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## **Adverse events related to ibuprofen treatment for patent ductus arteriosus in premature neonates**

Short title: Adverse events of ibuprofen in preterm

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## **Declaration of Interest**

All authors do not have any conflict of interest to declare.

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## **Abbreviations**

ADR	adverse drug reaction
BPD	bronchopulmonary dysplasia
COXi	cyclooxygenase inhibitors
ELBW	extremely low birth weight
GA	gestational age
IVH	intraventricular hemorrhage
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
NSAIDS	nonsteroidal anti-inflammatory drugs
PDA	patent ductus arteriosus
RCTs	randomized control trial
SGA	small for GA
WHO	World Health Organization

## **ABSTRACT**

**Objective:** Our study aimed to review adverse drug reactions (ADRs) associated with ibuprofen treatment of patent ductus arteriosus (PDA) in premature neonates

**Method:** We retrospectively evaluated electronic patient records from neonates treated with ibuprofen for PDA during 5 years in a French neonatal intensive care unit. Full chart review and targeted triggers were used to detect ADRs. The causality between suspected ADRs and medication was evaluated using the WHO causality assessment method by pharmacovigilance experts. Categorical variables were compared using chi-square tests or Fisher's test. Quantitative variables were compared using the Student *t* test. We explored the risk factors associated with ADR using univariate model analysis.

**Result:** Of 227 infants with a mean gestational age (GA) of 27 weeks (24-33), 12 (5%) developed intestinal perforation and seven, necrotizing enterocolitis (3%). The perforation occurred less frequently in infants older than 27 weeks GA (OR = 0.14; 95% CI = 0.03–0.66, *p* = 0.01). Other observed ADRs were acute renal failure (25 infants, 11%) and thrombocytopenia (five infants, 2%).

**Conclusion:** Gastrointestinal complications observed in infants treated with ibuprofen for PDA including gastrointestinal perforations occur in less mature infants. Active chart review of the patient's medical file with a trigger tool should be evaluated for routine ADR monitoring.

**Keywords:** premature newborns, patent ductus arteriosus, adverse drug reactions, ibuprofen

## 1. Introduction

Patent ductus arteriosus (PDA) is common in premature infants, occurring in 60–70% of infants younger than 28 weeks of gestation [1, 2]. Patent ductus arteriosus (PDA) is a potentially very harmful condition in the youngest preterm infants. In premature infants, PDA is associated with several complications such as pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC) [3]. The treatment of hemodynamically significant PDA reduces the incidence of significant PDA (67.4% PDA closure) and the need for surgical ligation and serious pulmonary hemorrhage. Despite numerous trials and systematic reviews, the clinical management of PDA in preterm infants is still a controversial topic [3-5]. The challenge for clinicians is choosing between a pharmacologic aggressive treatment or a more conservative approach of watchful waiting and spontaneous closure.

In our neonatal intensive care unit (NICU), for the past two decades, ibuprofen is the first choice for PDA closure in symptomatic and/or hemodynamically significant PDA according to cardiac sonography criteria. In real clinical settings, we observed cases of PDA closure failure with severe side effects related to ibuprofen. In many randomized control trial (RCTs), all adverse events were commonly reported but there was no confirmed evidence of a causal relationship between ibuprofen and adverse events, especially for digestive adverse events such as intestinal perforations and NEC. We aimed: (a) to describe gastrointestinal perforation and other adverse drug reactions (ADRs) associated with ibuprofen use to treat PDA in premature neonates; (b) to identify the risk factors of PDA closure failure and severe adverse effects if possible; (c) to test the feasibility of an active method to detect adverse events related to ibuprofen treatment in routine practice.

## **2. Methods**

Since 2008, our NICU has implemented a computer medical record for all of our patients using Philips software (IntelliSpace Critical Care, Anesthesia version F.00.001). We retrospectively evaluated electronic patient files from all neonates treated with ibuprofen for PDA during 5 years (from January 2009 to December 2013). Data were obtained by chart review. This study is part of the Remineo project and was approved by the local ethics committee on June 6, 2011 (CPP sud est II, n° C.A.L 2011-15). We included all cases from the database of infants receiving at least one dose of ibuprofen with the indication for PDA closure according to our standard protocol. Our protocol listed a treatment regimen including three injections of ibuprofen: 10 mg/kg on the first day (D1) and 5 mg/kg on the second and third days (D 2, D3). The dosing scheme was adjusted only to the weight of the infant on the day of treatment. Extension of the treatment comprised a second round of three injections like the first cure or any additional injection of 5 mg/kg/day on D4, D5, D6 (extended regimen) if there were no contraindications. An additional dose after D6 is very rare in our practice; it is a symptomatic treatment approach. Before treatment, the PDA was evaluated via echocardiography when clinical signs suggestive of PDA were present and treatment was initiated if a hemodynamically significant PDA was confirmed. All echocardiography studies were performed with ultrasound equipment (Hitachi model Ezu-Mtz and General Electric, GE system Scs Vivid S6), with phased sector ultrasound transducers (S 12-4 and/or S 8-3) incorporating color flow, pulsed wave Doppler, and continuous wave Doppler with adaptive Doppler technology. All echocardiography examinations were performed by trained neonatologists in the NICU. Hemodynamically significant PDA was defined by operators as the presence of left cardiac volume overload. We did not evaluate in detail how the decision for PDA treatment was made as this study focused on adverse effects of ibuprofen treatment. Baseline demographic data including gestational age, birth weight, and gender were recorded.

### **2.1. Detection and evaluation of ADRs**

In 2008, Takata et al. [6] developed a pediatric-focused tool for ADR detection. Our method of ADR detection is inspired from this trigger tool but adapted to our practice and to the case of ibuprofen.

Full chart review (drug administration charts, laboratory results, health parameter monitoring results, electronic clinical records, and hospital discharge reports) and targeted triggers (digestive troubles, stopping enteral feeding, reduced diuresis, increased uremia or creatinemia, hematologic abnormality, hemorrhagic disorders, any abnormality detected via laboratory or cranial sonographic tests etc.) were used to detect ADRs by one of the authors (DN). All of the adverse events screened for were assessed independently by one of the other authors, who was trained and had experience in pharmacovigilance (KN). We followed the WHO-UMC causality assessment method of pharmacovigilance with four categories of imputability: certain, probable, possible, unlikely [7] (Table 1).

Statistical analysis was performed using R software. Categorical variables were compared using chi-square tests or Fisher's exact test. Quantitative variables were compared using the Student *t* test. Univariable and multivariable analysis using logistic regression was conducted to explore the risk factors associated with ADRs.

### 3. Results

A total of 227 of 1330 neonates younger than 34 weeks at birth were included in the study. The mean gestational age (GA) was 27 weeks (24–33); 12 (5%) of the neonates had intestinal perforation and seven, necrotizing enterocolitis (3%). All neonates were treated with ibuprofen in the first week of life. The time between the last administration of ibuprofen and the occurrence of perforation varied between 0 and 6 days. Renal failure defined as oliguria of less than 1 ml/kg/h for at least 12 consecutive hours associated with an increase in creatinemia of more than 20% of the baseline value before treatment. The time between the first administration of ibuprofen treatment and 25 ADRs of renal failure varied between 12 h and 3 days. Renal failure was reversible during the first week after stopping ibuprofen injections. We defined thrombopenia as a platelet count of less than 100,000/mL occurring in the week after the first injection of ibuprofen. The ADRs of thrombopenia in two infants were normalized (>150,000/mL) in the week after the last ibuprofen injection. Figure 1 illustrates the efficacy of ibuprofen treatment.

We observed a total of 55 ADRs related to ibuprofen. Perforation occurred more frequently in less than 27 weeks' GA (odds ratio [OR] = 0.14; 95% confidence interval [CI] = 0.03–0.66,  $p = 0.01$ ). Other observed ADRs were acute renal failure (25 infants, 11%) and thrombocytopenia (five infants, 2%) (Figure 2). Because of the small number of events, we could not perform a multivariable analysis, and therefore only univariable analyses were performed.

Table 1 presents the WHO-UMC causality assessment method of 55 adverse events. The characteristics of the neonates included in the study are listed in Table 2.

#### 4. Discussion

The important observation from our study was that children with a lower gestational age were at greater risk of developing intestinal perforation after early exposure to ibuprofen. Intestinal perforation occurs as reported in the literature in the youngest and the least mature children [8]. Rao et al. [9] studied gastrointestinal complications related to the use of ibuprofen for the treatment of PDA in premature infants. They found that intestinal perforation occurred in the smallest children, the youngest in gestational age, and was even more frequent when the treatment was started early.

We noted a prevalence of 5% of intestinal perforations in our study. This figure is quite close to that reported in the literature: 5% in the study of Katakam et al. [10], 8.8% for Rao et al. [9]. In a systematic review, the overall perforation rate associated with ibuprofen was 4.6% [3].

In the literature there is an association between the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and the occurrence of intestinal perforation of premature infants, although the mechanism is not well understood. The effects of NSAIDs on prostaglandins and decreased blood flow to the intestine can contribute to the development of intestinal perforations [11]. If ibuprofen has effects similar to those reported for indomethacin on the epithelial enzyme synthesizing nitric oxide, there may be a similar risk for intestinal perforation. Apart from perforations, we found other digestive complications related to ibuprofen: seven children (3%) had NEC that evolved in most cases (71.4%) to digestive perforation, and one child died rather quickly as a result of an overwhelming NEC.

A case of gastric bleeding was noted that led to termination of the ibuprofen treatment. This complication of ibuprofen in premature infants was already reported in the literature, although it was quite rare. In their meta-analysis of RCTs, Terrin et al. reported a reduction in the risk of gastrointestinal bleeding in patients receiving paracetamol vs. cyclooxygenase inhibitors (COXi) therapy (2/125 vs. 9/125, respectively, relative risk [RR] = 0.2, 95% CI = 0.1–1.0) [12].

Regarding the effects of ibuprofen on the kidney of premature infants, in our series we found transient renal failure in 11% of patients on ibuprofen treatment; while the reported rate ranged from 5% to 10% in a systematic review [3]. Long-term follow-up of renal function in these children is necessary because some authors have found that ibuprofen is associated with a significant impairment of renal function, which persists during the first month of life, in some very premature infants [13].

Raaijmakers et al. [14] recently carried out a post hoc analysis to assess the impact of ibuprofen exposure on long-term renal function in former extremely low birth weight (ELBW) cases. In conclusion, they note that the absence of a decrease in renal function in young adolescents following ibuprofen administration in ELBW neonates in early neonatal life was somewhat reassuring.

Hematological toxicity, in particular a decrease in the number of platelets, is also a complication of ibuprofen treatment. We noted the occurrence of thrombocytopenia in 2% of our patients, which is comparable to the results of Linder et al. [15].

Although the data were recorded before 2014, ibuprofen continues to be our first-line option for treating PDA in our unit and in most NICUs in France in the year 2020. We believe that our study helps raise awareness for clinicians who have to consider the risk–benefit balance of using ibuprofen in this vulnerable population.

Despite the study being retrospective and from a single center, we have provided a description of ADRs related to ibuprofen treatment in a real clinical setting. The ADRs were searched via chart review of a reliable electronic database. All the ADRs were assessed for causality following the WHO-UMC method. We suggest that this method of detection of ADRs should be evaluated for routine application in practice.

## **5. Conclusion**

It is important in practice to assess the risk–benefit ratio for each preterm infant prior to initiation of PDA treatment. The individual data of all high-quality RCTs should be gathered to explore a specific population for whom the PDA treatment would be more beneficial and less risky in terms of severe complications.

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**Table 1:** WHO-UMC causality assessment method

Categories	Time sequence	Other drugs/disease ruled out	Dechallenge	Rechallenge
certain	yes	yes	yes	yes
probable	yes	yes	yes	no
possible	yes	no	no	no
unlikely	no	no	no	no

WHO–UMC: World Health Organization–Uppsala Monitoring Centre.

**Table 2:** Characteristics of the preterm infants included in the study

	<i>N</i> (%)	Average	Median	Min-Max
<b>Gestational age (weeks)</b>	<b>227</b>	<b>26.9</b>	<b>27.0</b>	<b>23 - 33</b>
<b>Birth weight (g)</b>	<b>227</b>	<b>936.8</b>	<b>895</b>	<b>520 - 1920</b>
<b>Birth weight (g)</b>				
<800	80 (35.2)			
800–<1000	73 (32.2)			
1000–<1500	63 (27.8)			
>1500	11 (4.8)			
<b>Treatment time (days)</b>		4,5 (3.5)	3.0	1 - 20
<b>Ligation PDA</b>	19 (8.4)			
<b>Number of treatments</b>				
1	181 (79.7)			
2	42 (18.5)			
3	4 (1.8)			
<b>Extended treatment (&gt; 3 injections)</b>	33 (14.5)			
<b>Adverse drug reactions</b>	55			
<b>Ductus arteriosus closed</b>	<b>161 (71)</b>			

PDA: patent ductus arteriosus.

**Table 3:** Causality assessment of adverse events

Categories/ADR	Certain	Probable	Possible
Intestinal perforation			12
NEC			7
Renal insufficiency		5	20
Thrombocytopenia		2	3
Gastric bleeding		1	
Enteropathy		4	
Death			1

ADR: adverse drug reaction; NEC: necrotizing enterocolitis.

### Legends for figures

**Fig. 1.** Efficacy of ibuprofen treatment (X-axis = PDA evolution; Y-axis = numbers of infants)

PDA: patent ductus arteriosus

**Fig. 2.** Observed adverse events related to ibuprofen treatment (X-axis = type of ADR; Y-axis = numbers of infants)

ADR: adverse drug reaction



