JPPT | Single-Center Retrospective Study

Pharmacologic Management of Patent Ductus Arteriosus in the Neonatal Intensive Care Unit: A Retrospective Study

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OBJECTIVE Patent ductus arteriosus (PDA) is common in premature neonates. The use and selection of pharmacologic therapy are controversial because of unclear long-term benefits and the potential of adverse effects. The objective of this review was to explore the safety and efficacy for indomethacin, ibuprofen, and acetaminophen for PDA management.

METHODS A chart review was conducted for neonates who received pharmacologic treatment for PDA at our institution between July 1, 2016, and May 30, 2023. Data collected included treatment success or failure; adverse reactions to the medications, including renal dysfunction, gastrointestinal perforation or bleeding, hepatotoxicity, and/or death; and complications, including bronchopulmonary dysplasia, pulmonary hypertension, surgical closure, and death before discharge.

RESULTS A total of 91 neonates met the inclusion criteria. The efficacy rates for the first treatment course were 25 of 31 (80.6%) for indomethacin, 4 of 16 (25%) for ibuprofen, and 27 of 44 (61.4%) for acetaminophen. Complications occurred in 12 of 31 (38.7%) for indomethacin, 9 of 16 (56.3%) for ibuprofen, and 0 of 44 (0%) for acetaminophen.

CONCLUSION Indomethacin and acetaminophen had good efficacy, though indomethacin had a high incidence of complications. Ibuprofen had lower efficacy than expected (25%) and concerning safety outcomes, which requires further investigation to see if ethnicity plays a role.

ABBREVIATIONS BPD, bronchopulmonary dysplasia; CYP, cytochrome P450; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus

KEYWORDS patent ductus arteriosus; indomethacin; ibuprofen; acetaminophen; infant; newborn.

J Pediatr Pharmacol Ther 2025;30(2):250–257

DOI: 10.5863/1551-6776-30.2.250

Introduction

In fetal circulation, the ductus arteriosus is an opening that allows blood to flow between the pulmonary artery and the aorta. Prostaglandins and low-oxygen tension contribute to maintaining this opening in utero.[1] After birth, this opening typically closes within 72 hours in term infants, but can be delayed in premature neonates, resulting in a patent ductus arteriosus (PDA).[2] This delayed closure may be due to differences in sensitivity of the premature vascular tissue to the changes in prostaglandin and oxygen occurring after birth.[3] Despite the closure being delayed, spontaneous closure is reported in up to 85% of premature neonates before hospital discharge.[4] Patent ductus arteriosus can lead to complications arising from blood shunting away from systemic circulation through the opening into pulmonary circulation leading to hypoperfusion of vital organs.[3] Pulmonary edema, pulmonary hemorrhage, chronic lung disease, and necrotizing enterocolitis are potential common complications associated with PDA.[5]

Managing PDA includes conservative measures, pharmacologic treatment, and/or surgical closure, though optimal management remains controversial. Conservative measures such as fluid restriction and ventilation strategies may be trialed as the PDA may close spontaneously. For neonates deemed to have a hemodynamically significant PDA, pharmacotherapy is often initiated. The characteristics of a hemodynamically significant PDA are not well defined, though typical considerations would be given to the size of the duct, the degree, velocity, and direction of blood flow, and the presence of systemic symptoms.[6] Pharmacologic options include indomethacin, ibuprofen, and acetaminophen. All 3 agents are hypothesized to promote ductal closure by reducing prostaglandin production via inhibiting the prostaglandin H2 synthetase enzyme.[7] Indomethacin and ibuprofen accomplish this through

inhibition of the cyclooxygenase site, and acetaminophen instead acts on the peroxidase site.[7] Controversy exists regarding agent selection and dosing regimen, including route, which may be influenced by heterogeneity of included patients in the literature. Therefore, this retrospective study aimed to explore the efficacy and safety surrounding indomethacin, ibuprofen, and acetaminophen for PDA management.

Materials and Methods

Neonates who received pharmacologic management for PDA in the 36-bed level 3 neonatal intensive care unit (NICU) of Surrey Memorial Hospital were identified from a list of inpatient neonatal prescriptions for indomethacin or acetaminophen between July 1, 2016, and June 30, 2022, and for ibuprofen between July 1, 2016, and May 30, 2023, because of an ibuprofen shortage during the initial study period. Neonates were included in the review if they had received indomethacin, ibuprofen, and/or acetaminophen for the treatment of their documented PDA, which was confirmed by a cardiologist using an echocardiogram. Managing PDA, including the use of pharmacologic agents and treatment timing, was at the discretion of the clinical team providing care. At the time of the study, there were no site-based guidelines. The timing of treatment largely depended on the availability of an echocardiogram, which was offered approximately once per week.

Our center follows the regional dosing guidelines for the 3 agents: indomethacin 0.2 mg/kg intravenous on day 1 followed by 0.2 mg/kg if 2 to 7 days old, or 0.25 mg/kg if more than 7 days old, given every 24 hours; ibuprofen lysine 10 mg/kg intravenous on day 1 followed by 5 mg/kg for subsequent doses every 24 hours; and acetaminophen 15 mg/kg intravenous or oral every 6 hours. Indomethacin and ibuprofen are recommended to be ordered as a 3-day course, and acetaminophen is suggested to be ordered for a minimum of 3 days with the possibility of extending up to 10 days. As echocardiograms were only available weekly, treatment with acetaminophen was often continued until the follow-up imaging occurred. Acetaminophen serum concentrations are not used to guide treatment.

Data collected for the primary efficacy outcome included follow-up echocardiogram reports where a medication course was considered effective if a repeat echocardiogram showed a small or restrictive PDA or physician documentation of a presumed PDA closure.[8] For the purpose of this review, we focused on the first course of treatment. Patients who switched agents because of safety concerns were analyzed according to the first medication they received. Secondary outcomes for safety were assessed in terms of the following documented adverse events during the treatment course, which considered medication duration of action: renal dysfunction, which included oliguria (urine output less than 0.5 mL/kg/hr for 6 hours or more) and/or acute kidney injury (defined by an increase in serum creatinine of greater than 26 µmol/L; 0.3mg/dL), gastrointestinal perforation or bleeding, elevation of alanine transaminase by 50 U/L or more, medication discontinued because of safety concerns, or death.[9] Concurrent nephrotoxic medications were also collected. Complications documented during the NICU stay were also collected, including diagnosis of bronchopulmonary dysplasia (BPD), defined as respiratory support at 36-weeks postmenstrual age; pulmonary hypertension as diagnosed by a cardiologist with an echocardiogram at or beyond 36-weeks postmenstrual age; PDA requiring surgical closure; and/or death before hospital discharge.

We used a convenience sample to ensure as many patients as possible were included. Descriptive statistics were used to describe the study endpoints. Means were compared with a Kruskall-Wallis rank sum test, and categorical data was compared using either Fisher's exact test or χ^2 test. Statistical significance was defined as $p \leq 0.05$. A power calculation was not completed, as the initial intent of the study was to collect baseline data. As this project was considered "quality improvement," ethics approval and informed consent were not required.

Results

A total of 333 neonates were identified from the pharmacy list; 242 received acetaminophen for an indication other than a PDA treatment, resulting in 91 patients being included.

The mean gestational age was 25.9 weeks, and the mean birth weight was 778.1 grams (Table 1). The patients in the acetaminophen group were older on average than patients in the indomethacin ($p = 0.002$) and ibuprofen groups ($p = 0.01$). Patients who received acetaminophen were also of a higher birth weight compared with those who received indomethacin ($p = 0.01$) and ibuprofen ($p = 0.03$). Gestational age and birth weight among those who received ibuprofen and indomethacin were similar ($p = 0.69$ and $p = 0.87$, respectively). Most of the patients had a large PDA (n = 52, 57.8%) (Table 1), and 49 (54.4%) had evidence of left heart volume overload, as stated on the echocardiogram report. Thirty-one patients received indomethacin for their first course, 16 received ibuprofen, and 44 received acetaminophen. The medications were prescribed following the regional dosing guidelines. Doses were within 5% of the recommended dose and no dose adjustments were made for renal dysfunction. If there were significant renal dysfunction or other adverse events, subsequent doses were held. For the acetaminophen courses, most patients received a mix of intravenous and oral doses, though the number of each type was not collected. The average day of life treatment started at 11.3, 6.1, and 10.7 days for indomethacin, ibuprofen, and acetaminophen, respectively (Table 2).

Table 1. Baseline characteristics

Characteristic	Overall (N = 91)	Indomethacin (n = 31)	Ibuprofen (n = 16)	Acetaminophen (n = 44)	p value
Gestational age (mean), wk	25.9 (23–33.3)	25.3 (23.3–28.6)	25.1 (23–27)	26.6 (23.3–33.3)	p = 0.002*
Birth weight (mean), g	778.1 (330–1530)	710.9 (463–1205)	702.1 (470 –1020)	853 (330–1530)	p = 0.01†
Small for gestational age, n (%)	21 (23)	7 (22.6)	3 (18.8)	11 (25)	p = 0.95
Male sex, no. (%)	49 (53.8)	18 (58.1)	8 (50)	23 (52.3)	p = 0.85
5-min Apgar (mean)	6.9 (1–9)	6.6 (1–9)	6.7 (3–9)	7.2 (4–9)	p = 0.58
Surfactant, n (%)	82 (90.1)	29 (93.5)	14 (87.5)	39 (88.6)	p = 0.72
Caesarean delivery, n (%)	73 (80.2)	25 (80.6)	12 (75)	36 (81.8)	p = 0.88
Singleton, n (%)	65 (71.4)	22 (71)	12 (75)	31 (70.5)	p > 0.999
Maternal diabetes, n (%)	22 (24.2)	5 (16.1)	4 (25)	13 (29.5)	p = 0.44
Maternal hypertension, n (%)	19 (20.1)	7 (22.6)	3 (18.8)	9 (20.5)	p > 0.999
Antenatal corticosteroid, n (%)	82 (90.1)	30 (96.8)	15 (93.8)	37 (84.1)	p = 0.2
Echocardiogram findings	Overall (n = 90‡)	n = 31	n = 15*	n = 44	
Large PDA, n (%)	52 (57.8)	22 (71)	7 (46.7)	23 (52.3)	p = 0.18
Volume overload–no. (%)	49 (54.4)	13 (41.9)	5 (33.3)	31 (70.5)	p = 0.01§

PDA, patent ductus arteriosus

* Significance driven by indomethacin vs acetaminophen (p = 0.002) and ibuprofen vs acetaminophen (p = 0.01). Indomethacin vs ibuprofen not statistically significant (p = 0.69).
† Significance driven by ibuprofen vs acetaminophen (p = 0.03) and indomethacin vs acetaminophen (p = 0.01). Indomethacin vs ibuprofen not statistically significant (p = 0.87).
‡ One patient excluded because of no pretreatment echocardiogram.
§ Significance driven by acetaminophen vs ibuprofen (p = 0.01) and acetaminophen vs indomethacin (p = 0.01).

Table 2. Details of Treatment Course

	Overall (N = 91)	Indomethacin (n = 31)	Ibuprofen (n = 16)	Acetaminophen (n = 44)
DOL treatment initiated, mean (range), days	10.1 (1–45)	11.3 (3–45)	6.1 (1–11)	10.7 (2–27)
Treatment duration, mean (range), days	4.6 (1–10)	2.9 (1–3)	2.6 (1–3)	6.5 (3–10)
Patients requiring repeat treatment, n (%)	33 (36.2)	7 (22.6)	12 (75)	14 (31.8)

DOL, day of life

Ibuprofen and indomethacin appeared to be associated with more success when started earlier (Table 3).

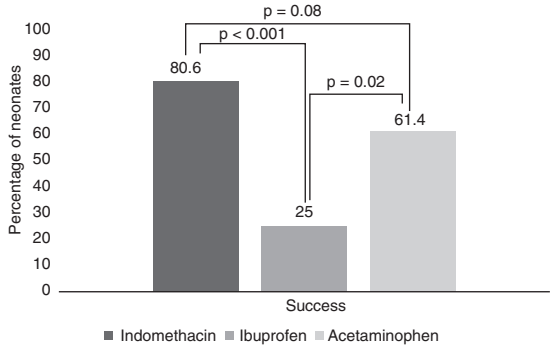
Treatment success with the first course of treatment was 56 of 91 (61.5%) neonates, with 4 of 91 (4.4%) having an unknown outcome due to death before a repeat echocardiogram or being transferred to another site. Treatment was successful in 25 of 31 (80.6%) neonates with indomethacin (1/31, 3.2% unknown), 4 of 16 (25%)

Table 3. Factors Impacting Efficacy

		Gestational Age, Mean (Range), Weeks	Birth Weight, Mean (Range), Grams	Day Of Life At Treatment Initiation, Mean (Range)	Treatment Duration, Mean (Range), Days
Overall (N = 87)	Success (n = 56)	26.3 (23–33.3)	802 (463–1530)	10.5 (2–9)	4.9 (1–10)
	Failure (n = 31)	25.5 (23.3–28.1)	750.1 (330–1397)	9.5 (2–26)	4.2 (1–10)
Indomethacin (n = 30*)	Success (n = 25)	25.4 (23.3–28.6)	736.8 (463–1205)	11 (3–45)	2.9 (1–3)
	Failure (n = 5)	24.9 (24.1–25.9)	608 (520–670)	12 (6–18)	3 (3–3)
Ibuprofen (n = 15*)	Success (n = 4)	24.5 (23–26.7)	657.5 (510–820)	4.5 (1–9)	3 (3–3)
	Failure (n = 11)	25.4 (23.3–27)	718.7 (470–1020)	6.5 (2–11)	2.5 (1–3)
Acetaminophen (n = 42*)	Success (n = 27)	27.3 (23.3–33.3)	883.9 (514–1530)	10.9 (2–27)	7 (3–10)
	Failure (n = 15)	25.7 (23.9–28.1)	820.5 (330–1397)	10.9 (5–26)	5.9 (1–10)

* Patients with an unknown efficacy outcome were excluded from this analysis.

Figure 1. Comparison of PDA treatment efficacy based on pharmacologic agent given for first course (n = 91).



neonates with ibuprofen (1/16, 6.3% unknown), and 27 of 44 (61.4%) neonates with acetaminophen (2/44, 4.5% unknown). Ibuprofen had the lowest efficacy, and this difference was statistically significant compared with indomethacin ($p < 0.001$) and acetaminophen ($p = 0.02$) (Figure 1).

The number of neonates that experienced an adverse event was 21 of 91 (23.1%), with the most common being renal dysfunction (Figure 2a). The most common concomitant nephrotoxic medication was vancomycin, which was used in 12 of 21 (70.6%) of the neonates experiencing renal dysfunction. Indomethacin use led to 12 of 31 (38.7%) neonates experiencing at least 1 adverse event, where 9 of 31 (29%) experienced a renal side effect, and 5 of 31 (16.1%) had a suspected or confirmed gastrointestinal perforation or bleeding (Figure 2a). For ibuprofen, 9 of 16 (56.3%) neonates had an adverse event, where 8 of 16 (50%) experienced a renal adverse event, and 2 of 16 (12.5%) died. One death was secondary to complications of acute renal failure. This patient was started on ibuprofen and received 2 doses before experiencing a rise in serum creatinine, requiring early discontinuation of ibuprofen. There were no concurrent nephrotoxic medications at the time of the kidney injury. Vancomycin was started 3 days later for suspected sepsis. The blood culture was negative at 24 hours and was reported to be positive for *Staphylococcus epidermidis* near 48 hours. The patient went into renal failure the following day and subsequently experienced arrhythmias secondary to severe hyperkalemia, which ultimately led to their death. Although the mechanism for the renal failure may have been multifactorial, ibuprofen may have been the precipitating factor, and the long half-life of ibuprofen in premature neonates meant that it continued to contribute to the nephrotoxicity until death. The other death was related to bleeding complications from thrombocytopenia. Ibuprofen was started on day of life 1 with a baseline

platelet count of 133 × 10^9/L. The platelets fell to 53 × 10^9/L after the second dose, requiring transfusions; however, the patient remained thrombocytopenic. The patient became hemodynamically unstable and went on to require multiple transfusions of blood products before dying on day of life 9. Repeat head imaging before death showed progression of intraventricular hemorrhages. Sepsis was investigated as a contributing factor; however, blood cultures remained negative for the entirety of their stay. The Naranjo adverse drug reaction probability score for both incidents was 4, suggesting ibuprofen was the possible cause for the events.[10] For acetaminophen, 0 of 44 (0%) neonates experienced an adverse event. Ibuprofen was associated with high rates of BPD (13/13, 100%), pulmonary hypertension (4/13, 30.8%), and death during NICU stays (3/16, 18.8%) (Figure 2b).

Discussion

In our study, management of PDA with ibuprofen had a very low success rate of 25% compared with indomethacin at 80.6% and acetaminophen at 61.4%. The ibuprofen efficacy rate varied dramatically from what was reported by Van Overmeire et al,[11] who reported an efficacy rate of 70%. In contrast, Badillo et al[12] reported a first-course closure rate of 39.8% in very-low-birth-weight neonates with intravenous ibuprofen and 30% for oral ibuprofen, which is similar

Figure 2a. Medication-related adverse events (n = 91).*

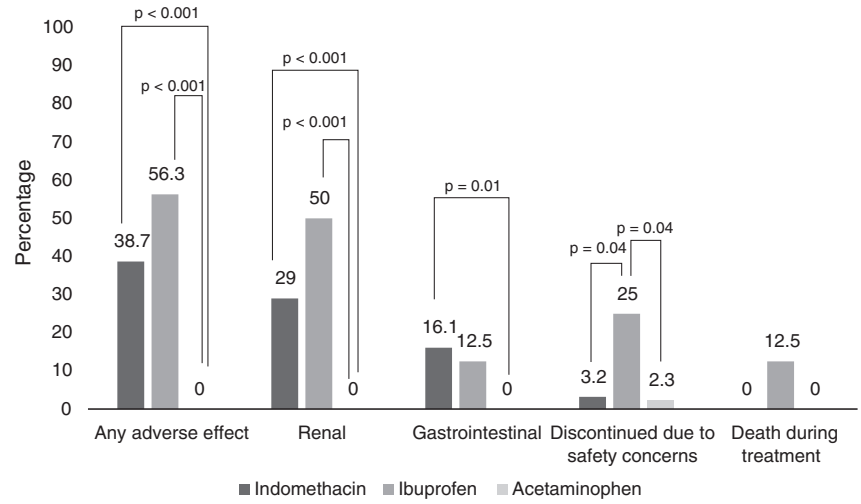
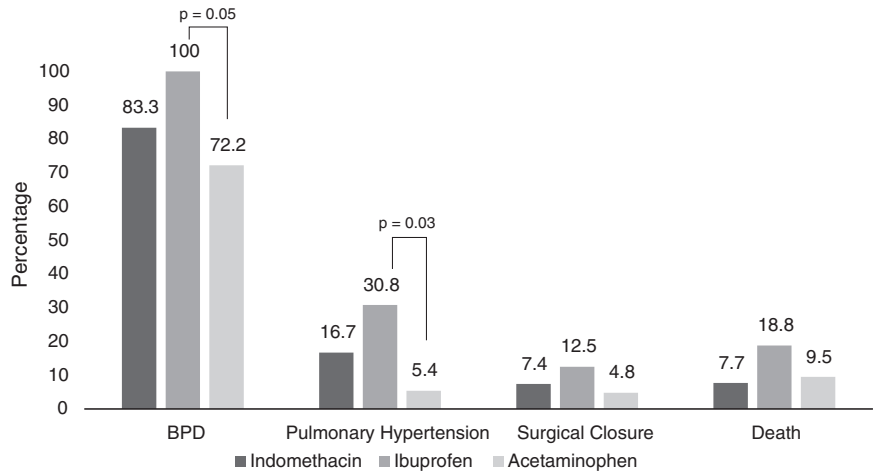


Figure 2b. NICU outcomes and complications.*†



* Comparisons reaching statistical significance ($p \leq 0.05$) are shown. All other comparisons were not significant at $p > 0.05$.

† Patients with missing outcome and/or complications data were excluded from analysis.

to the rate observed in our population. Our study's efficacy rates for indomethacin and acetaminophen were more consistent with those reported for indomethacin by Van Overmeire et al[11] at 66% and for acetaminophen by Ohlsson et al[13] at 74.2%. The patients in the ibuprofen group seemed to receive treatment earlier on average compared with those in the indomethacin and acetaminophen groups. As some literature has shown that early treatment is associated with greater success in closing a PDA, we would have expected to see greater efficacy with the ibuprofen group compared with the others.[14,15] It did appear that within the ibuprofen and indomethacin groups, those who had success were treated earlier on average, which is consistent with the literature. It is unclear why ibuprofen had poorer efficacy overall, especially compared with indomethacin, where the patient characteristics were similar. With respect to the duration of treatment, although this was longer in the acetaminophen group, the overall exposure to medication was similar between the groups, given the respective half-lives of the agents in neonates.[16]

The incidence of ibuprofen adverse events was higher at 56.3% and more concerning than expected. Su et al[17] reported the incidence of oliguria as 15.3% for indomethacin and 6.7% for ibuprofen, which are lower than the incidence in our study with 32.3% for indomethacin and 50% for ibuprofen. The difference in rates may be due to a difference in the definition of renal events, although our study's rate of renal adverse events was higher for ibuprofen than indomethacin. There were also 2 deaths during the ibuprofen treatment course. Acetaminophen had the best safety profile, with no neonates experiencing an adverse event, which is similar to Dani et al,[18] who reported a 2% incidence of elevations in liver enzymes and a 2% incidence of gastrointestinal perforation with acetaminophen.

Complications during the NICU stay were also the highest in the ibuprofen group. The Canadian Neonatal Network reported for 2021 that 50% of neonates born at 27 weeks and 84% of neonates born less than 24 weeks had BPD at 36 weeks.[19] This is consistent with the rate of BPD seen in our indomethacin (83.3%) and acetaminophen (72.2%) groups; however, the ibuprofen group saw an incidence of 100%, which was higher than expected. Of note, Hundscheid et al[8] identified a similar trend in which ibuprofen use was associated with an increased incidence of BPD. Arjaans et al[20] reported an incidence of pulmonary hypertension after 36 weeks of 5%, which is consistent with our findings for acetaminophen at 5.4%. However, in contrast, the incidence of pulmonary hypertension was 3-fold higher for indomethacin at 16.7% and 6-fold higher for ibuprofen at 30.8%. Multiple case reports have been published describing the development of pulmonary hypertension as a complication of ibuprofen use in neonates.[21,22] Kim et al[22] reported that lower gestational age, birth weight less than the third percentile, and maternal hypertension were among some of the risk factors associated with the development of pulmonary hypertension after ibuprofen use. Similar to Mitra et al,[23] PDA management with medications did not reduce the incidence of long-term outcomes observed in the NICU, and, in our population, the use of ibuprofen was associated with an increased rate of NICU complications. A potential confounder is the ibuprofen patients were marginally smaller and more premature on average compared with the acetaminophen group, putting them at higher risk of developing BPD and pulmonary hypertension. However, the indomethacin group, with a more comparable population to ibuprofen, still appeared to be associated with lower rates of complications overall, though not statistically significant. We note that the acetaminophen group had the highest incidence of volume overload on their echocardiograms, indicating more hemodynamically significant ducts. We would have anticipated these patients to be at high risk of developing complications, such as BPD and pulmonary hypertension. However, rates remained low in this group.

As the rates of ibuprofen success and safety vary in the literature, we hypothesize that genetics may play a role. Ibuprofen is metabolized by cytochrome P450 (CYP) enzymes, and polymorphisms with these enzymes lead to differences in metabolism.[24] Studies exploring the incidence of polymorphisms with the CYP enzymes have suggested links to different ethnicities.[25] Although we did not collect ethnicity, our site provides care to a predominantly South Asian population. We hypothesize that differences in ibuprofen metabolism or clearance in this population may be associated with lower efficacy and higher rates of adverse events. While the impact of certain CYP polymorphisms on PDA treatment has been studied previously, and the results have been inconclusive, they do suggest that ethnicity may play a role.[26] Durrmeyer et al[26] found in their review that Caucasian neonates were less likely to respond to ibuprofen treatment (60%); however, there was a large percentage of neonates in the non-Caucasian group that also did not respond to treatment (40%). The captured ethnicities were not provided, and we note this review was conducted in France, where we would anticipate a different ethnic population. Multiple studies have confirmed differences in the frequency of *CYP2C9* and *CYP2C8* gene variants between South Asian and Caucasian populations.[27,28] Dorji et al[27] reported frequencies of 11.3% in South Asians and 5.6% in Caucasians for the *CYP2C9*3* variant. Jose et al[28] commented that there was also marked interethnic variation in the distribution of these polymorphisms. Carriers of this variant have a significant reduction in the clearance of ibuprofen and appear to be at higher risk of adverse effects, while indomethacin clearance has not been reported to be impacted.[29] Although indomethacin is also

metabolized by CYP enzymes, the specific enzymes involved differ among the 2 agents with indomethacin involving CYP2C9 predominantly and ibuprofen involving CYP2C9 and CYP2C8.[30] Ibuprofen metabolism and clearance is also thought to be more complex due to the presence of (R) and (S) enantiomers, which follow separate metabolic pathways and may impact PDA closure in different ways.[30] The (R) enantiomer has been reported to be responsible for many of the adverse effects associated with ibuprofen, while the (S) enantiomer is responsible for the pharmacological action.[31,32] It is unclear whether there is variation in the amount of inversion from (R) to (S) conversion; however, this may contribute to differences in safety and efficacy. The possible differences between ibuprofen and indomethacin metabolism in our population may explain why indomethacin had good efficacy while ibuprofen did not, as well as the unexpectedly high rates of adverse events for ibuprofen. More research exploring the possible impacts of genetics and pharmacogenomic variations on ibuprofen metabolism is necessary to guide which neonates may benefit from ibuprofen therapy and which would be at higher risk of serious adverse events. Awareness of the neonate's ibuprofen metabolism could improve outcomes if we could test the patient before ibuprofen administration. If we could determine the serum concentration and percentage of different enantiomers, it may help determine the type of metabolizer, but it is unlikely to improve clinical outcomes, as the medication would have already been administered.

Another factor we explored was whether the injectable ibuprofen product used at our site may have contributed to our results, as various salt forms have been studied in the literature. Ibuprofen lysine, arginine, and tromethamine salts have been used to treat PDA. Ibuprofen lysine, used at our site, appears to be the most extensively studied ibuprofen product with good efficacy and safety.[33]

Limitations

There are a few limitations in our review that should be acknowledged. Owing to the retrospective nature of the study, there were limitations on what information could be collected, and medication selection was at the discretion of the prescribing team. Ethnicity was not collected and can be difficult to obtain retrospectively. The small sample size in the ibuprofen group is another limitation, and, as stated, it was due to supply issues. Extending the time frame of the study to capture more patients in this group helped double the sample size; however, it still falls short compared with the other groups. Although this may limit our ability to confidently draw conclusions about ibuprofen, we believe the study is still important to highlight the safety concerns we saw in our population. As closing the PDA has not consistently shown benefit in the literature, the risk of using ibuprofen should warrant caution until further investigation is completed to explore what is behind the variation in efficacy and safety seen among different centers.

Conclusion

This review raises questions about the safety of ibuprofen use. Ibuprofen had a low efficacy rate and was associated with a high rate of adverse effects in our population, which contrasts with what the current literature states. The mechanism behind the reduced efficacy and high side effect burden is unknown. As treatment of the PDA has not been shown to improve long-term outcomes when pharmacologic therapy is contemplated, we recommend acetaminophen be considered because of its favorable efficacy and safety profile. More research is needed to identify neonates at high risk of experiencing adverse events and/or limited benefit from pharmacologic treatment, especially with respect to ibuprofen.

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Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors attest to meeting the four criteria recommended by the ICMJE for authorship of this manuscript.

Acknowledgements. The authors would like to acknowledge the Fraser Health Department of Evaluation and Research Services for assistance with statistical analysis.

Submitted. February 12, 2024

Accepted. June 17, 2024

References

1. Hermes-DeSantis ER, Clyman RI. Patent ductus arteriosus: pathophysiology and management. *J Perinatol*. 2006;26 Suppl 1:S14–S18; discussion S22–S23.
2. Gentile R, Stevenson G, Dooley T, et al. Pulsed Doppler echocardiographic determination of time of ductal closure in normal newborn infants. *J Pediatr.* 1981;98(3):443–438.
3. Capozzi G, Santoro G. Patent ductus arteriosus: pathophysiology, hemodynamic effects and clinical complications. *J Matern Fetal Neonatal Med*. 2011;24 Suppl 1:15–16.

4. Semberova J, Sirc J, Miletin J, et al. Spontaneous closure of patent ductus arteriosus in infants ≤1500 g. *Pediatrics*. 2017;140(2):e20164258.
5. Sallmon H, Koehne P, Hansmann G. recent advances in the treatment of preterm newborn infants with patent ductus arteriosus. *Clin Perinatol*. 2016;43(1):113–129
6. Shepherd JL, Noori S. What is a hemodynamically significant PDA in preterm infants? *Congenit Heart Dis*. 2019;14:21–26.
7. Ferguson JM. Pharmacotherapy for patent ductus arteriosus closure. *Congenit Heart Dis*. 2019;14:52–56.
8. Hundscheid T, Onland W, Kooi EMW, et al. Expectant management or early ibuprofen for patent ductus arteriosus. *N Engl J Med*. 2023;388(11):980–990.
9. Coleman C, Perez AT, Selewski DT. Neonatal acute kidney injury. *Front Pediatr*. 2022;10.
10. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245.
11. Van Overmeire B, Smets K, Lecoutere D, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. *N Engl J Med*. 2000;343(10):674–681.
12. Badillo MC, Abdul Alim AA, Chandran S, et al. Safety and efficacy of oral and parenteral ibuprofen for closure of patent ductus arteriosus in very low birth weight Asian neonates - a retrospective audit. *Arch Clin Med Case Rep*. 2021;5:182–192.
13. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. *Cochrane Database Syst Rev*. 2020;1(1):CD010061.
14. Gupta S, Subhedar NV, Bell JL, et al. Trial of selective early treatment of patent ductus arteriosus with ibuprofen. *N Engl J Med*. 2024 Jan 25;390(4):314–325.
15. Van Overmeire B, Van de Broek H, Van Laer P, et al. Early versus late indomethacin treatment for patent ductus arteriosus in premature infants with respiratory distress syndrome. *J Pediatr*. 2001;138(2):205–111.
16. Neofax. IBM Micromedex Solutions. Accessed April 10 2024. http://www.micromedexsolutions.com
17. Su BH, Lin HC, Chiu HY, et al. Comparison of ibuprofen and indometacin for early-targeted treatment of patent ductus arteriosus in extremely premature infants: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed*. 2008;93(2):F94–F99.
18. Dani C, Lista G, Bianchi S, et al. Intravenous paracetamol in comparison with ibuprofen for the treatment of patent ductus arteriosus in preterm infants: a randomized controlled trial. *Eur J Pediatr*. 2021;180(3):807–816.
19. Beltempo M, Shah P, Yoon E, et al. Annual Report 2021. Canadian Neonatal Network. Accessed October 1, 2023. http://www.canadianneonatalnetwork.org/portal/Portals/0/Annual%20Reports/2021%20CNN%20annual%20report%20final_amended.pdf
20. Arjaans S, Zwart EAH, Roofthooft M, et al. Pulmonary hypertension in extremely preterm infants: a call to standardize echocardiographic screening and follow-up policy. *Eur J Pediatr*. 2021;180(6):1855–1865.
21. Amendolia B, Lynn M, Bhat V, et al. Severe pulmonary hypertension with therapeutic L-lysine ibuprofen in 2 preterm neonates. *Pediatrics*. 2012;129(5):e1360–e1363.
22. Kim SY, Shin SH, Kim HS, et al. Pulmonary arterial hypertension after ibuprofen treatment for patent ductus arteriosus in very low birth weight infants. *J Pediatr*. 2016;179:49–53.e1.
23. Mitra S, de Boode WP, Weisz DE, Shah PS. Interventions for patent ductus arteriosus (PDA) in preterm infants: an overview of Cochrane Systematic Reviews. *Cochrane Database Syst Rev*. 2023;4(4):CD013588
24. López-Rodríguez R, Novalbos J, Gallego-Sandín S, et al. Influence of CYP2C8 and CYP2C9 polymorphisms on pharmacokinetic and pharmacodynamic parameters of racemic and enantiomeric forms of ibuprofen in healthy volunteers. *Pharmacol Res*. 2008;58(1):77–84.
25. Daly AK, Rettie AE, Fowler DM, Miners JO. Pharmacogenomics of CYP2C9: functional and clinical considerations. *J Pers Med*. 2017;8(1):1
26. Durrmeyer X, Hovhannisyan S, Médard Y, et al. Are cytochrome P450 CYP2C8 and CYP2C9 polymorphisms associated with ibuprofen response in very preterm infants? *PLoS One*. 2010;5(8):e12329.
27. Dorji PW, Tshering G, Na-Bangchang K. CYP2C9, CYP2C19, CYP2D6 and CYP3A5 polymorphisms in South- East and East Asian populations: a systematic review. *J Clin Pharm Ther*. 2019;44(4):508–524.
28. Jose R, Chandrasekaran A, Sam SS, et al. CYP2C9 and CYP2C19 genetic polymorphisms: frequencies in the south Indian population. *Fundam Clin Pharmacol*. 2005;19(1):101–105.
29. Theken KN, Lee CR, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for *CYP2C9* and nonsteroidal anti-inflammatory drugs. *Clin Pharmacol Ther*. 2020;108:191–200.
30. Lewis TR, Shelton EL, Van Driest SL, et al. Genetics of the patent ductus arteriosus (PDA) and pharmacogenetics of PDA treatment. *Semin Fetal Neonatal Med*. 2018;23(4):232–238.
31. Mazaleuskaya LL, Theken KN, Gong L, et al. PharmGKB summary: ibuprofen pathways. *Pharmacogenet Genomics*. 2015;25(2):96–106.
32. Jose C, Briand LE, Michlig M, et al. Isolation of ibuprofen enantiomers and racemic esters through electrodialysis. *J Membr Biol*. 2021;618:118714.
33. Hermes-Desantis ER, Aranda JV. Clinical experience with intravenous Ibuprofen lysine in the pharmacologic closure of patent ductus arteriosus. *J Pediatr Pharmacol Ther*. 2007;12(3):171–182.