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Editorial

Patent Ductus Arteriosus: Indomethacin, Ibuprofen, Surgery, or No Treatment at All?

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Patent ductus arteriosus (PDA) occurs in over 50% of neonates below 28 weeks gestational age.[1] Most clinicians prefer to treat PDA, although some have argued treatment is not necessary.[2-4] The hemodynamic consequences of PDA involve the following: excess pulmonary circulation resulting in an increased risk for respiratory failure, pulmonary edema and decreased alveolar growth associated with chronic lung disease (CLD); and systemic hypoperfusion that may result in, renal dysfunction and necrotizing enterocolitis (NEC).[5-8] Hemodynamically significant PDA can also decrease cerebral oxygenation and tissue oxygen extraction, which may predispose the infant to neurologic damage.[9] The argument for treating hemodynamically significant PDA[10] is more compelling to this author, than questioning the need for treating PDA.[2,3] Consequently, withholding therapy to close a hemodynamically significant PDA would not meet equipoise and should not be done outside clinical trials with appropriate informed consent. Evidence that long-term sequelae of PDA are altered by its closure is inconclusive;[6] however, this may be attributed to a reluctance to perform studies that compare treatment with no treatment.[2,10,11]

Treatment options primarily include surgical ligation or drug therapy with cyclooxygenase inhibitors. Reports have identified serious negative consequences of surgical ligation, including well known surgical complications such as pneumothorax, chylothorax, and infection.[12] Vocal cord paralysis was also reported in up to 40% of cases and was associated with feeding and respiratory complications.[13] More recent studies have documented an association between PDA ligation and neurodevelopmental abnormalities, CLD, and severe retinopathy of prematurity (ROP).[14,15] Also, PDA surgical ligation has failed to improve the clinical status of neonates with PDA.[16] Likewise, preterm baboon studies actually showed no beneficial effects on lung function or alveolar growth.[17,18] Conversely, pharmacologic closure prevented the interrupted alveolar development associated with PDA and surgical ligation.[11,18] In the absence of an acceptable surgical alternative the role of drug therapy and successful PDA closure rate is increasingly important.

ABBREVIATIONS CLD, chronic lung disease; MRI, magnetic resonance imaging; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PK-PD, pharmacokinetic-pharmacodynamic; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; VLBW, very low birth weight

Two cyclooxygenase inhibitors are available in North America for PDA closure, indomethacin (Indocin, Ovation Pharmaceutical Inc., Deerfield, IL) and ibuprofen lysine (NeoProfen, Ovation Pharmaceutical Inc., Deerfield, IL. Each has advantages and disadvantages and most institutions will elect to carry only one of the products on formulary, since both drugs are very expensive.

When standard dosing of each drug is admin-

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istered, success rates for PDA closure are similar for indomethacin and ibuprofen.[19-21] Realistic response rate in very low birth weight (VLBW) infants is 40% to 60% compared to >80% in more mature infants.[4,19,20,22,23] Reopening rates may be up to 20% of neonates with PDA closure.[24] Postnatal age ≥ 10 days also is associated with decreased response rates.[25] The relatively low PDA closure rate in VLBW infants and older neonates is not due to pharmacodynamic differences, but rather pharmacokinetic differences.[25] We demonstrated that the concentration-response curves were the same for all age groups, and that permanent PDA closure could be achieved in over 90% of VLBW infants if an individualized pharmacokinetic-pharmacodynamic (PK-PD) dosing approach for indomethacin was used.[25] Sperandio et al also used an escalating indomethacin dosing strategy that achieved closure for 98% of PDA cases.[26] A pilot study showed that administration of larger doses of ibuprofen (i.e., 15 mg/kg followed by 7.5 mg/kg every 24 hours for 2 doses) improved response rates.[27] Although a recent study argued that neither larger doses nor higher plasma concentrations achieved better PDA closure rates,[23] the design flaws in this study preclude its consideration. Both drugs appear very effective for PDA closure, and optimal doses could achieve permanent PDA closure in over 90% of premature.

Toxicity is the main area that distinguishes indomethacin and ibuprofen. The adverse effects can be separated into reversible short-term (e.g., decreased organ perfusion and decreased renal function) and long-term effects (e.g., CLD, risk for bilirubin displacement causing kernicterus, and impaired neurodevelopment). The primary benefits of ibuprofen over indomethacin are seen when the short-term adverse effects are compared.

Unlike indomethacin, an infusion of ibuprofen does not alter cerebral, mesenteric, or renal blood flow. Although Indomethacin diminishes cerebral, and mesenteric blood flow, the effect is not clinically important. Necrotizing enterocolitis is no longer thought to be linked to indomethacin, even at larger doses and high concentrations, and intestinal perforation is equally an issue with both indomethacin and ibuprofen.[28] The only advantage of ibuprofen over indomethacin that has been demonstrated to date, is the safer renal profile noted with ibuprofen. In studies directly comparing rapid administration (i.e.,15 minutes or less) of the two drugs for PDA closure, ibuprofen resulted in a significantly lower increase in serum creatinine, and a significantly lower decrease in urine output.[19,20] The actual rate of oliguria was reported in one study as 19% for indomethacin and 7% for ibuprofen.[19] This would imply that one case of oliguria could be avoided for every 8 patients treated with ibuprofen instead of rapidly administered indomethacin. Although the renal effects are usually reversible within 1-2 days, the altered renal function may require modified fluid intake during this time. Oliguria rates with indomethacin can be markedly reduced if concurrent furosemide is administered;[25] however, this approach requires additional medication with attendant electrolyte management issues. One could argue that the main short-term benefit of ibuprofen is the faster rate of administration since renal toxicity and diminished organ perfusion effects are lost when indomethacin is administered slowly.[29,30]

The long-term benefits and toxicity risks appear to favor indomethacin. In a recent meta-analysis,[31] a higher rate of CLD was noted for ibuprofen compared to indomethacin. A diagnosis of CLD was primarily based on the need for oxygen therapy at 28 days (indomethacin 40%, ibuprofen 55%). This was significantly different and implies a number needed to harm of 7 patients if ibuprofen is selected over indomethacin. Although the CLD rates at 36 weeks postconceptional age (indomethacin 19%, ibuprofen 24%), are interesting, especially in light of the CLD rates at 28 days postnatal age, the differences are not statistically significant. If the difference persisted in a larger study population, the number needed to harm by using ibuprofen instead of indomethacin would be between 12 and 20 patients.[19,20,31] It will be important to monitor future comparative trials and meta-analyses for ibuprofen-associated CLD. An adverse pulmonary effect of ibuprofen is pharmacologically plausible in light of recent data demonstrating that at ibuprofen peak serum concentrations below 50 mg/L, neutrophil migration into the lungs of patients with cystic fibrosis and in healthy volunteers was increased, whereas it was decreased at concentrations above 50 mg/L.[32] Systemic activation and transendothelial migration of neutrophils into lungs of neonates with respiratory distress has been implicated in the pathophysiology of CLD,[33,34] and may explain

the higher CLD rates with use of ibuprofen for PDA closure, where target peak concentrations are typically below 50 mg/L. Indomethacin has also been shown to inhibit neutrophil activation in animal studies,[34] but it is not as well studied as ibuprofen. Whether indomethacin has a dichotomous effect on neutrophil migration into lungs at different indomethacin concentrations, as shown for ibuprofen, is unknown.

Perhaps more important, are the long-term brain and neurodevelopment outcomes associated with therapy. These data are currently available only for indomethacin. Despite the cerebral vasoconstriction caused by rapid infusion indomethacin administration, and concern for associated consequence of periventricular leukomalacia (PVL) and impaired neurodevelopment, evidence indicates that indomethacin reduces the incidence of PVL documented with MRI.[35] Neurodevelopment, especially language processing, is either unaffected, or may be improved in males.[36,37] The improved neurodevelopment in males at both 54 months and 8 years was seen even when only patients without intraventricular hemorrhage were compared. In the meta-analysis of trials comparing indomethacin and ibuprofen outcomes, the rate of PVL documented with cranial ultrasound was not statistically different.[31] Long-term studies of neurodevelopment for neonates treated with ibuprofen would be useful, as equal benefits for such important outcomes cannot be assumed.

Ibuprofen has been shown *in-vitro* to displace bilirubin from albumin binding sites.[38] The magnitude of displacement rivals sulfisoxazole at serum ibuprofen concentrations somewhere between 50 and 100 mg/L. Studies with indomethacin have shown it does not displace bilirubin from albumin, probably because it binds to different sites on the albumin molecule. A sequential comparison of neurodevelopmental outcomes in premature infants treated with indomethacin or ibuprofen was encouraging in their findings.[39] Many patients in both groups had hyperbilirubinemia requiring phototherapy. By 2 years of age the neurodevelopmental and hearing outcomes were the same for the indomethacin and ibuprofen groups. Although four infants in the ibuprofen group suffered from neurodevelopmental impairments, the authors did not have an adequate explanation beyond elevated bilirubin and concurrent ibuprofen. While this is not evidence of causation it raises the need for caution. We recently observed a possible case of kernicterus due to bilirubin displacement caused by ibuprofen;[40] however, ibuprofen was used for fever and larger doses (10 mg/kg/dose, 3 doses in 48 hours) were administered than those recommended by the FDA for PDA closure.

For bilirubin displacement to be an important problem, ibuprofen serum concentrations must exceed 50 mg/L,[38] which is not usually the case. The clinical study submitted to the FDA by Ovation Pharmaceuticals Inc. examined unbound bilirubin concentrations during ibuprofen therapy with standard doses in 15 patients and did not observe increases in unbound bilirubin at serum ibuprofen concentrations from 1 to 40 mg/L. In one pharmacokinetic study, ibuprofen peak serum concentrations of 80 and 92 mg/L were achieved in 2 of the 13 patients after the third dose.[41] If recommendations from larger dose[42] are implemented, it is probable that more patients will achieve these higher concentrations, making a case for routine therapeutic drug monitoring. Results of hearing tests from larger trials would be useful since auditory neuropathy may be an early sign of bilirubin toxicity, even when other symptoms are not present.[43] Additional clinical studies addressing this possible problem need to be performed. If ibuprofen does cause kernicterus, a potentially irreversible and severe neurologic problem, it would considerably overshadow any renal benefits of ibuprofen.

Recently, concerns have been raised about the use of large doses of indomethacin and higher rates of retinopathy of prematurity (ROP). Because the study did not consider confounding variables, associating indomethacin with ROP at this time would be inappropriate. In a letter to the editor Hammerman proposed an alternative mechanism,[44] that should be a stimulus for further investigation.

The decision regarding which drug to select depends on whether one wishes to take advantage of the short-term temporary reduction in nephrotoxicity, a documented benefit of ibuprofen; or the less well documented, long-term issues which appear to favor indomethacin (i.e., chronic lung disease, avoiding bilirubin binding problems and kernicterus risk, and proven neurodevelopmental safety and language processing). These long-term outcomes require more studies with ibuprofen to diffuse speculation. Until adequate

data is generated for ibuprofen, the choice between these two expensive drugs is based on each clinician's comfort with competing risks. One factor that may tip the scales in favor of ibuprofen, is that oral dosing has been used safely and successfully.[45,46] If the cost of oral treatment was in the tens of dollars, rather than the thousands of dollars currently required, this would certainly influence drug selection for some. For this author, oral therapy is not yet an option because of the adverse mesenteric blood flow effects of patent ductus arteriosus[8] and the very high osmolarity of oral ibuprofen preparations.[47]

Given the relative consequences of untreated hemodynamically significant PDA, and relatively high rate of undesirable surgical complications, it seems reasonable to implement more aggressive dosing strategies for pharmacological closure. Strategies that have used such escalating doses with or without therapeutic drug monitoring have documented high PDA closure rates and low short-term toxicity rates. Since these more aggressive dosing strategies may achieve ibuprofen serum concentrations known to displace bilirubin from albumin binding sites, and since long-term neurodevelopmental follow-up is still not available for ibuprofen-treated neonates, it seems preferable to use indomethacin for PDA closure. If indomethacin is used, infusion of the dose over 1-2 hours may minimize diminished organ perfusion and associated problems.

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