

Evidence on the Effectiveness and Safety of Pharmacological Treatment for the Patent Ductus Arteriosus in Premature Newborns

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Abstract

Background: Patent ductus arteriosus (PDA) is the most common cardiovascular problem in preterm infants; evidence regarding the best treatment approach is lacking. Currently available medical options to treat a PDA include Indomethacin (INDO), Ibuprofen (IBU) and Acetaminophen or Paracetamol (PARA) and wide variation exists in the pharmacological clinical approach for PDA closure. The purpose of this commentary is to raise nonjudgmental awareness of current evidence on effectiveness and known or potential adverse effects when a clinical decision for pharmacological treatment has already been made.

Objectives: To identify the current evidence on effectiveness and safety of the pharmacological treatment of PDA in premature newborns, describe potential risks of the drugs utilized for ductal closure and present data from 813 preterm infants who were treated for PDA and reported to SIBEN's network.

Methods: Identify and dissect the most recent evidence published on effectiveness and safety on the three drugs currently used for PDA closure and analyze three years of data at SIBEN's network on preterm infants who received pharmacological treatment for a PDA. Statistics include Chi2 and Fisher's exact test.

Results: Effectiveness and safety of INDO, IBU and PARA for ductal closure in preterm infants reveal some differences which are detailed in the manuscript. To date, oral IBU at high dose seems to be an effective and safe treatment for PDA closure, and INDO maybe just as good. There is still a need for appropriate pharmacodynamic and follow-up studies examining both the route and dose of PARA, before it can be concluded that PARA is an effective and safe drug for PDA closure. Data from the 813 preterm infants < 1,500 grams at SIBEN's network who received pharmacological treatment for a PDA showed increased morbidity in the PARA group.

Conclusion: As with many of the treatments in the neonatal period, our duty is "first do no harm" and the risk benefit ratio should always be kept in mind when caring for fragile neonates. The most effective therapeutic medications with better known safety profiles based on current evidence should be the ones to be used.

Keywords: Patent Ductus Arteriosus; Preterm Infants; Indomethacin; Ibuprofen; Acetaminophen

Abbreviations

PDA: Patent Ductus Arteriosus; PDA: HS-PDA: Hemodynamically Significant; INDO: Indomethacin; IBU: Ibuprofen; PARA: Paracetamol; RDS: Respiratory Distress Syndrome; NEC: Necrotizing Enterocolitis; IVH: Intra Ventricular Hemorrhage; BPD: Broncho Pulmonary Dysplasia; SIBEN: Iberoamerican Society of Neonatology

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Introduction

The purpose of this commentary is to raise nonjudgmental awareness and attention to current issues related to the pharmacological treatment of the patent ductus arteriosus (PDA) in preterm infants. There are thousands of published articles on this topic, including many issues like prophylaxis, the best opportunity to treat a hemodynamically significant PDA (HS-PDA) and the potential unintended consequences of a conservative management strategy. In this manuscript we will not refer to those issues. We will focus on the existing evidence to date regarding the effectiveness and safety of the pharmacological treatment for PDA in premature newborns for the three most commonly used drugs: indomethacin (INDO), ibuprofen (IBU) and acetaminophen or paracetamol (PARA) and the scope of the problem of drug and dose selection and potential adverse effects when a clinical decision for pharmacological treatment has already been made. We will summarize concisely issues regarding INDO, IBU, PARA, including some background, historical aspects, a brief analysis of a few recent studies, randomized controlled trials (RCT) and metanalysis and present data on 813 preterm infants who received treatment for PDA as reported to the network of the Iberoamerican Society of Neonatology (SIBEN).

Background

From the early 1970's it had been noted that PDA often complicated the clinical course of prematurely born infants with respiratory distress syndrome (RDS).

PDA is considered an alteration in the adaptation to the extrauterine environment and its lack of closure has been associated with developmental issues like RDS, less ductal musculature in the media, lower constrictive response to oxygen and greater sensitivity to prostaglandins. The incidence of PDA is directly associated with gestational age and birth weight: it occurs in up to 80-90% of newborns <26 weeks of gestational age, 50-75% in <28 weeks and 40% in infants from 29 to 32 weeks of gestational age [1-6]. Clinical examination and echocardiogram are used for diagnosis, obtaining its dimensions and defining whether it is a HS-PDA or not. Controversy exists as to the clinical decision to treat or not to treat, when to treat and with which drug. PDA pharmacological treatment must be individualized, according to gestational age, postnatal age, respiratory condition, hemodynamic impact, and if it is considered to be a HS-PDA or not.

A HS-PDA that persists for a prolonged period of time, like more than 2-3 weeks, is not inconsequential [5-8]. In such infants there is greater morbidity, with more days of mechanical ventilation and O_2 , a higher incidence of severe bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), grades III and IV IVH, necrotizing enterocolitis (NEC). Additionally, the infants with a prolonged HS-PDA take longer to achieve full enteral nutrition and have more days of parenteral nutrition, cholestasis, osteopenia, and malnutrition with extrauterine growth restriction and some may also develop pulmonary hypertension. Furthermore, more deaths have been reported [6-8].

Historical aspects

INDO is a non-steroidal anti-inflammatory drug, cyclo-oxygenase inhibitor and prostaglandin synthesis inhibitor. In 1976 the first two clinical reports using INDO to promote closure of the PDA in preterm babies were published in the same issue of the New England Journal of Medicine [9,10]. Many articles on the use of INDO were published subsequently, as it has been the drug on which more publications exist [4,5,11].

The complications associated with the use of INDO encouraged the search for an alternate drug to treat a PDA. IBU, a propionic acid derivative, non-selective cyclo-oxygenase inhibitor and inhibitor of prostaglandin synthesis, was studied in newborn piglets [12] and as prophylaxis to prevent PDA in preterm infants in 1996 [13]. It was not until 2000 that a trial comparing INDO and IBU was performed and published also in the in the New England Journal of Medicine [14]. It showed that IBU on the third day of life was as efficacious as INDO for the treatment of PDA in preterm infants with RDS and was significantly less likely to induce oliguria, without gastrointestinal hemodynamic disturbance.

Regarding PARA, constriction of the fetal ductus was shown in the sheep in 1985 [15] and, in 2002, a constricted ductus arteriosus was confirmed by fetal echocardiography in a woman who took 500 mg of PARA twice daily orally for three days as a medication for pain [16]. It was only in 2011 that PARA was suggested as an alternative for treating a PDA in a report of five preterm infants with a large HS-PDA [17]. To date, it is not known exactly how paracetamol works to close the PDA, but probably involves inhibition of prostaglandin synthesis but unlike IBU, PARA apparently acts on the peroxidase region of the enzyme prostaglandin synthetase [18,19].

The current clinical conundrum is which of the three drugs best combine safety and effectiveness to treat a HS-PDA in preterm infants.

Objectives

To identify the current evidence on effectiveness and safety of the pharmacological treatment of PDA in premature newborns, describe potential risks of the drugs utilized for ductal closure and present data from 813 preterm infants who were treated for PDA and reported to SIBEN's network.

Methods

Identify the most recent evidence published on the three drugs currently used for PDA closure (INDO, IBU and PARA) focusing on effectiveness and safety and analyze three years of data at SIBEN's network on 813 preterm infants < 1,500 grams at birth who received pharmacological treatment for a PDA. Once the variables were selected, the data were transferred to statistical software for analysis (STATA 12.0). Descriptive statistics included mean, median, standard deviations and quartiles for numerical variables and frequencies or percentages for categorical data. Comparisons between groups were made using contingency tables, Chi² and Fisher's exact test. A p value <0.05 was considered statistically significant.

Advantages and side effects of INDO for ductal closure in preterm infants

INDO used as prophylaxis has been shown to be effective to decrease the prevalence of PDA and also severe intra ventricular hemorrhage (IVH) [20]. US and European neonatal centers that regularly administer prophylactic INDO have lower rates of broncho pulmonary dysplasia (BPD) and BPD/death than centers that only consider PDA treatment later during neonatal hospitalization [21]. Prophylactic INDO could then be used in a specific group of extremely low birth weight infants and especially in NICUs with a high incidence of IVH and/or without the possibility of surgery for the treatment of HS-DAP. This issue has been debated extensively and we will not expand much further about it in this manuscript regarding the positive effect on IVH incidence and induced (early) patent ductus arteriosus closure [20]. Especially in the United States prophylactic indomethacin administration (low dose indomethacin starting within 6 h after birth up to day 3-5) has been utilized in many centers [22]. In 2001 the TIPP trial showed also a decreased incidence of severe IVH [23]. A recent large study did show improved survival after indomethacin prophylaxis in especially the extremely preterm infants [22]. This seemed to be confirmed by a recent meta-analysis which showed a positive effect on mortality of a prophylactic indomethacin regime [24]. Also, preterm infants who receive caffeine very early have less PDA (OR, 0.74; 95% CI, 0.62-0.89) and less BPD or death (OR= 0.81; 95% CI, 0.67-0.98) [25,26]. Caffeine is a safe and effective drug for prophylaxis of PDA, but not for treatment of an established PDA; therefore, we will not provide any additional information on the use of neonatal caffeine.

The success rate of INDO for PDA closure reported in the literature has been variable, between 60%-80% [4,27]. This has depended on gestational age, post-natal age, gender, and other factors.

Adverse effects of INDO are various and they include [18]:

- Impairment of renal function, oligo-anuria, hyperkalemia
- Intestinal effects with decreased mesenteric blood flow; NEC, intestinal perforation

- Platelet dysfunction
- Reduction of cerebral blood flow
- Cerebral white matter damage.

Because of potential oligo-anuria, reducing water or fluid intake is indicated to avoid excess water and weight gain at all costs. Due to potential alterations of the mesenteric blood flow the recommendation is not to feed enterally for 24-48 hours while INDO is being administered. If the newborn was previously feeding, it is advisable to discontinue the feedings at least 4 hours prior to the start of therapy and to restart progressively once the treatment is finished and the hemodynamic status has improved. In regards to tolerance to trophic stimulation no differences between INDO and IBU have been found [4].

Long term studies show benefits in reducing IVH when used prophylactically and no abnormal long-term neurodevelopmental or hepatic adverse effects have been described in thousands of babies followed up for many months [22,28].

The dose of IV INDO is summarized in Table 1, with a minimum administration time of 30 minutes and up to 1 hour.

	< 48 hours of life	> 48 hours of life	> 7 days of age
First dose	0,2 mg/Kg	0,2 mg/Kg	0.2 mg/Kg
Second dose	0,1 mg/kg	0,2 mg/Kg	0.25 mg/Kg
Third dose	0,1 mg/Kg	0,2 mg/Kg	0.25 mg/Kg

Table 1: Dose of IV indomethacin. Three doses in total, every 12 hours, constitute a complete treatment course.

Advantages and side effects of IBU for ductal closure in preterm infants

Prophylactic IBU has not been as well studied as INDO has, but it does not reduce IVH. Prophylactic oral IBU can reduce the risk of PDA (typical RR 0.47, 95% CI 0.30 to 0.74), produces oliguria much less frequently than INDO, and also has a lower incidence of NEC. However, current evidence does not support the use of ibuprofen for the prevention of PDA [29].

The success rate of IBU for PDA closure reported in the literature has been variable, between 60%-80%. The best estimates of IBU failure are between 26-29% [29,30]. Oral IBU at high doses promoted 71.7% of PDA closure and with standard doses 63.8%. Also, PDA closed faster in the high-dose IBU group than in the standard-dose group (mean time to closure 3.9 ± 1.0 versus 4.4 ± 1.0 days, p = .009) [30]. Table 2 shows the three doses that are recommended for IV and PO IBU.

	IV	ORAL "Standard"	ORAL "High"
First dose	10 mg/kg	10 mg/kg	20 mg/kg
Second dose	5 mg/kg	5 mg/kg	10 mg/kg
Third dose	5 mg/kg	5 mg/kg	10 mg/kg

Table 2: Dose of IBU: 3 doses in total, IV or PO, every 24 hours, constitute a complete treatment course.

A review and metanalysis of 39 trials (2843 infants) found that IBU was as effective as INDO in closing a PDA, caused fewer transient adverse effects on the kidneys, reduced the risk of NEC [31] and has less effects on the velocity of blood flow to various organs.

It would seem then that the best drug is oral IBU at “high doses” [29-31]. However, it must be remembered that both IBU and INDO have lower effectiveness in newborns <26 weeks’ gestation and also when the treatment is started after 4-5 days of life. These are important issues to include in stratification when clinical studies are performed and when comparisons between drugs are made.

Adverse effects of IBU [18] are:

- Interference with bilirubin binding to albumin
- Pulmonary hypertension
- Rarely and more frequent in infants < 26 weeks of gestation and < 1,000 grams: oliguria, decrease in serum sodium level, increase in serum creatinine level, thrombocytopenia.

No abnormal long-term neurodevelopmental or hepatic adverse effects have been reported in the thousands of babies treated with IBU.

Advantages and side effects of PARA for ductal closure in preterm infants

Administration of oral or IV PARA gained attention more recently, as a number of case reports and case series suggested that PARA may be an alternative for the closure of a PDA. We will expand more on this drug as the current recommendations for its use are not clear. At least 19 ongoing trials have been registered [19] and results of such trials are required before any recommendations for the possible routine use of PARA in the newborn population can be made.

Exactly how paracetamol works to close the PDA is not known; probably involves inhibition of prostaglandin synthesis but unlike IBU, PARA apparently acts on the peroxidase region of the enzyme prostaglandin synthetase.

As prophylaxis, a retrospective single center published in 2020 compared preterm infants < 32 weeks’ gestation in the “control” cohort (between 1/1/2012 and 30/9/2014) to the intervention cohort (1/10/2014 to 30/6/2017). The latter group received “low dose” PARA (10 mg/kg every 8 hours starting in the first 24 hours for 72 hours). PDA prevalence was reduced from 38% to 14% [32]. However, there are significant limitations of studies of this sort. Better trials are needed to attest effectiveness and safety, particularly in the smallest infants.

For PDA closure the effectiveness and success rate of PARA is very low in some studies (6%) and up to 65% in others [27,30,33]. The initial rate of acetaminophen-induced constriction of the ductus may be only 27%. In a metaanalysis it was found to be 37.9% [30].

A recent RCT of intravenous PARA versus INDO for treatment of HS-PDA in very low birth weight sick infants [33] with only 17 infants in the PARA group and 20 in the INDO showed that only 5.9% closed with PARA and 47% received transcatheter closure, much worse than with INDO. The study had to be suspended by the review board due to the high rate of need for closure by catheterization in the PARA group.

In an RCT in a single center performed between January 2012 to December 2015, IV PARA (15 mg/kg every 6 hours for 3 days) was found to be as effective as IBU, but the dose used for IBU was lower than currently recommended [27].

In another single center RCT 110 babies were randomized between October 2014 and January 2016 to compare oral PARA (15 mg/kg every 6 hours) vs oral IBU at lower doses than currently recommended) for PDA closure. No significant difference was found between the two groups with respect to PDA closure (RR 0.97, 95%CI 0.78-1.20, p = 1), mortality or cardio-respiratory morbidity [34].

A systematic review suggests that there is no difference in effectiveness with other drugs [35]. However, the evaluation included infants with birthweight 1500-2500 grams, when actually infants with > 1,200 grams rarely require treatment, due to spontaneous closure or no HS-PDA.

Oral PARA was found to be less effective than oral IBU at recommended doses in very low and extremely low birth weight infants [36]. Subgroup analysis indicated that paracetamol was minimally effective in extremely low birth weight newborns, with closure of the PDA in 13%. This study demonstrated that paracetamol may be a poor medical alternative for the management of PDA in preterm infants with very low birth weight and even more so in infants with extremely low birth weight [36].

In other publication, when PARA failed in moderate to large persistent PDA infants were treated with INDO. The final rate of constriction after acetaminophen + indomethacin was 60%, similar to the rate in infants who received indomethacin alone which was 62% [4,5,37,38].

Finally, as we have mentioned before, the Cochrane review of 2020 shows low-quality evidence for all studies on effectiveness and safety of PARA, according to Grading of Recommendations, Assessment, Development and Evaluations (GRADE) [19].

In summary with current evidence to date, it could be said that oral or IV PARA is less effective than oral or IV IBU and IV INDO.

There are several issues of concern regarding PARA treatment for PDA closure in very preterm infants. One of them is that the dose is not precisely defined, with variable dosing reported in the various publications. Other concerns relate to the metabolism of PARA in neonates and the potentially serious adverse effects.

A loading dose of 20 mg/kg followed by 10 mg/kg every 6 hours of intravenous PARA is suggested to achieve a compartment concentration of 11 mg/L in late preterm and term neonates. Many professionals use higher doses for preterm infants with PDA than those recommended for term newborns for other medical indications. However, the higher doses suggested in extreme preterm neonates to induce PDA closure have not yet been sufficiently evaluated regarding efficacy or safety. For example, oral or IV PARA has been used at 15-20 mg/kg every 6-8 hours during 3 days and up to 7 days.

Maturation-related changes in PARA disposition, metabolic, and elimination clearance occur throughout childhood, but are most prominent in early life. Neonates have an overall lower paracetamol metabolic and elimination clearance capacity, and the between-subject variability is explained by covariates such as size or weight, organ function, or disease characteristics [39,40]. The metabolism of PARA is hepatic and we never know with certainty how is the liver function of a preterm newborn, more so if the infant is critically ill. Additionally, genetic factors are involved in the individual variability that exists in the metabolism of this drug.

A group of preterm newborns received PARA by infusion over 30 minutes, 15 mg/kg every 12 hours (<28 weeks' gestation) or every 8 h (≥ 28 weeks' gestation) for 48 hours. A pharmacogenetic effect on the metabolism of PARA was observed with variation of sequences in the promoter region of the UDP-glucuronosyltransferase enzyme. This affects the clearance of PARA by glucuronidation and oxidation [41]. When administering PARA in daily practice we do not know what the infant's metabolic capacity is.

In a RCT of PARA and its metabolites, with doses of 10, 15, or 20 mg/kg IV in preterm infants 24-32 weeks of gestational age, the area under the concentration-time curve in plasma was related to dose and gestational age, and there was an increase in glucuronidation dependent on gestational age. Compared to adults, very low glucuronide exposure and high exposure to sulfate, cysteine, and mercapturate metabolites were found in these preterm infants [42].

IV acetaminophen pharmacokinetics in neonates has also been studied after multiple doses [43]. With 15 mg/kg every 6 hours for 4 days, unconjugated bilirubin levels were associated with reduced clearance, dictating dose reduction [43].

In neonates, the dose and the weight/size relationship are the most relevant covariants of the pharmacokinetics of PARA. For all of the above reasons, several authors address the need on focused pharmacovigilance to explore the potential causal association between PARA exposure during perinatal life and infancy and it is warranted to carefully evaluate subsequent adverse events [39-43].

Known adverse effects in animals, older children and adults, pregnancy and neonates are:

- Elevation of liver enzymes.
- Liver failure
- Atopy
- Hypothermia
- Hypotension
- Impaired fertility and neurodevelopment
- Altered adult behavior and cognitive deficits
- Death (liver failure)
- There is evidence of serious adverse effects on children exposed to PARA during pregnancy: affects reproductive function, alters testicular descent in the fetus, decreases testicular testosterone and is associated with long-term attention deficits and hyperactivity
- In neonates, it crosses the blood-brain barrier, causes depletion of cerebral glutathione, causes neurotoxicity and is associated with autism spectrum.

Long term studies

The serious potential risks of PARA have not been fully evaluated in the long term. A few studies have reported neurodevelopmental outcomes after PARA for PDA in premature infants. One compared the effects of PARA and IBU on neurodevelopmental outcomes at 18 to 24 months of corrected age [44]. There were only 61 infants evaluated, 30 in the paracetamol group and 31 in the ibuprofen group. Two other manuscripts reported follow up at a corrected age of 2 years and at 5 years [45,46], but only 44 infants were included.

The number of preterm infants in studies of PARA effectiveness and especially of long-term safety is scarce. Owing to the small number of studies and the stratification leading to a decrease in sample size, it is difficult to conduct a more detailed analysis, making it difficult to draw accurate conclusions.

There is still a need to perform these studies with a large enough sample size of tiny babies in order to avoid reaching conclusions with high probability of Type II errors, i.e.: saying that something does not happen when it actually exists in the real world. Therefore, larger trials are needed on the safety and efficacy of PARA prophylaxis and treatment of HS-PDA in very preterm infants.

The concerns are that PARA works on the endocannabinoid system, which refers to brain development. The effects of neonatal PARA exposure on brain development may only be seen later in life with alterations of adult behavior and cognitive deficits [47]. Additionally, PARA has been shown to cause direct toxicity in rat cortical neurons *in vitro* as well as *in vivo*, resulting in apoptosis of the rat cortical neurons [48].

Consequently, rigorous RCTs and cohort studies are needed to clarify the effects of PARA on the neurodevelopmental outcomes of infants. Recently, an elegant commentary [49] underscores the need for appropriate pharmacodynamic and follow-up studies examining both the route and dose of PARA, as well as the population being studied, before it can be concluded that PARA is an effective and safe drug to use when PDA treatment is needed.

When using any drug, safety and efficacy should be studied in different subgroups of premature infants. Characteristics that affect therapeutic efficacy and potential long-term effects include gestational age, birth weight, dosages, administration route, and timing. At least 19 ongoing trials of PARA have been registered [19]. Results of such trials are required before any recommendations for the possible routine use of PARA in the newborn population can be made.

Data on 813 preterm infants who received pharmacological treatment for PDA closure reported to the network of the Iberoamerican Society of Neonatology (SIBEN)

Preterm newborns with birth weight ≤ 1500 grams, from 43 neonatal centers in 8 different countries of Latin America are reported to the data base at SIBEN’s network. In the years 2018-2020, 813 preterm infants, with mean birth weight of 1112 ± 266 grams and mean gestational age of 28 ± 2 weeks, were treated for a PDA. Of them, 273 (34%) received IBU, 283 (35%) INDO and 250 (31%) were treated with PARA. The number of infants < 1,000 grams and < 27weeks were no different between the three treatment groups.

Of the infants treated with IBU, 27% of the time the route of administration was IV and 73% was PO. All infants given INDO received it IV (100%). Of the infants treated with PARA, 87% received it IV and 13% PO. Table 3 shows a summary of the most important findings in these preterm infants with birth weight < 1,500 grams who received PDA treatment with any one of the three drugs.

Data in SIBEN’s network data base included several other factors, like severe BPD at 36 weeks post conceptional age and severe IVH. Severe BPD occurred in 36% with INDO, 41% with IBU and 48% with PARA. The differences did not reach statistical difference but the trend was worse for PARA. The incidence of severe IVH in newborns who had a cranial ultrasound done was not statistically different either, and there was no benefit identified for INDO over the other two drugs.

The effectiveness of continuous quality improvement (CQI) for developing professional practice and improving health care outcomes has been proven. Based on the data presented in Table 3, in 2021 we at SIBEN started a CQI project for treatment of HS-PDA. In the first 10 months of 2021, use of PARA decreased from 31% to 18%.

	IBU* 273 (34%)	INDO 283 (35%)	PARA* 250 (31%)	Fisher’s p value
PDA Closure	73%	72%	63%	0,04
Death	24%	25%	32%	0,06
Pulmonary Hemorrhage	11%	12%	26%	0,002
NEC	19%	18%	30%	0,02

Table 3: Effectivity, mortality and morbidity in infants < 1,500 grams treated with PDA according to the type of drug used (n = 813).

Discussion

PDA is the most common cardiovascular problem that develops in preterm infants and evidence regarding the best treatment approach is lacking. Currently available medical options to treat a PDA include INDO, IBU and PARA and wide variation exists in PDA treatment practices as shown in the published literature and in table 3.

In medicine, ethics and prudence imply that treatments with equal or better effectiveness and without potential serious long-term risks should be used before using less effective and not so well studied treatments, as there could be potential unknown risks when insufficiently evaluated drugs are used. The risk benefit ratio of any treatment should always be considered.

In most of the trials with PARA there is not enough power to establish if it is a safe drug without adverse effects in the population of extremely vulnerable neonates. In addition, the few pharmacokinetic and metabolic studies suggest there is a risk for accumulation of the drug.

The data in table 3 lends support to the fact that in clinical practice PARA has a lower effectivity for PDA closure and a higher frequency of complications compared to IBU and INDO. These data, together with the information from current metanalysis and systematic reviews discussed in this manuscript should suggest cautiousness about the safety of PARA for PDA closure in tiny preterm infants. More studies are needed to confirm if PARA shows a real safety profile. Its long-term outcomes should be well studied before considering PARA as first choice drug for PDA treatment.

As discussed in this manuscript, oral IBU at high dose (Table 2) seems to be an effective and safe treatment for PDA closure to date, and IV INDO maybe just as good.

Conclusion

As with many of the treatments in the neonatal period, our duty is “first do no harm”, or “primum non nocere” from the Latin. Even though every weapon in the physician’s armamentarium is double-edged and every treatment has a potential harm, the risk benefit ratio should always be kept in mind when caring for fragile neonates. In a recent commentary [50], it was mentioned that the PDA remains “enigmatic” and it is difficult to know with certainty who to treat and who not. The author asks rhetorically: “If there was a safe procedure, would you recommend PDA closure for all preterm infants?” Unfortunately, we are still waiting for that risk-free procedure or drug to appear.

In the meantime, the most effective therapeutic medications with better known safety profiles based on current evidence should be the ones to be used until adequate studies with sufficient power, satisfactory stratification by gestational age and birth weight and with very low or no likelihood of being affected by Type I or Type II errors are published.

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