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Changes in urinary PGE₂ after ibuprofen treatment in preterm infants with patent ductus arteriosus

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Abstract

Purpose To investigate changes in urinary PGE₂ after ibuprofen treatment in preterm infants with patent ductus arteriosus (PDA).

Methods 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 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 noninvasively collected in both groups to measure urinary PGE₂ concentrations (enzyme immunoassay method), and renal function was investigated.

Results Urinary PGE₂ decreased significantly both in 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%).

Conclusions Ibuprofen markedly reduces (59.4%) urinary PGE₂ and may alter renal function in the newborn.

Keywords Ibuprofen · Nonsteroidal anti-inflammatory drugs · Prostaglandin E₂ · Urine · Preterm infants · Patent ductus arteriosus

Introduction

The ductus arteriosus is a fetal blood vessel connecting the descending aorta to the pulmonary artery [1, 2]. In full-term infants, the ductus normally undergoes spontaneous closure within 24–48 h after delivery. However, in premature infants, the ductus commonly remains open for many days after birth. Accordingly, 70% of preterm infants born before 28 weeks of gestation require either medical or surgical closure of a patent ductus arteriosus (PDA) [3]. Ductal closure represents the main outcome of a successful treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) in the newborn [3], although this kind of treatment may cause renal damage, including acute renal failure with or without oliguria, relevant proteinuria, fluid metabolism alterations, and hyperkalemia [4].

Ibuprofen is a relatively weak cyclooxygenase inhibitor [5] with proven efficacy in closing the ductus arteriosus in newborns [6–8] without affecting renal hemodynamics [9]. A number of clinical studies in the newborn have suggested good renal safety of ibuprofen, when compared with indomethacin [6, 8–12].

However, renal safety of ibuprofen was not confirmed by other studies. The administration of this drug or other NSAIDs (aspirin and indomethacin) has been found to induce intense renal vasoconstriction resulting in impaired renal function in newborn rabbits [13]. Furthermore, a multivariate logistic analysis of the risk factors for acute renal failure (ARF) demonstrated that postnatal administra-

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tion of ibuprofen negatively affected renal function (odds ratio for ARF 4.4) in preterm infants [14]. This is more frequent in very low birth weight infants, in whom NSAIDs are more commonly used [14]. Finally, a severe case of ARF has been recently reported in a preterm infant treated with oral ibuprofen [15].

The nephrotoxic effects of NSAIDs are related to their mechanism of action, namely the block of prostaglandin synthesis through the inhibition of cyclooxygenase [16]. Prostaglandin E₂ (PGE₂) is the main prostanoid synthesized along the nephron [17], with the renal medullary interstitial cells and collecting tubules as major sites of production [18]. This prostanoid modulates intrarenal vascular tone and salt and water excretion [19], exerting a protective action against the high levels of vasoconstrictive angiotensin II [20]. The renal protective role played by the vasodilatory prostaglandins is particularly important during the neonatal period, when the immature kidney is perfused at very low perfusion pressure [13]. The immature neonatal kidney is considered a prostaglandin-dependent organ because of its susceptibility to a transient lack of prostaglandins [21, 22].

Urinary excretion of PGE₂ predominantly reflects the renal origin of this mediator [23, 24]. Accordingly, measurement of urinary PGE₂ excretion as an index of renal synthesis of this prostaglandin may represent a noninvasive and sensitive method to investigate the homeostatic function of the kidney in early life [25, 26].

Unfortunately, neonatal clinical studies investigating pharmacokinetics and pharmacodynamics of ibuprofen using appropriate biomarkers for *in vivo* prostaglandin synthesis are almost completely missing in the literature.

The aim of this prospective study was to evaluate the influence of ibuprofen treatment on urinary PGE₂ excretion in preterm infants with PDA, and to verify whether ibuprofen-induced changes in urinary PGE₂ are related to efficacy and/or nephrotoxicity of this pharmacological agent.

Methods

Study population

All preterm infants with gestational ages less than 33 weeks admitted at birth to the Neonatal Intensive Care Unit (NICU) at the University of Cagliari (Italy) and alive at 48–72 h after birth were eligible. This prospective, observational study was designed to enroll 20 consecutive preterm infants treated with ibuprofen for PDA (case group), and 20 consecutive preterm infants without PDA (control group) from an established starting point. In order to obtain a control group that was as comparable as possible to the case group, the same upper limit of gestational age at birth was

chosen for both groups, since the anatomic and functional characteristics of preterm infants are mainly affected by this variable. No other selection criteria were used for controls.

Exclusion criteria were severe perinatal asphyxia (defined as a 5-min Apgar score <4), major congenital malformations, fetal hydrops, congenital nephropathies and uropathies, acute renal failure (defined as serum creatinine values ≥ 1.3 mg/dl at 48–72 h of life), persistent pulmonary hypertension, and intraventricular hemorrhage.

For each newborn infant, we recorded the major demographic and clinical data as well as any factor potentially influencing renal function, particularly drug treatments.

Before starting ibuprofen, all parents of newborns with significant PDA were informed of this pathological condition, of the conventional ibuprofen treatment, and of the need for monitoring the safety of this drug because of its potential side effects.

As the study did not involve any intervention apart from the usual medical procedures, and confidentiality and anonymity of the subjects were maintained, ethics approval was not required.

Cardiac evaluation

The reliable early diagnosis of a PDA in preterm infants is based on echocardiography, considering that clinical signs are poor for detecting a significant PDA in the first 4 days of life [27]. Evaluation of the hemodynamic impact of ductal shunting is a crucial issue in the echocardiographic diagnosis of PDA in order to determine the need to prescribe pharmacological treatment.

All eligible infants underwent two-dimensional echocardiography, supplemented with Doppler and color Doppler imaging performed by a skilled pediatric cardiologist at 48–72 h of life. The criteria for hemodynamically significant PDA were ductal diameter of >1.4 mm, left atrial-to-aortic root ratio of >1.3:1 and retrograde diastolic flow in the descending aorta exceeding 30% of the antegrade flow.

Treatment protocol

Eligible preterm infants with echocardiographic evidence of a hemodynamically significant PDA at 48–72 h of life (case group) received three doses of ibuprofen (a first dose of 10 mg/kg, followed by two doses of 5 mg/kg each, after 24 and 48 h). The medication was infused continuously over a period of 15 min. Ibuprofen was carefully prepared for intravenous use from a commercially available product for parenteral administration (Arfen, Lisapharma, Erba, Italy), delivered in vials containing 400 mg of dry, sterile powder of ibuprofen lysine.

Newborns failing to respond to the first course of ibuprofen therapy were treated with a second course of

ibuprofen. In the case of unresponsiveness to the second course, the protocol established a rescue treatment with three intravenous doses of indomethacin (0.2 mg/kg of body weight, given at 12-h intervals). If PDA was also refractory to indomethacin, cardiological and clinical conditions of the newborn were closely monitored to decide if and when to perform surgical ligation of ductus arteriosus.

Eligible preterm infants who had no echocardiographic evidence of a PDA at 48–72 h of life (control group) did not receive any NSAID treatment.

Concomitant treatment including respiratory support, therapy with surfactant, and blood transfusion was carried out as needed.

Standard daily fluid intakes for enrolled preterm infants were as follows: 60–70 mL/kg on day 1; 70–80 mL/kg on day 2; 80–90 mL/kg on day 3; 100 mL/kg on day 4; 120 mL/kg on day 5; 140 mL/kg on day 6; 150 mL/kg on day 7. Additionally, fluid intakes were individually modified when necessary.

Samples

Blood and urine samples were collected at 48–72 h (T_0) and 108–144 h of life (T_1), namely just before and 12–24 h after ibuprofen treatment.

Urine samples were collected using a previously validated, noninvasive method based on the use of a cotton wool ball [28] and stored at -80° until analysis. In our institution, urine collection through this method is routinely used to measure urine output, without any hazard or side effect to the baby.

No extra procedures (e.g., extra blood samples) were carried out for the purposes of this study.

Clinical and instrumental monitoring

All infants enrolled in the present study were carefully monitored from a clinical viewpoint to detect potential harmful side effects of ibuprofen treatment. Echocardiographic examinations were systematically performed by a skilled pediatric cardiologist to monitor PDA over time. Each newborn underwent serial cranial ultrasound examinations from birth to discharge, in order to detect brain lesions. During the first week of life, renal function was monitored in all patients by using diuresis quantification and serum creatinine determination as recommended for very preterm infants, and particularly for those receiving potentially nephrotoxic drugs.

In the neonate, noninvasive quantification of diuresis is very difficult to obtain. The method of urine collection we used was chosen for ethical reasons in that it is easy and nontraumatic, even though it does not guarantee an accurate quantification of the total volume of urine. For the purposes

of this study, patients were classified as oliguric (diuresis $<1.0 \text{ mL kg}^{-1} \text{ h}^{-1}$) or nonoliguric (diuresis $\geq 1.0 \text{ mL kg}^{-1} \text{ h}^{-1}$) on the basis of a semiquantitative evaluation of diuresis at both time points.

In all eligible patients, serum creatinine was measured by Jaffe's method first at 48–72 h of life (T_0); all newborns with serum creatinine values $\geq 1.3 \text{ mg/L}$ (ARF) at this time point were excluded from the study. Serum creatinine concentration at T_0 was also used as pretreatment value in the preterm infants who received ibuprofen to induce ductal closure. A second measurement of serum creatinine was performed in both case and control groups at 108–144 h of life (T_1) to investigate possible variations in renal function over time, whether induced by ibuprofen treatment or not. Serum creatinine values $\geq 1.3 \text{ mg/L}$ at T_1 were considered indicative of ARF.

Moreover, we measured the urinary concentration of PGE_2 as an early biomarker of NSAID-induced nephrotoxicity at T_0 and T_1 .

PGE_2 assay

Urine samples were analyzed for PGE_2 using a commercially available kit (Cayman Chem, Ann Arbor, MI, USA). Due to the rapid metabolism of PGE_2 in vivo, concentrations detected in urine are very low: a more accurate index of PGE_2 biosynthesis and excretion is obtained by converting PGE_2 to a single, stable derivative (prostaglandin E metabolite, PGEM) easily quantifiable by an enzyme immunoassay (EIA) procedure. Briefly, the assay is based on the competition between free PGEM and a PGEM-acetylcholinesterase conjugate (PGEM tracer) for a limited number of PGEM-specific rabbit antiserum binding sites; the amount of tracer binding to rabbit antiserum will be inversely proportional to the concentration of PGEM in the well. This rabbit antiserum-PGEM (either free or tracer) complex binds to the mouse monoclonal anti-rabbit antibody previously attached to the well. The plate is washed to remove any unbound reagent and Ellman's reagent (which contains the substrate to acetylcholinesterase) is added to the well. The product of this enzymatic reaction has a distinct yellow color and absorbs strongly at 412 nm. The intensity of the color, determined spectrophotometrically, is proportional to the amount of PGEM tracer bound to the well, which is inversely proportional to the amount of free PGEM present in the well during incubation. Urinary excretion rates of PGE_2 were expressed as picograms per milliliter. Sensitivity of the assay was 2 pg/mL.

Statistics

Paired *t*-test, unpaired *t*-test (for continuous variables), and chi-square test (for categorical variables) were used as

Table 1 Main demographic and clinical characteristics of the study population

	Study population (<i>n</i> =40)	Ibuprofen group (<i>n</i> =20)	Control group (<i>n</i> =20)	<i>P</i> value
Sex (M/F)	17/23	9/11	8/12	NS ^a
Gestational age (weeks)	29.5±2.1	28.6±2.3	30.4±1.5	0.006 ^b
Birth weight (g)	1,305±465	1,142±356	1,469±510	0.024 ^b
Small-for-gestational-age infants	7 (17.5%)	3 (15%)	4 (20%)	NS ^a
5-min Apgar score	7.4±1.8	7.5±1.6	7.2±2.0	NS ^b
Respiratory distress syndrome	29 (72.5%)	19 (95.0%)	10 (50.0%)	0.005 ^a
Mechanical ventilation	27 (67.5%)	18 (90%)	9 (45%)	0.007 ^a

Values are mean ± standard deviation or number of study participants with percentage *in parenthesis*

^a Comparison of two proportions

^b Unpaired *t*-test

appropriate for analysis. A *P* value <0.05 was considered as statistically significant.

Results

Twenty preterm infants with a significant PDA, and 20 without echocardiographic evidence of PDA (control group) were prospectively enrolled over an 18-month period. The main demographic and clinical characteristics of the study population are illustrated in Table 1. Compared to the control group, neonates treated with ibuprofen were characterized by a significantly lower mean gestational age and birth weight, in addition to a significantly higher incidence of respiratory distress syndrome (RDS) and need for mechanical ventilation.

Closure of the ductus arteriosus was observed in 12 out of 20 neonates (60%) treated with the first course of ibuprofen, and the same result was achieved in 2 infants (10%) following the second course of treatment. Therefore, ibuprofen was effective in a total of 14 out of 20 (70%) cases. The six patients who did not respond to treatment were subsequently treated with indomethacin; the latter led to a satisfactory outcome in four patients. The two remaining patients who did not respond to drug treatment were closely monitored to assess evolution of PDA and its hemodynamic implications. On the basis of the monitoring findings, PDA was treated surgically in one infant (case 6), while the other infant (case 5) manifested spontaneous ductal closure 25 days after drug withdrawal.

Urinary PGE₂ concentrations detected in the two study groups are shown in Figs. 1 and 2. Nineteen out of 20 infants (95%) exposed to ibuprofen manifested a marked decrease (*P*<0.001) in urinary PGE₂ from T₀ to T₁. Moreover, in nine, particularly low urinary concentrations (<20 pg/mL) were achieved. Similarly, throughout the same time interval, patients included in the control group presented a statistically significant (*P*<0.001) decrease in urinary PGE₂ concentrations (Fig. 2). However, urinary

PGE₂ concentrations at T₁ were significantly lower (*P*<0.001) in the ibuprofen-treated group than in controls (Table 2).

The ibuprofen-treated group of neonates was subsequently divided into two subgroups according to the clinical response manifested during the first course of treatment: responders (*n*=12) and nonresponders (*n*=8). No statistically significant differences were observed between responders and nonresponders as regards gestational age (mean±SD, 29±2.4 vs. 28±2 weeks) and birth weight (1,161±404 vs. 1,114±294 g). The decrease in urinary PGE₂ concentrations in both subgroups between time points T₀ and T₁ was highly significant (*P*<0.001). A comparison of the urinary PGE₂ concentrations reported for the two subgroups revealed no statistically significant differences for either time T₀ (61.2±14.2 vs. 75.6±17.5 pg/mL) or time T₁ (28.8±21.3 vs. 24.6±12.2 pg/mL). Figure 3 illustrates the percentage variation (Δ%) in urinary PGE₂ concentration throughout the time interval T₀ to T₁ in the 20 infants treated with ibuprofen.

In addition to urinary PGE₂ concentrations, serum creatinine levels, indicative of renal function, were measured in all patients (Table 2). In the time interval T₀ to T₁, creatinine levels remained unchanged in the ibuprofen-treated group but significantly decreased (*P*<0.001) in the control group. Moreover, no significant differences in

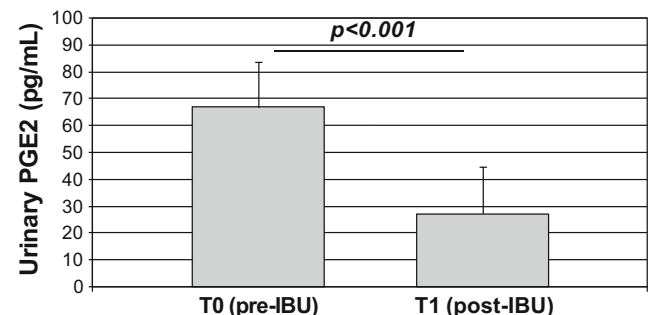


Fig. 1 Mean concentrations (+SD) of urinary PGE₂ measured in ibuprofen-treated infants (*n*=20) at times T₀ and T₁

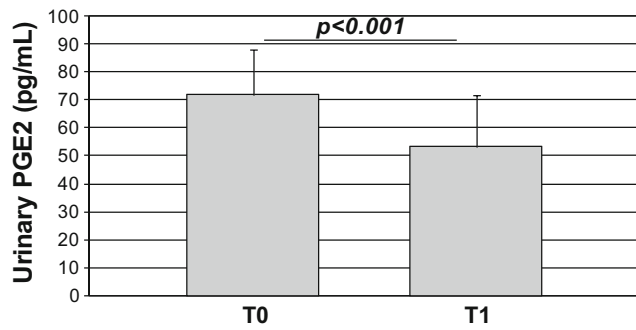


Fig. 2 Mean concentrations (+SD) of urinary PGE₂ measured in the control group (*n*=20) at times T₀ and T₁

creatinine levels were observed between the two groups either at time T₀ or at time T₁.

Oliguria (diuresis <math>< 1.0 \text{ mL kg}^{-1} \text{ h}^{-1}</math>) was not found in any patient at T₀, while it was present in the three ibuprofen-treated patients who developed ARF at T₁.

The main clinical outcomes observed in our sample are reported in Table 3. No significant differences were found between the two groups as regards mortality and incidence of acute renal failure, necrotizing enterocolitis/intestinal perforation, periventricular/intraventricular hemorrhage, and periventricular leukomalacia. These outcomes were recorded in seven premature newborns, five from the ibuprofen-treated group and two controls. Compared to the remaining 33 subjects enrolled in the study, these 7 infants featured a significantly lower gestational age (27.3 ± 1.9 vs. 29.9 ± 1.9 weeks, $P=0.002$) and birth weight (976 ± 295 vs. $1,375 \pm 467$ g, $P=0.037$).

Furthermore, we attempted to determine whether an association was manifested between the changes observed in urinary PGE₂ concentrations and the occurrence of clinically relevant outcomes. The examination of patients treated with ibuprofen revealed that the highest reductions in prostanoid levels were associated with the occurrence of ARF. The three ibuprofen-treated subjects who developed

Table 2 Concentrations of urinary PGE₂ and serum creatinine measured at times T₀ and T₁ in the group of ibuprofen-treated preterm infants and in the control group

Parameter	Ibuprofen group (<i>n</i> =20)	Control group (<i>n</i> =20)	<i>P</i> value
Urinary PGE ₂ (pg/mL) at T ₀	67 ± 16.8	71.7 ± 16.2	NS ^a
Urinary PGE ₂ (pg/mL) at T ₁	27.2 ± 17.9	53.2 ± 18.4	<math>< 0.001^a</math>
Serum creatinine (mg/dL) at T ₀	0.92 ± 0.22	0.92 ± 0.20	NS ^a
Serum creatinine (mg/dL) at T ₁	0.92 ± 0.35	0.81 ± 0.17	NS ^a

^a Unpaired *t*-test

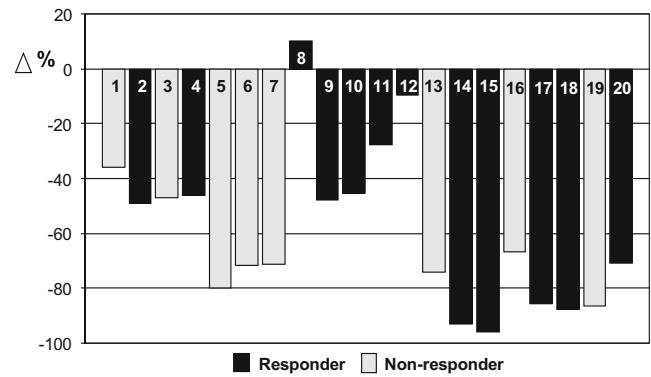


Fig. 3 Percentage variation ($\Delta\%$) in urinary PGE₂ concentration for each of the 20 ibuprofen-treated infants in the time interval T₀ to T₁. Responder indicates those responding to first course of ibuprofen. Nonresponder indicates those with no response to first course of ibuprofen

ARF showed a dramatic reduction in urinary PGE₂ concentrations, which decreased from 89 to 18 pg/mL (79.8% decrease, case 5), from 60 to 17 pg/mL (71.7% decrease, case 6), and from 35 to 1.5 pg/mL (95.7% decrease, case 15) (Fig. 3).

Interestingly, necrotizing enterocolitis/intestinal perforation manifested concomitantly with ARF in two neonates treated with ibuprofen (cases 6 and 15). This intestinal complication occurred also in two controls, who showed only a modest reduction in urinary PGE₂ (7.3 and 17.7%, respectively) from T₀ to T₁.

In one subject (case 14) affected by periventricular/intraventricular hemorrhage, urinary PGE₂ concentrations decreased from 65 to 4.5 pg/mL, a reduction of 93% (Fig. 3).

The two deceased patients (cases 1 and 6), both nonresponders to ibuprofen treatment (Fig. 3), were born prematurely after a gestation of 27 and 24 weeks, respectively. The first neonate died at a post-natal age of 11 days following severe RDS leading to untreatable respiratory failure. The second neonate died at a post-natal age of

Table 3 Clinical outcomes observed in the two study groups

Outcome	Ibuprofen group (<i>n</i> =20)	Control group (<i>n</i> =20)	<i>P</i> value ^a
In-hospital death	2 (10%)	0	NS
Acute renal failure	3 (15%)	0	NS
Necrotizing enterocolitis/intestinal perforation	2 (10%)	2 (10%)	NS
Periventricular/intraventricular hemorrhage	1 (5%)	0	NS
Periventricular leukomalacia	1 (5%)	0	NS

Values are number (%) of study participants

^a Comparison of two proportions

112 days following complications manifested subsequent to abdominal surgery.

Regarding pharmacological treatments, antibiotics were the only drugs other than ibuprofen that were given during the time period from birth to T_1 . In the case group, three patients were treated with one antibiotic (a third-generation cephalosporin in two patients; a glycopeptide in one patient), five patients received two antibiotics (a β -lactam antibiotic and an aminoglycoside in four patients; a third-generation cephalosporin and an aminoglycoside in one patient), and three patients received three antibiotics (a β -lactam antibiotic, a third-generation cephalosporin, and aztreonam in one patient; a β -lactam antibiotic, an aminoglycoside, and a glycopeptide in one patient; a β -lactam antibiotic, an aminoglycoside, and a third-generation cephalosporin in one patient); the remaining nine patients did not receive any drug other than ibuprofen. In the control group, two patients were treated with one antibiotic (an aminoglycoside), two patients received two antibiotics (a β -lactam antibiotic and an aminoglycoside), and the remaining sixteen patients did not receive any drug.

Discussion

The pharmacological treatment of PDA in preterm infants remains a widely controversial issue [29]. At the current state of knowledge, early pharmacological treatment of PDA with ibuprofen would appear to represent the most feasible therapeutic option [30]. Accordingly, the first step of our diagnostic-therapeutic protocol was implemented at an age of 48–72 h.

An overall 70% efficacy of ibuprofen treatment (two courses) in closing the ductus arteriosus was observed in our study. The majority (four out of six) of PDA patients not responding to two courses of ibuprofen presented a good response to rescue treatment with indomethacin. Thus, from our data the therapeutic strategy based on a sequential administration of the two NSAIDs produced a positive outcome in 90% of all PDA-treated cases, confirming the results of previous studies [10].

As regards the renal tolerability of ibuprofen, there are contrasting data. In fact, this drug has been shown to have a better renal tolerability compared to other NSAIDs (namely indomethacin) in newborn patients [30, 31], even though it is capable of inducing nephrotoxic damage. The side effects of ibuprofen on glomerular filtration rate (–20%) have been quantified in preterm infants on the basis of the pharmacokinetics of amikacin and vancomycin [32].

In our study the comparison between the two groups of patients highlighted an over-time discrepancy in serum creatinine behavior. The significant decrease in serum creatinine levels observed between T_0 and T_1 in the control

group seems to reflect a physiologic process of functional adaptation of the kidney to post-natal life in the preterm infant. In contrast, in the group of patients treated with ibuprofen, there was no decrease in serum creatinine levels from T_0 to T_1 , supporting the hypothesis of a nephrotoxic effect of the drug. The latter finding is in agreement with the results of a retrospective study by Fanos et al. [33] in which efficacy and renal tolerability of ibuprofen and indomethacin were compared in preterm infants affected by PDA. Moreover, elevations in serum creatinine levels indicative of acute renal failure were found in 3 out of 20 (15%) ibuprofen-treated neonates. Nonetheless, a complete and rapid normalizing of kidney function was subsequently achieved in all three patients. In contrast, serum creatinine levels remained within normal values in all neonates in the control group.

These data should be evaluated taking into account that serum creatinine is a late indicator of renal damage due to the so-called blind creatinine period, while urinary biomarkers may detect preclinical damage making it possible to prevent further injury to the kidney.

The great vulnerability of the neonatal kidney to drug-induced toxicity is ascribed mainly to its specific anatomic-functional characteristics, and particularly to its excretory and detoxifying role, its extensive capillary surface area, its high blood flow, and the high degree of specialization of tubular cells. The mechanism underlying NSAID nephrotoxicity likely involves an inhibition of renal prostaglandin synthesis leading to decreased renal perfusion and glomerular filtration rates [34].

The main aim of the present study was to evaluate whether and how a treatment with ibuprofen can affect urinary PGE_2 excretion in a population of preterm infants with PDA compared to a control group. To date, literature findings reporting reference values for urine PGE_2 concentrations in the newborn are somewhat lacking [35]. Recently, we reviewed the literature on this topic [26].

In the present study, the group of infants exposed to ibuprofen treatment showed a marked decrease (59.4%) in urinary PGE_2 concentrations during the time interval T_0 to T_1 , underlining the strong inhibition exerted by the drug on renal synthesis of PGE_2 . In the same time interval, the control group also displayed a statistically significant, although less marked, decrease in urinary PGE_2 concentrations. The latter “physiological” decrease may result from the rapid alteration of balance between chemical vasodilators (PGE_2 , NO, and others) and vasoconstrictors (angiotensin II, catecholamines, and others) in the immature kidney during the phase of adaptation to extra-uterine life. The significantly lower urinary PGE_2 concentrations observed at T_1 in subjects exposed to ibuprofen compared to controls provide a confirmation of the drug-induced inhibition of physiological PGE_2 production by the kidney.

Briefly, ibuprofen treatment administered during the first few days of life produces a decrease in PGE₂ synthesis by the immature kidney, enhancing the physiological reduction in urinary excretion of this prostanoid during the phase of adaptation to extra-uterine life. Thus, if on the one hand PGE₂ inhibition produces a beneficial effect in eliciting the closure of ductus arteriosus, on the other hand it features disadvantages, including the risk of nephrotoxic effects.

It is noteworthy that both responders ($n=12$) and nonresponders ($n=8$) manifested similar pre- and post-treatment urinary levels of PGE₂ and a marked, significant decrease in urinary concentrations of this prostanoid over the time interval T₀ to T₁. This finding suggests that there is no relationship between urinary PGE₂ excretion and clinical efficacy of ibuprofen, which might be explained by the different modulation of ibuprofen action in each target organ, or by the involvement of other vasoactive chemical mediators (e.g., NO) in the process of ductal closure.

Our findings should be interpreted with caution in the light of some limitations of the study. The size of the study population was relatively small, due to the difficulty in recruiting sufficient numbers of preterm infants of low gestational age in an acceptable period of time. Additionally, more information on the mechanisms underlying the renal effects of ibuprofen could have been obtained by studying the pharmacokinetics of the drug and investigating the renin-angiotensin system in our patients. However, these investigations would have required a more invasive approach for the small babies, in contrast with our approach which was aimed at evaluating a reliable noninvasive way of monitoring ibuprofen nephrotoxicity. As regards the study design, concerns might be raised about the enrollment criteria of the control group. In fact, significant differences in gestational age, birth weight, rate of RDS, and need for mechanical ventilation were found between the two groups. However, this methodological problem is hardly avoidable in clinical studies investigating the neonatal pathological conditions strongly related to prematurity such as RDS and PDA.

Definitive conclusions cannot be drawn about the relationship between reduction in urinary PGE₂ levels and occurrence of ibuprofen-induced nephrotoxicity, due to the limitations of the present study. However, the dramatic decrease in the urinary levels of PGE₂ observed in the 3 out of 20 (15%) ibuprofen-treated neonates who developed ARF suggests that this prostanoid may play a crucial role in maintaining normal renal function in early life.

Finally, concerns have been raised about the long-term renal effects of neonatal exposure to COX-inhibitors. At present, there are no data concerning ibuprofen treatment, even though preterm infants perinatally exposed to indomethacin have not shown long-term effects on renal growth, structure, or function [36]. Nevertheless, the

possibility that ibuprofen administration to neonates may induce long-term renal adverse effects cannot be ruled out considering the recent observation that an ARF, although only transient, could inhibit post-natal glomerulogenesis in extremely preterm infants [37].

Conclusions

Data reported in the literature indicate ibuprofen as an effective drug for use in the closure of PDA, displaying a lower, but not negligible, degree of renal toxicity compared to other NSAIDs.

In our study population, the renal safety of ibuprofen was evaluated by the simultaneous determination of serum creatinine concentration and urinary PGE₂. To our knowledge, this study is the first on this topic. In particular, the measurement of urinary PGE₂ in the premature infant was found to be helpful and might constitute a novel approach for the early detection of NSAID-induced nephrotoxicity. However, larger prospective studies are required to confirm these preliminary data and to investigate long-term renal effects of ibuprofen treatment.

In the future, the determination of urinary PGE₂ might also be employed for new clinical applications such as the detection of the phenotype underlying NSAID renal toxicity, thereby constituting a helpful, economical tool aimed at achieving a tailored treatment, as an alternative to other innovative technologies such as pharmacogenomics and metabonomics.

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