirubin, neither the number of days of phototherapy treatment nor neurodevelopmental outcome at 2 years of age differed between the ibuprofen and indomethacin groups. Zecca and colleagues¹²⁵ also detected an association between ibuprofen and increased peak serum bilirubin levels and a longer need for phototherapy. However, both of these reports are retrospective and several clinical studies show that the risks for hyperbilirubinemia are limited.^{35,126–128}

Cerebrovascular and Other Effects

Ibuprofen has limited effects on cerebrovascular perfusion.^{129–131} In contrast, indomethacin is known to induce significant reductions in cerebral blood flow.^{129,130,132–139} Cerebral oxygenation is also affected by indomethacin treatment.^{130,133,140,141} Alterations in cerebral perfusion are, therefore, an important concern for indomethacin use in neonates. However, studies indicate that prophylactic indomethacin is protective against high-grade IVH^{86,101} and may reduce the incidence of white matter injury.⁸⁶ Moreover, neurodevelopmental outcomes of indomethacin-treated infants are no different than controls at 18 months¹⁰¹ and 36 months^{142,143} and may be improved at 4.5 and 8 years of age.^{144–146} The accumulated results of numerous studies have not shown an overall increase in the incidence of other potential morbidities, including retinopathy of prematurity and chronic lung disease.¹⁴⁷

Summary

Indomethacin effectively induces closure of the ductus arteriosus and decreases the need for surgical ligation; but compared with ibuprofen, the use of indomethacin is associated with increased concerns for gastrointestinal complications and decreased renal function. The difference between these drugs may be caused by indomethacin effects on noncyclooxygenase pathways. A transient decrease in urine output and an increase in creatinine can usually be medically supported. However, the complications arising from an episode of SIP or NEC in a very premature infant are often serious and, in the worst scenario, can lead to loss of life. Although indomethacin may have a useful role in *prophylaxis* for PDA (see later discussion),¹⁴⁸ current evidence does not support the routine use of indomethacin over ibuprofen for the treatment of the hsPDA when side effects are considered.

Ibuprofen is as effective as indomethacin in closing a PDA. Although ibuprofen does have some side effects, particularly on renal function, these effects are less when compared with indomethacin. If closure of an hsPDA is warranted, IV ibuprofen is an acceptable treatment option with the realization that there are associated side effects.

PROPHYLACTIC TREATMENT TO PREVENT IVH OR hsPDA

Preventive strategies for IVH co-evolved with efforts to effectively treat PDA. Because the smallest preterm infants are at the greatest risk of developing an hsPDA, both indomethacin and ibuprofen have been used in attempts to prevent progression to an hsPDA, reduce left-to-right shunting of blood away from vital organ systems, and avoid surgery.¹⁴⁹

Efficacy to Prevent Intraventricular Hemorrhage

The early trials of indomethacin for treatment of PDA occurred as efforts to identify compounds for prevention of IVH in premature infants were taking place. In 1983, the two intersected when Laura Ment and colleagues¹⁵⁰ published the first report of indomethacin successfully preventing IVH in the newborn beagle puppy. The mechanism of action of indomethacin on the cerebral vasculature is not completely known but is likely unrelated to the closure of the ductus arteriosus.^{151,152}

This discovery was followed by a series of short-term clinical trials in neonates.^{113,151,153,154} Although there was initially conflicting evidence on the effectiveness of IVH prevention, especially in infants weighing less than 1000 g,^{154,155} it was subsequently shown that prophylactic indomethacin (administered at <12 hours of age) was effective in reducing higher-grade IVH. In 1988, Bandstra and colleagues¹¹³ randomized almost 200 infants born at less than 1300 g to either receive 3 doses of indomethacin starting within 12 hours of birth or placebo. They found that prophylactic indomethacin significantly reduced the incidence of grade 2 to 4 IVH compared with control (23% vs 46%, $P < .002$). Ment and colleagues¹⁵⁶ reported a multicenter study involving more than 400 infants weighing between 600 and 1250 g given either 3 doses of indomethacin starting within 12 hours of birth or placebo. A significant decrease in all forms of IVH was noted ($P = .03$), but especially in grade 4 IVH. In the placebo group, 10 out of 222 infants experienced grade 4 IVH compared with only 1 out of 209 in the intervention group ($P = .01$). There were no differences in adverse events between the 2 groups and no extension of IVH in infants who already had a grade 1 or 2 hemorrhage by 11 hours of age.

More recently, in a group of 1200 infants born weighing less than 1000 g randomized to either receive indomethacin or placebo, the TIPP trial also reported that prophylactic indomethacin decreases severe (grade 3–4) IVH compared with placebo (9% vs 13%, $P = .02$).¹⁰¹

Although prophylactic indomethacin has been shown to decrease severe forms of IVH, the long-term effect on neurodevelopmental outcomes is equivocal or only somewhat improved. Couser and colleagues¹⁴² found comparable head growth and neuro-developmental outcomes in prophylactic indomethacin- and placebo-treated infants at the 36-month follow-up. In the multicenter trial by Ment and colleagues,¹⁴³ there was a decrease in the presence of ventriculomegaly at term in infants who had received prophylactic indomethacin (0% vs 5%, $P = .027$) and no statistically significant difference in survival at 36 months ($P = .09$). At 54 months, there was no difference in the incidence of cerebral palsy between the 2 groups. There was a significantly lower number of children who received indomethacin with an IQ less than 70 on the full-scale Wechsler Preschool and Primary Scale of Intelligence-Revised (9% vs 17%, $P = .035$). Children who received indomethacin also performed better on the Peabody Picture Vocabulary Test-Revised (PPVT-R) ($P = .02$).¹⁴⁴ At 8 years of age, there was no difference between the 2 groups regarding neurologic assessment, school performance, or cognitive functioning. There was no evidence at any age of adverse effects attributable to indomethacin.^{145,146} Boys who received prophylactic indomethacin had significantly higher verbal scores on the PPVT-R when compared with control boys ($P = .017$).¹⁴⁵

Although the TIPP trial also found a significant decrease in severe periventricular and intraventricular hemorrhage in infants given prophylactic indomethacin, there was no difference at 18 months in mortality or severe neurosensory impairment (cerebral palsy, cognitive delay [mental developmental index <70], deafness, and blindness).¹⁰¹ Controversy exists regarding the study design and the interpretation of these results.^{147,148,157}

Ibuprofen does not appear to confer protection against IVH.^{112,158} In a trial of 415 infants given either prophylactic ibuprofen or placebo, Van Overmeire and colleagues¹¹¹ found no difference in any form of IVH between the 2 groups. This finding was supported by a trial by Dani and colleagues¹⁵⁹ that also found that prophylactic ibuprofen was ineffective in preventing grade 2 to 4 IVH.

Efficacy to Prevent hsPDA

Multiple prospective, randomized, placebo-controlled trials show a statistically significant reduction in PDA when prophylactic indomethacin was given within the first 24 hours of life versus placebo.^{101,113,155,156,160} For example, in 199 infants with a birth weight less than 1300 g, Bandstra and colleagues¹¹³ saw a significant reduction in PDA at several days of life in infants who received prophylactic indomethacin (0.2 mg/kg IV $\times$ 1 within the first 12 hours of life followed by 2 doses of 0.1 mg/kg IV every 12 hours). PDA was present in 11% of the treatment group compared with 42% of infants who received the placebo ($P < .001$).

Although only a secondary outcome, the multicenter TIPP trial found a significant reduction ($P < .001$) in PDA from 50% in infants who received placebo to 24% in infants who received indomethacin prophylaxis.¹⁰¹ Even a single dose of indomethacin (0.2 mg/kg IV) given within the first 24 hours of life significantly reduced the presence of PDA from 56% in the placebo group to 7% in the treatment group ($P < .007$).¹⁵⁵ A systematic review of 19 randomized controlled trials showed that prophylactic indomethacin significantly reduced the risks for any reported type of PDA and the need for surgical ligation.⁸⁶ Further randomized trials of prophylactic indomethacin were deemed unnecessary. However, prophylactic treatment of PDA was only recommended by the Cochrane investigators in neonatal units without ready access to cardiac services or if cost-benefit analyses were favorable.⁸⁶

In multiple randomized controlled trials in comparison to placebo, patients who received IV ibuprofen prophylaxis had a significant decrease in PDA by 72 hours after treatment.^{12,105,111,112,159,161,162} The largest of these studies included 415 infants in a multicenter trial by Van Overmeire.¹¹¹ In that study, 84% of the infants who received 3 doses of prophylactic ibuprofen (10 mg/kg IV <6 hours of life, then 5 mg/kg IV at 24 and 48 hours) had closure of their PDA on the third day of life compared with 60% of infants who received placebo ($P < .0001$). Ibuprofen prophylaxis had the most effect on PDA closure in infants whose birth weight was 500 to 750 g.¹¹¹ However, a study by Varvarigou¹² in 1996 involving 34 infants aged less than 31 weeks specified that infants receiving only 1 dose of IV ibuprofen, like placebo, did not have a significant decrease in PDA compared with infants receiving 3 doses.

The use of oral ibuprofen for prophylaxis has been studied. In 2006, one randomized controlled study by Sangtawesin¹⁰⁷ with 42 patients found a significant decrease in the presence of PDA in infants who received 3 doses of ibuprofen suspension 10 mg/kg dose (first dose within first 24 hours of life and then again at 24 and 48 hours after the first dose) administered via gastric tube compared with placebo. However, Gournay and colleagues¹¹² discontinued a 2004 study because of severe pulmonary hypertension in 3 infants that received prophylactic ibuprofen. These episodes may be related to the acidic formulation of

tromethamine ibuprofen; however, a case report in 2006 reported an acute episode of pulmonary hypertension in a patient who received L-lysine ibuprofen for PDA prophylaxis.¹⁶³

Efficacy to Prevent Surgical Ligation

Prophylactic indomethacin is also associated with a significant decrease in the need for surgical ligation of PDA.^{50,86,101,160} The TIPP trial investigators found a decreased need for surgical ligation of hsPDA in the patients who received prophylactic indomethacin compared with placebo (12% vs 7%, $P<.001$) with a number needed to treat of 20.¹⁰¹

Although the study was stopped early because of the development of pulmonary hypertension in 3 infants, Gournay and colleagues¹¹² found a significant decrease in the need for surgical ligation in infants who received prophylactic IV ibuprofen (10 mg/kg within the first 6 hours of life, then a 5 mg/kg dose at 24 and 48 hours) compared with those who received placebo. In a recent retrospective cohort study, Tefft¹⁶⁴ reported that prophylactic ibuprofen administration significantly reduced the need for surgical ligation and observed that numerous other studies found similar results, although they did not reach statistical significance.

In reviewing 19 different trials evaluating the effectiveness of prophylactic indomethacin, no other side effects, such as BPD (oxygen requirement at 28 days of life), days requiring mechanical ventilation, pulmonary hemorrhage, excessive bleeding, thrombocytopenia, visual impairment, hearing impairment, or cerebral palsy, were found more often in patients who received prophylactic indomethacin versus control.⁸⁶

Dosing Regimens for Indomethacin Prophylaxis

There are different opinions regarding dosing regimens for indomethacin when used as prophylaxis. Plasma clearance depends on postnatal age, resulting in a rapid decline in half-life over the first week of life.^{165–167} An initial dose of 0.1 to 0.2 mg/kg IV has been used in the first 2 to 24 hours of life, and follow-up doses of 0.1 to 0.2 mg/kg IV have been given every 12 to 24 hours after the initial dose for 1 to 6 total doses. Many studies gave an initial dose of 0.2 mg/kg IV, with follow-up doses of 0.1 mg/kg IV. In the studies that gave more than 3 total doses, a lower dose of 0.1 mg/kg IV was used. Out of 19 trials included in a meta-analysis, 15 used a 3-dose regimen.⁸⁶ Three trials used 4, 5, or 6 total doses, whereas Krueger and colleagues¹⁵⁵ provided a single dose based on the pharmacokinetics of indomethacin and the minimization of side effects. The optimal dosing of IV indomethacin for prophylaxis is not currently known.⁸⁶

Summary

Both indomethacin and ibuprofen administered prophylactically reduce the need for later medical or surgical closure of the PDA. There is little evidence to date, however, that prophylactic closure of the PDA improves long-term outcomes or decreases other morbidities. Indomethacin prophylaxis has been shown in multiple studies to decrease the incidence of severe IVH, but there is insufficient long-term data to determine whether this has an impact on neurodevelopmental outcomes.

Although prophylactic ibuprofen does significantly improve the PDA closure rate and decreases the need for surgical ligation, there are well-documented side effects observed in patients who received prophylactic ibuprofen. Prophylactic ibuprofen has not been shown to decrease the incidence of severe IVH, and along with the increased potential risks of pulmonary hypertension and decreased urine output, ibuprofen cannot be recommended for use as prophylactic management of PDA in the preterm infant.

OBSERVATIONAL TREATMENT OF PDA

Justification for PDA treatment was traditionally based on evidence that prolonged exposure to a significant left-to-right shunt was deleterious. Morbidities attributed to the presence of an hsPDA have included BPD, pulmonary hemorrhage, increased RDS severity, NEC, renal impairment, IVH, periventricular leukomalacia, and death.¹⁰² However, numerous investigators have challenged the cause-and-effect relationship between PDA and these outcomes and questioned whether exposure to the risks of medical or surgical interventions is warranted.^{101–104,168–170}

Arguments for Treatment

Historical, prospective trials reported increased mortality in preterm infants with a symptomatic PDA compared with those without PDA.^{171–174} Thereafter, 2 small, randomized clinical trials that examined the consequences of an untreated, persistent symptomatic PDA demonstrated increased mortality, increased need for respiratory support, and worse outcomes.^{175,176}

In one report, Alexander and colleagues¹⁷⁷ compared outcomes among 298 extremely low-birth-weight infants with echocardiographically proven PDA. Infants treated with indomethacin or surgical ligation had significantly better survival rates compared with infants with untreated PDA. Nonsurvival was associated with immaturity, sepsis, and congestive heart failure, but study design did not permit the evaluation of relationships between PDA and other outcomes. In Western Australia, Brooks and colleagues¹⁷⁸ performed a retrospective analysis of 252 infants born at 28 weeks or less in a nursery lacking access to a pediatric surgeon to determine if closure of PDA was necessary. This study revealed that infants who had a persistent PDA despite treatment with indomethacin, even after adjustment for gestational age, had a 4-fold increased risk of death compared with infants who either did not have a PDA or who had PDA closure after indomethacin treatment ($P = .033$). No other morbidities were increased in the group without PDA closure. Noori and colleagues⁷⁵ reported another single-center, retrospective analysis evaluating the risk of persistent PDA. The study included 301 infants born at 29 weeks or less with a birth weight less than 1500 g and found a significant 8-fold increase in mortality in infants who had a persistent PDA after 14 days of age compared with infants with a closed PDA. The increase in mortality was still present after adjusting for gestational age ($P < .001$). A third, more recent retrospective study found an increased risk of a combined outcome of mortality and chronic lung disease (CLD) from 40% to 54% in infants who had more conservative management of PDA with decreased use of indomethacin, ibuprofen, or surgical ligation as compared with infants who received traditional treatment of PDA using indomethacin and surgical ligation ($P = .04$).¹⁷⁹ Thus, the presence of a persistent, untreated, symptomatic PDA may be associated with worse outcomes and increased mortality.

Arguments Against Treatment

Herrman and colleagues¹⁸⁰ performed a retrospective, observational cohort study on VLBW infants discharged from their unit with a PDA. Among 310 infants who survived, 21 had a documented PDA at the time of discharge. Two of the 21 infants were discharged on oxygen, with 2 on diuretic therapy and 2 on both. All of the infants survived to 18 months of age, and 18 out of 21 infants had spontaneous closure of their ductus. Two infants required transcatheter coil embolization and one still had a persistent PDA at 18 months chronologic age. Almost all of the infants with PDA at discharge had a small PDA, with 2 infants having a small to moderate PDA.

A recent meta-analysis of 10 trials comparing the use of indomethacin and ibuprofen versus placebo (with rescue therapy if needed) for the treatment of PDA performed by Jones and colleagues¹⁸¹ found that there was no associated reduction in the risk of major morbidities or mortality with PDA closure. Their risk-to-benefit ratios revealed that treating 100 infants with ibuprofen compared with placebo to achieve PDA closure could cause 14 cases of CLD, 3 cases of IVH, and 1 death, whereas indomethacin could cause 2 cases of CLD and 2 cases of IVH. In contrast to the strict criteria for Cochrane reviews, Benitz¹⁰² recently performed a systematic review of the literature by pooling the results from all available randomized clinical trials of PDA treatment. The intention was to avoid exclusion of any evidence that might be informative. It was concluded that later treatment, if any, might be beneficial; but the absence of improved long-term outcomes should limit all pharmacologic therapies for PDA to patients who are enrolled in on-going clinical trials.¹⁰²

SUMMARY

Symptomatic PDA is a well-documented complication of premature birth and is associated with multiple other morbidities. Studies over the past decade have challenged the seemingly foregone conclusion that a symptomatic PDA should be treated on the grounds that short-term morbidities and long-term outcomes may not be improved by PDA closure and infants are unnecessarily exposed to potentially harmful therapies. Yet, no randomized, double-blinded clinical trials comparing the treatment of symptomatic PDA versus placebo without rescue treatment have been done. The determination of whether or not a PDA should be treated is outside the scope of this review. For clinicians who decide that pharmacologic closure of the ductus is warranted, NSAIDs are currently the only available choice.

The use of indomethacin and ibuprofen for prophylaxis and treatment of PDA has been carefully studied and reported in the literature; however, thoroughly documented adverse effects associated with either medication limit recommendations for treatment. Indomethacin, but not ibuprofen, is an effective agent for the prevention of IVH and should be considered in patient populations in which elevated rates of IVH are a concern. Indomethacin, when used as a *prophylactic* measure for PDA, reduces the risks for development of an hsPDA and prevents pulmonary hemorrhage and the need for surgical ligation. In the smallest premature infants, these seem to be laudable goals, although risk-benefit ratios should be weighed. Indomethacin and ibuprofen, when used in *treatment* mode, are both effective measures to induce closure of an hsPDA. However, optimal treatment regimens require additional study. Recently, Hammerman and colleagues¹⁸² reported the off-label use of enteral paracetamol to successfully close a refractory hsPDA in 5 VLBW infants. With no observed side effects, this report is an exciting new development for the medical treatment of hsPDA, which has not seen a new therapy in more than a decade. The justification for PDA treatment is a topic of current debate but would benefit from additional treatment options that pose fewer risks.

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Fig. 1.

Structure of common NSAIDs. The NSAID parent compound, salicylic acid, was purified in 1829 and commercially synthesized in the mid-1800s. By 1897, salicylic acid had been successfully acetylated and was marketed as aspirin in 1899. Subsequent NSAID development led to the production of phenacetin (1887), acetaminophen (1888), phenylbutazone (1949), the fenamates (1950s), ibuprofen (1961), and indomethacin (1963).

Fig. 2. Structure of COX-1 and COX-2 substrate binding channels. Amino acid residues, Val 434, Arg 513, and Val 523, create a side pocket in COX-2, whereas the larger residues, Ile 434, His 513, and Ile 532, in the COX-1 channel block the bulky side chains of selective COX-2 inhibitors. (*Adapted from* Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. *J Clin Invest* 2006;116(1):4–15; with permission.)

Fig. 3.

Relative selectivity of different NSAIDs for COX-1 or COX-2. Values were extrapolated from inhibition curves for each compound against COX-1 and COX-2 that were generated in a human modified whole blood assay. Bars represent the ratio of IC₈₀ concentrations, plotted logarithmically. (*Adapted from* Warner TD, Mitchell JA. Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. *FASEB J* 2004;18(7):790–804; with permission.)