

Ibuprofen and acute kidney injury in the newborn

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The pharmacological treatment of patent ductus arteriosus (PDA) in preterm infants remains a controversial issue, particularly with regard to the type of drug to be prescribed (ibuprofen or indomethacin) and the timing of the treatment, given their comparable effectiveness. For many years, indomethacin has been the drug of choice in the treatment of PDA. In April 2006, the United States Food and Drug Administration approved the use of ibuprofen lysine for closure of clinically significant PDA in premature infants <32 weeks' gestation and weighing 500-1500 g. The available knowledge on the effects of ibuprofen on renal function in the neonate is discussed herein, since the good renal tolerability of this drug is a major argument in favor of its use in the routine treatment of PDA.

Key words: *ibuprofen, indomethacin, kidney injury, newborn, patent ductus arteriosus.*

The pharmacological treatment of patent ductus arteriosus (PDA) in preterm infants remains a controversial issue, particularly with regard to the type of drug to be prescribed (ibuprofen or indomethacin) and the timing of the treatment, given their comparable effectiveness¹.

For many years, indomethacin has been the drug of choice in the treatment of PDA. However, undesirable adverse effects of this drug (alterations in renal, gastrointestinal and cerebral perfusion and possible subsequent transient renal dysfunction, necrotizing enterocolitis, etc.) have prompted researchers to seek alternative pharmacological agents.

In April 2006, the United States Food and Drug Administration approved the use of ibuprofen lysine for closure of clinically significant PDA in premature infants <32 weeks' gestation and weighing 500-1500 g. Ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), inhibits both cyclooxygenase (COX)-1 and COX-2, which are enzymes necessary for the synthesis of various prostaglandins. NSAIDs can be used for closure of PDA in premature infants because the immature ductus arteriosus is more sensitive to prostaglandin E₂ (PGE₂), which is a potent vasodilator of this blood vessel^{2,3}.

Regarding pharmacokinetics, ibuprofen is 95% protein bound and has a volume of distribution of 320 ml/kg⁴. In adults, the liver mainly metabolizes this drug, and 80% of the dose is excreted in the urine as hydroxyl and carboxyl metabolites⁴.

A number of studies and meta-analyses comparing indomethacin with ibuprofen for the prophylaxis or treatment of PDA are now available. The most recent published data support the use of either drug for the treatment of PDA. As both drugs are equally effective in closing a PDA (70-85% rates of success), the clinician needs to weigh the potential side effects of one drug versus the other when making a decision on which to use⁵. Regarding nephrotoxic effects, both indomethacin and ibuprofen are capable of inducing oliguria (Table I) and increased creatininemia in the newborn. However, in preterm infants treated with ibuprofen, the urine output is decreased and creatininemia is increased but less so when compared to indomethacin^{13,14}. Furthermore, it should be taken into consideration that neonatal renal damage may also be related to prenatal administration of NSAIDs to the mother^{15,16}.

Table 1. The Oliguric Effect of Indomethacin (Indo) and Ibuprofen (Ibu) in the Major Randomized Trials Comparing the Two Drugs for Closure of Patent Ductus Arteriosus

Reference	Year	N	Gestational age (wks)	Oliguria (%)	
				Indo	Ibu
Pezzati ⁶	1999	17	<33	“Significant”	-
Van Overmeire ⁷	2000	148	24-32	19	7
Lago ⁸	2002	175	≤34	15	1
Chotigeat ⁹	2003	30	≤35	73.3	20
Su ¹⁰	2003	63	≤32	“Significant”	-
Gimeno Navarro ¹¹	2005	47	<34	29	9
Su BH ¹²	2008	119	≤28	15.3	6.7

%. Percentage of study participants. Ibu: Ibuprofen. Indo: Indomethacin. N: Number of study participants. wks: Weeks.

Drug transporters such as the renal organic anion transporters (e.g., OATs), cation transporters (e.g., OCTs), and ABC-transporters (e.g., P-glycoprotein and multidrug resistance protein) play an important role in influencing the rate and rapidity of xenobiotics excretion by the kidney. In particular, OATs mediate the renal transport of NSAIDs^{17,18}. In rats, the expression levels of OAT1, OAT2 and OAT3 increased from birth to 45 days postpartum; this translates to humans ranging in age from birth to prepuberty¹⁹.

The nephrotoxic effects of NSAIDs are related to their mechanism of action, namely the block of prostaglandin synthesis through the inhibition of COX²⁰. PGE2 is the main prostanoid synthesized along the nephron, with the renal medullary interstitial cells and collecting tubules as the major sites of production. Urinary excretion of PGE2 predominantly reflects the renal origin of this mediator. This prostanoid modulates both intrarenal vascular tone and salt and water excretion. In particular, PGE2 contributes to regulating renal perfusion and glomerular filtration rate in virtue of their vasodilating properties, by counteracting the action of vasoconstrictive substances such as angiotensin II, catecholamines, vasopressin, and endothelin^{21,22}. The action mechanism of NSAIDs explains the major pathophysiologic effect of NSAIDs on the kidney, namely the alteration of intraglomerular renal perfusion.

Thus, the administration of NSAIDs should be carefully weighed in subjects suffering from conditions associated with high levels of vasoconstrictive substances (hypovolemia,

cardiac failure, sepsis, hypertension, etc.), in whom these drugs may preferentially induce renal damage^{20,23}. Therefore, it must be taken into account that NSAIDs-induced nephrotoxicity is not easy to define in the newborn because they are generally administered to sick, often seriously ill newborns, in whom hemodynamic abnormalities and/or electrolyte derangements may be important contributors to the renal damage²⁴.

The aim of this review was to discuss the available knowledge on the effects of ibuprofen on renal function in the neonate, since the good renal tolerability of this drug is a major argument in favor of its use in the routine treatment of PDA.

Predisposing Factors to Ibuprofen Nephrotoxicity

Reported predisposing factors for NSAIDs-associated nephrotoxicity in the newborn include very low birth weight, dose regimens, genetic factors, and concomitant use of drugs such as aminoglycosides.

The immature neonatal kidney is considered a prostaglandin-dependent organ because of its susceptibility to a transient lack of prostaglandins. Thus, very low birth weight infants and, even more so, extremely low birth weight infants are categories of newborns at particularly high risk for ibuprofen-induced acute kidney injury.

Currently, a recommended dose regimen of intravenous ibuprofen is 10-5-5 mg/kg at 24-hour intervals. In terms of efficacy and safety,

the administration of a fixed dose of ibuprofen (or indomethacin) to the newborn regardless of the gestational and/or postnatal age is a paradox, overlooking specific clearance rates and distribution volume based on the age of the infants. A recent study has suggested that a higher dosing (20-10-10 mg/kg) of ibuprofen may result in higher rates of ductal closure, even though it is associated with increased risk of oliguria and renal complications²⁵. It must be underlined that these results have been found in a small study population, and have not yet been validated. Furthermore, plasma levels of ibuprofen need to be monitored if this dosing scheme is used. Thus, numerous issues pertaining to the pharmacokinetics/pharmacodynamics of these drugs, when used during the neonatal period, remain to be clarified^{25,26}.

There are two ibuprofen enantiomers, characterized by different half-lives ($T_{1/2}$ = 25 hours for enantiomer S; $T_{1/2}$ = 10 hours for enantiomer R), efficacy and probably toxicity at the level of different organ systems, including the kidney. In particular, the nephrotoxicity induced by ibuprofen enantiomers needs to be further investigated²⁷.

The influence produced by genetic polymorphism on the metabolism of the drugs influencing the cytochrome P450 2C9 has been well documented, revealing the presence of extensive metabolizers and poor metabolizers. Moreover, the cytochrome P450 2C9 may have a progressive expression since birth and/or could be influenced (inhibited or induced) by the coadministration of drugs^{18,28}. Coadministration of aminoglycosides and NSAIDs can worsen the outcome of nephrotoxicity. Aminoglycoside nephrotoxicity often manifests as nonoliguric acute renal failure and tubular dysfunction, whereas NSAID-induced nephrotoxicity may present as an abrupt reduction in renal function, and particularly as a reduction in glomerular filtration rate. The risk of drug interactions between aminoglycosides and NSAIDs appears to be more pronounced in young children than in neonates and infants. This can be partly explained by the enhanced renal clearance rate in the former category of subjects¹⁸, such that high levels of both drugs are frequently delivered to the proximal tubule and the glomerulus²⁹.

Retrospective calculations of the pharmacokinetics of amikacin in 73 preterm infants of <31 weeks' gestation who received either placebo or ibuprofen-lysine showed that the median serum half-life of amikacin was significantly longer (16.4 vs. 12.4; $p < 0.02$), and amikacin clearance was significantly lower (0.36 vs. 0.6 ml/kg/min; $p < 0.005$) in infants who received ibuprofen-lysine³⁰. These observations agree with other data obtained by the same authors, and demonstrate that ibuprofen reduces the clearance of amikacin and vancomycin. Considering that amikacin is eliminated almost exclusively by glomerular filtration, a decrease in its clearance means a decrease in the glomerular filtration rate^{31,32}. This effect has been found to be independent of gestational age in preterm infants of 24-34 weeks' gestation on respiratory support³³.

Ibuprofen Nephrotoxic Effects

As compared with indomethacin, ibuprofen has been shown to be significantly less likely to induce oliguria and to increase serum creatinine when used for closure of PDA⁷. The latter finding is in agreement with the results of our retrospective study in which the efficacy and renal tolerability of ibuprofen and indomethacin were compared in preterm infants affected by PDA³⁴.

A recent review and metaanalysis found that ibuprofen was as effective as indomethacin in closing PDA, while no significant differences were observed in the incidence of complications except for less renal impairment with ibuprofen³⁵. In the opinion of other authors³⁶, sufficient evidence indicates that the currently proposed dosing regimen of ibuprofen has an efficacy similar to that of indomethacin but shows a better renal tolerability when employed for the treatment of established PDA in premature infants³⁶.

Recently, Hammerman et al.³⁷ have shown that the treatment of a PDA with continuous indomethacin has effects similar to those of ibuprofen on urine output, renal function and blood flow velocities in the renal, superior mesenteric and anterior cerebral arteries. Similar results after intravenous or oral administration of ibuprofen have been reported, although the latter associated with fewer adverse effects was shown in a prospective,

randomized, single-masked pilot study. The efficacy and tolerability of oral ibuprofen were compared with those of intravenous ibuprofen for early closure of PDA in very low birth weight infants. During the week following the treatment, oliguria developed in none of 32 patients treated with oral ibuprofen, and in 3 of 32 newborns treated with intravenous ibuprofen ($p < 0.23$). These findings suggest a good safety profile of ibuprofen³⁸.

In contrast, the renal safety of intravenous or oral ibuprofen was not confirmed by other studies. Renal and urinary disorders (oliguria, fluid retention and hematuria) are considered common (1-10%) by Keady and Grosso³⁹ during ibuprofen treatment. Three hundred and nine cases of NSAID-associated renal adverse events (acute renal failure in 80% of cases) were reported to the French Pharmacovigilance system from January 1995 to December 2002, including 275 adults, 29 children, and only 5 newborns⁴⁰, which addressed several limitations to reaching conclusions because of the low number of babies. In a study conducted in a Brazilian neonatal intensive care unit (NICU), PDA was found in 29 newborns (26.8%), of which 17 (58.6%) received one course of oral ibuprofen, 8 (27.6%) received two courses, and 4 (13.8%) were treated with three courses. The rate of ductal closure was 96.5%. Despite the elevated efficacy of the drug, 19 (65.5%) neonates developed acute renal failure, even though renal function normalized in all cases⁴¹. Moreover, two severe cases of acute renal failure have been reported recently in preterm infants treated with oral ibuprofen^{42,43}.

The adverse effects of postnatal ibuprofen on renal function have been confirmed from the results of a multivariate logistic analysis of the risk factors for acute renal failure conducted in preterm infants. These effects are more frequent in very low birth weight infants, in whom NSAIDs are more commonly used⁴⁴. Further information about NSAID nephrotoxicity may be obtained by using new suitable biomarkers of glomerular filtration such as cystatin C^{45,46}. Although this biomarker did seem promising to evaluate glomerular clearance in preterm infants until a few years ago, its poor correlation to plasma creatinine in preterm infants did not enable its extensive use⁴⁷.

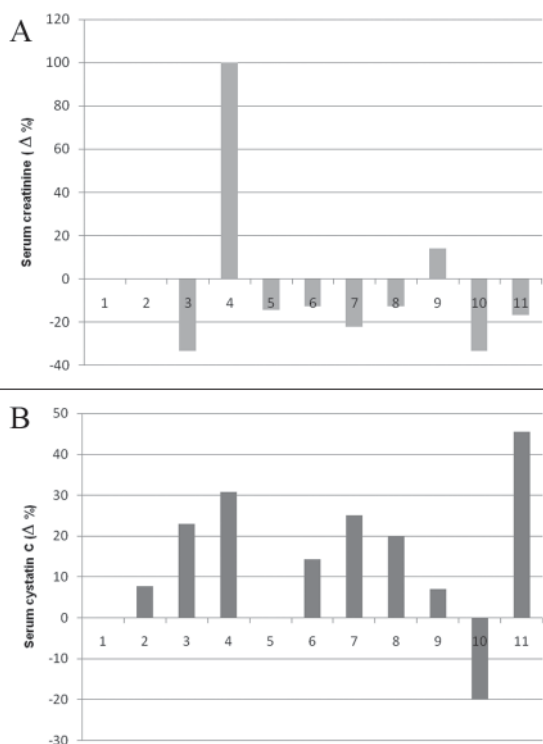


Fig. 1-A and 1-B: Effects of a conventional treatment with ibuprofen on serum levels of creatinine and cystatin C in 11 preterm infants with significant patent ductus arteriosus. For each patient, the ibuprofen-induced changes in both biomarkers are expressed as percentage variations ($\Delta\%$).

Our unpublished preliminary data support a significant influence of ibuprofen treatment on serum levels of cystatin C during the so called "blind-creatinine period". Figures 1-a and 1-b show the changes (percentage variations from baseline values) in serum levels of creatinine and cystatin C, which were found in 11 preterm infants treated with ibuprofen for a significant PDA. Of note, ibuprofen treatment induced a significant increase (mean $\Delta\% = 13.9\%$) in serum levels of cystatin C while, in the same time interval, serum creatinine was unchanged (mean $\Delta\% = -2.8\%$). These findings suggest that ibuprofen may alter the glomerular filtration even if the serum creatinine is unchanged. Other alterations following ibuprofen and indomethacin administration include a decrease in endothelin-1 and arginine vasopressin along with a reduction in urinary sodium excretion and fractional excretion of sodium⁴⁸⁻⁵⁰. Taken together, these observations cast doubt on the renal tolerability of ibuprofen.

Concerns about the renal safety of ibuprofen are further supported by animal studies. In newborn rabbits, the administration of ibuprofen (ibuprofen-lysine) or other NSAIDs (aspirin and indomethacin) has been found to induce intense renal vasoconstriction resulting in impaired renal function⁵¹. In a neonatal rat model, renal changes following the administration of indomethacin, ibuprofen and gentamicin were investigated by light and electron microscopy. In this experimental model, all three drugs caused significant glomerular and tubular injuries⁵². As noted by Guignard and Gouyon⁵³, “differences in the renal side effects of ibuprofen and indomethacin, if they exist, may depend on the ratio of their respective activities on the two cyclooxygenase isoenzymes COX-1 and COX-2, indomethacin inhibiting COX-1 more than COX-2”.

In pharmacological research, the half maximal (50%) inhibitory concentration (IC) of a drug, which is termed as IC₅₀, is commonly used as a measure of antagonist drug potency. The selectivity of a NSAID for inhibition of COX-1 is expressed as the ratio of IC₅₀ for COX-2/COX-1. In particular, indomethacin IC₅₀ for COX-2/COX-1 ratio is approximately 60 compared with 15 for ibuprofen. Furthermore, indomethacin inhibits COX-1 activity by binding to its active site while ibuprofen inhibits COX by substrate competition with arachidonic acid, and therefore its potency is dependent on enzyme concentrations^{54,55}.

An experimental study by Hasan et al.⁵⁶ examined the hypothesis that the early administration of postnatal ibuprofen has less adverse effects on neonatal rat renal prostanoids, COX-2 expression and angiotensin II compared with indomethacin. Newborn rats were treated with injections of human therapeutic doses of ibuprofen or indomethacin on the first three days of life. The results of this study demonstrated that indomethacin has more potent suppressive effects on renal COX-2 and vasodilator prostanoids, which are important regulators of renal development and function. These sustained effects of early postnatal administration of indomethacin may partly explain the greater severity of its adverse renal effects compared to those of ibuprofen⁵⁶.

Very recently, the use of urinary biomarkers has been widely proposed for the early diagnosis of acute kidney injury in clinical settings⁵⁷⁻⁶¹. The measurement of urinary PGE₂ as an index of renal synthesis of this primary prostaglandin has been shown to represent a non-invasive and sensitive method of investigating the homeostatic function of the kidney in early life under both physiological and pathological conditions²². We recently investigated changes in urinary PGE₂ after ibuprofen treatment in preterm infants with PDA. Twenty preterm infants with a hemodynamically significant PDA (gestational age, 28.6±2.3 weeks) and 20 controls (gestational age, 30.4±1.5 weeks) were prospectively enrolled at 48–72 hours (h) of life. After enrollment, the former underwent conventional ibuprofen-lysine treatment. At 48–72 h (T₀) and 108–144 h of life (T₁), urine samples were non-invasively collected in both groups to measure urinary PGE₂ concentrations, and renal function was investigated. Urinary PGE₂ decreased significantly both in the ibuprofen-treated patients (66.95±16.78 vs. 27.15±17.92 pg/ml, p<0.001) and in controls (71.7±16.2 vs. 53.2±18.4 pg/ml, p<0.001) from T₀ to T₁. However, urinary PGE₂ at T₁ was significantly lower (p<0.001) in the ibuprofen group compared to the control group. Acute renal failure occurred in three ibuprofen-treated patients (15%). These findings indicate that ibuprofen markedly reduces (59.4%) urinary PGE₂ and may alter renal function in the newborn⁶². The measurement of urinary PGE₂ in premature infants might constitute a novel approach for the prevention and early detection of NSAID-induced nephrotoxicity. In particular, close attention should be given to the following situations: a) low urinary PGE₂ values (<35 pg/ml) before ibuprofen treatment; b) PGE₂ values rapidly decreasing during ibuprofen treatment; and c) very low urinary PGE₂ values (<5 pg/ml) during and/or after ibuprofen treatment. In the first case, the choice to treat or not to treat should be carefully weighed against the potential harms. In the second case, the decision to continue with a second or third dose should be reconsidered. In the third case, significant adverse renal effects should be expected.

The current knowledge on the long-term renal effects of neonatal exposure to NSAIDs is scarce and restricted to indomethacin. Preterm

infants perinatally exposed to indomethacin, examined at the age of 2-4 years, showed no long-term effects on renal growth, structure or function⁶³. Moreover, continuous slow infusion of indomethacin showed similar benefits to ibuprofen without safety concerns in its effect on urine output, renal function and blood flow velocities in the renal arteries⁶⁴. Larger prospective studies are required to confirm these observations and to investigate long-term renal effects of ibuprofen treatment

Conclusions

Ibuprofen is considered less nephrotoxic than indomethacin, but it may not be exempt from causing adverse renal effects, especially under conditions in which renal prostaglandin activation is maximal in an attempt to balance angiotensin II activity. In particular, close attention must be paid to the administration of ibuprofen in the more premature infants early after birth.

In the opinion of the authors, the determination of urinary PGE₂ could be routinely employed in the near future for the prevention and early detection of NSAID renal toxicity. This urinary biomarker may represent a helpful, economical tool aimed at achieving an individually tailored pharmacological treatment and at improving the prevention strategies of iatrogenic damage in early life. In the future, the use of a panel of serum and urinary biomarkers will probably be the best strategy for an early and accurate detection of the NSAID-induced nephrotoxicity.

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