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ORIGINAL ARTICLE

Ibuprofen in very preterm infants impairs renal function for the first month of life

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Abstract We carried out a study aiming to determine the renal effect of ibuprofen treatment for patent ductus arteriosus (PDA) in very preterm infants during the first month of life. Infants aged 27−31 weeks gestation were enrolled from October 2004 to August 2006. They were assigned to two different groups according to ibuprofen exposure during care of their PDA status assessed by echocardiography. Infants of both groups were matched based on gestational age, Clinical Risk Index for Babies score, birth weight and inclusion center. Renal function was evaluated at baseline and weekly for 1 month. One hundred and forty-eight infants were enrolled. Glomerular filtration rate (GFR) was significantly decreased in the ibuprofen group after treatment withdrawal (GFR on day 7, ibuprofen versus no ibuprofen: 12.8±6.2 vs. 18.1±12.1 ml/min/1.73 m^2; $P<0.001$). Adjusted analysis proved this decrease to be sustained during the first month of life. Tubular function was also impaired during the first month in ibuprofen-treated infants. Ibuprofen administered for PDA is associated with a decreased GFR during the first month of life. Renal function of infants receiving ibuprofen should be carefully monitored and drugs that are eliminated by glomerular filtration handled cautiously during this period.

Keywords Ibuprofen · Renal impairment · Very low birth weight · Patent ductus arteriosus · Neonates

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Introduction

Patent ductus arteriosus (PDA) is frequent in very preterm infants. Medical treatment with non-steroidal anti-inflammatory drugs [1–3] is largely spread for PDA closure to avoid increased morbidity due to hemodynamic changes and cardiovascular instability induced by PDA [4–6]. Yet, if ibuprofen is administered in this indication in neonatal intensive care units, some questions remain controversial.

Ibuprofen has fewer side effects than the previously used indomethacin, particularly on glomerular filtration rate (GFR) [7, 8]. Yet, if some studies did not show any renal side effect of this drug [9] and others determined renal alteration to precede ibuprofen treatment [10], expanded use of ibuprofen has highlighted its possible renal impact

during treatment or immediately after treatment withdrawal, with decreased urine output and/or increased serum creatinine [11–13]. These studies did not focus on the renal side effects of ibuprofen as primary outcome, and some of them used prophylactic ibuprofen, which has proven to be potentially harmful for preterm infants. Thus, information on the amplitude and duration of these renal side effects is still lacking. The importance in GFR reduction during treatment is evidenced by a 21% reduction in amikacin clearance demonstrated after ibuprofen treatment [14]. Moreover, a recent meta-analysis, focusing on indomethacin−ibuprofen comparison, confirmed these data and emphasized the lower serum creatinine levels and lower incidence of decreased urine output after treatment with ibuprofen in comparison with indomethacin [15]. Nevertheless, some publications still specify that ibuprofen renal side effects remain an issue [16, 17].

We conducted a multicenter clinical controlled trial with very preterm infants receiving ibuprofen for PDA treatment compared with matched preterm infants not receiving ibuprofen (ductus arteriosus not requiring treatment). Our goal was to confirm the magnitude of GFR reduction on day 7 and to determine whether this reduction in GFR may last during the first month of life and also be associated with tubular function impairment.

Methods

This multicenter clinical trial was organized in three academic perinatal centers in France and approved by the ethics committee (Comité de Protection des Personnes de Lorraine). The study was registered with ClinicalTrials.gov registry (Number: NCT00217191) (www.clinicaltrials.gov) and was funded by the French National Hospital Clinical Research Program (PHRC 17-6, year 2004).

Selection criteria

Eligibility criteria were gestation at delivery between 27 weeks 0 days and 31 weeks 6 days, and written informed parental consent was obtained within the first 2 days of the infant's life. Infants were ineligible if they presented with antenatal renal malformation on fetal ultrasound, contraindication to ibuprofen treatment (arterial pulmonary hypertension defined as a right to left shunting in the ductus, or a bidirectional shunting being mainly right to left; and/or platelet count <50,000/mm^3), renal failure defined as plasma creatinine >130 μmol/L or plasma urea >9.1 mmol/L [18] 2 days after birth. Infants were excluded if urine output was <1 ml/kg per hour within the 6 h preceding the first ibuprofen infusion or if ibuprofen treatment was started beyond day 7 (day of birth=day 0).

Intervention: ibuprofen treatment

A first echocardiography was performed on day 2±1 and a daily control followed until PDA closure. PDA treatment criteria were: (1) ductus diameter >2 mm [19]; (2) velocity flow in the ductus >2 m/s [20]; (3) left pulmonary artery end-diastolic blood flow >0.2 m/s [21]; (4) mean velocity pulmonary blood flow > 0.4 m/s [21]. Echocardiography was performed using an ALOKA prosound SSD-alpha 5 (ALOKA Sarl, Decines, France). Two-dimensional echocardiography with pulsed Doppler recordings of the left pulmonary artery and the ductus arteriosus were performed with a 7.5-MHz transducer. Infants presenting with at least two criteria on the first echocardiography immediately received ibuprofen (treatment day 1: 10 mg/kg; two following days: 5 mg/kg [22]) and were assigned to the ibuprofen group. First ibuprofen dose was always infused after measurement of baseline GFR. Ibuprofen administration was stopped before the end of the usual 3-days' cure if infants presented with oligoanuria (urine output <1 ml/kg per hour) or renal insufficiency (plasma creatinine >130 μmol/L or urea >9.1 mmol/L). Infants presenting with less than two criteria did not receive ibuprofen and were assigned to the no ibuprofen group.

Matching criteria

Infants administered ibuprofen (study group) and control infants were matched according to potential confounding factors: gestational age, Clinical Risk Index for Babies (CRIB) score [23], birth weight, and inclusion center. If more than one infant receiving ibuprofen could be matched to a control infant, the control infant with the birth date the closest to that of the study group infant was chosen.

Outcomes

Primary outcome measure

For GFR evaluation on day 7, urine was collected for a 12-h period in a urine bag, special care being provided to avoid leaks. Blood sample for creatinine measurement was performed on day 7, at the end of the urine collection, by venous puncture, and immediately sent to the lab to avoid sample hemolysis. Creatinine was dosed by colorimetric method.

Secondary outcomes

GFR was estimated on day 2 with the Schwartz formula using the specific k for preterm infants (0.33) [24]. It was then measured with plasma sample and 12-h urine collection by colorimetric method on days 14±1, 21±1, and 28±

1. Blood and urine ionogram were measured weekly during the first month of life. Blood samples were performed by venous puncture along with plasma creatinine dosage. Tubular function was estimated by sodium fractional excretion (FENa) measurement [18]. One milliliter of the total 12-h urine output was extracted for dosing urinary microalbumin [25] and alpha-1-microglobulin on days 7, 14±1, 21±1, and 28±1. Urine output was measured using urine bags during the ibuprofen treatment period and by weighing napkins on the other days. Napkins were weighed as soon as they were wet or at least every 2 h to avoid significant evaporation. The infant's weight and fluid intake were measured daily.

Sample size

The primary outcome was GFR on day 7. Normal GFR values in preterm infants were estimated based upon data from Bueva et al. [18]. To show 30% GFR reduction on day 7, at least 120 infants (60 pairs) were needed, with a two-tailed type 1 error rate of 0.05 and a power of 80%. Inclusion of 20% more infants was needed to anticipate loss to follow-up. Hence, 144 inclusions were awaited in this trial.

Statistical analysis

Baseline GFR was measured on day 2 in both groups. Primary outcome was compared between infants in the study and control groups in bivariate analysis with a paired Student's *t* test. A generalized linear regression model, with adjustment on the matching criteria, was performed for GFR on day 7. It included all factors meeting *P* values <0.20 in bivariate analysis. For the secondary outcomes—urine output, variation of GFR from day 2 to day 28, and tubular function evaluation during the first month of life—differences between ibuprofen and no ibuprofen groups were tested using paired Student's *t* tests in bivariate analysis. A linear mixed model with repeated measures was performed, taking into account time to evaluate the difference in the maturation process among study and control infants during the first month of life. This difference in renal function maturation among groups was assessed by a time−ibuprofen interaction (this time−ibuprofen interaction measured the effect of ibuprofen on GFR over the first month of life compared with the no ibuprofen group). General characteristics between ibuprofen and no ibuprofen groups were compared using MacNemar tests for dichotomous variables and paired Student's *t* tests for continuous variables. Data were collected prospectively, and analysis was by intention to treat. Statistical significance was determined for $P<0.05$. All analyses were performed using SAS statistical software, version 9.1 (SAS Institute, Cary, NC, USA).

Results

Study population

Participant flow is presented Fig. 1. One hundred and forty-eight infants, matched in 74 pairs, were included in this study from October 2004 to August 2006. The follow-up period ended on September 2006.

Mean gestational age was 28.3±1.2 weeks (mean ± standard deviation), and mean birth weight was 1,114.3± 281.2 g. General characteristics of the study population are presented Table 1. The demographic characteristics were similar in the two groups, except for hyaline membrane disease (HMD), which was significantly more frequent in infants exposed to ibuprofen. At baseline measurement (before onset of ibuprofen treatment), GFR was similar in infants that had or not presented with HMD on day 0 (GFR on day 2, HMD versus no HMD: 3.0±3.9 vs. 2.8±0.8 ml/min/1.73 m^2; $P=0.75$).

Infants lost to follow-up

Five infants (3.4%) were lost to follow-up on day 14, nine on day 21 (total $n=14$; 9.4%), and nine on day 28 (total $n=23$; 15.5%). There was no difference in percentages of infants lost to follow-up among groups. These infants were lost for renal function measurement due to back transfer to facility wards closer to their parents' home. However, data on oxygen requirement at 28 days, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and death were collected. For renal function evaluation, 53 infants were still alive and not lost to follow-up in the ibuprofen group and 64 in the no ibuprofen group on day 28. Demographic characteristics of infants lost to follow-up were not different from those of infants still in the study, except for nephrotoxic drug prescription, which had been more frequent in infants not lost to follow-up (lost to follow-up versus not lost to follow-up, day 28: 29.4% vs. 59.6%, $P=0.02$).

Patent ductus arteriosus

All infants in the ibuprofen group received ibuprofen. Two of 74 (2.7%) received one dose only, and 3/74 (4.0%) received two doses because of acute renal insufficiency ($n=2$), and oligoanuria ($n=3$), respectively. The first dose of ibuprofen was administered on day 2.2±1.1, and ibuprofen treatment was effective in 78.4% infants. Fourteen infants received more than three doses of ibuprofen, one received indomethacin, and nine underwent surgery. No infant presented with an open ductus after treatment. Twenty-one of 74 (28.4%) infants in the no ibuprofen group had an open ductus arteriosus on the first echocardiography but did not meet treatment criteria. In all cases, PDA was closed by day 7.

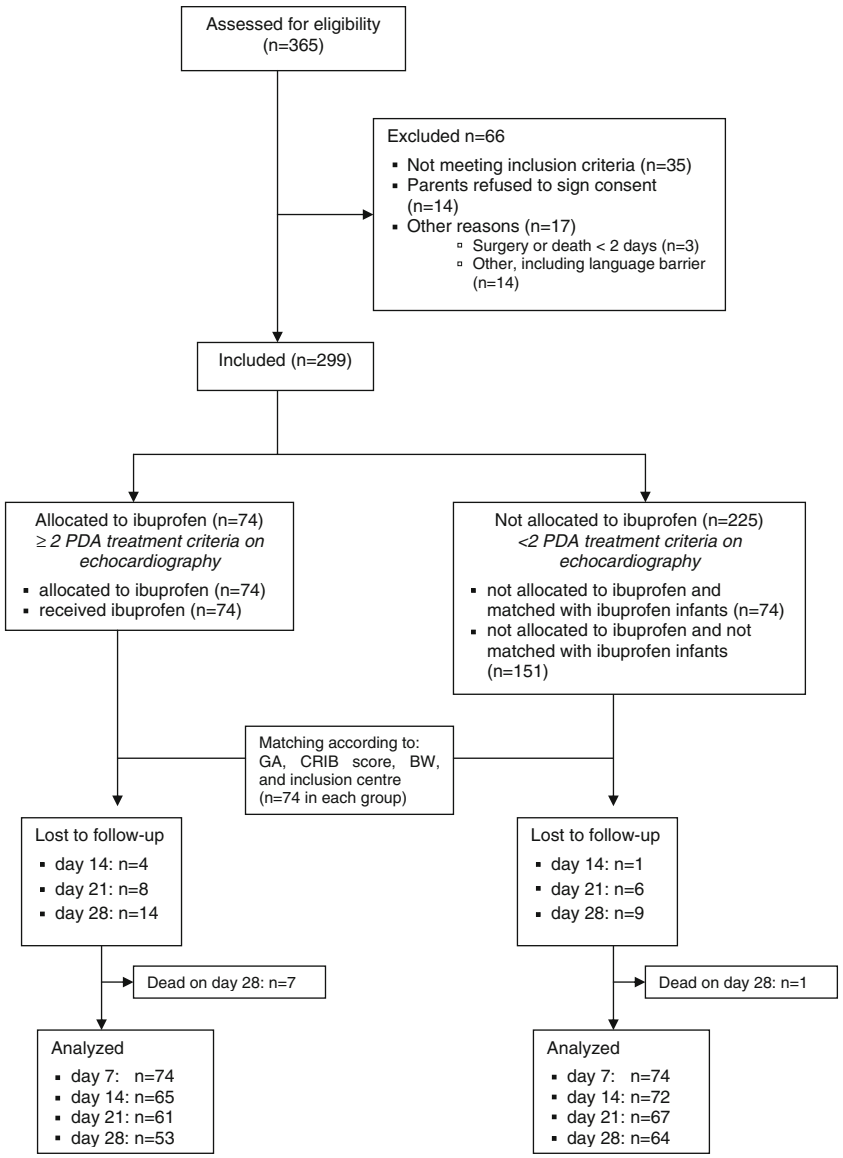

Fig. 1 Participant flow. *PDA* patent ductus arteriosus, *GA* Gestational Age, *CRIB* Clinical Risk Index for Babies, *BW* birth weight

Primary outcome

Ibuprofen treatment was associated with a significantly lower GFR on day 7: 12.8±6.2 vs. 18.1±12.1 ml/min/1.73 m^2; $P<0.001$. Mean GFR in the ibuprofen group was nearly 30% lower than the mean GFR in the no ibuprofen group. Noteworthy, baseline GFR measured on day 2 was similar in both groups (ibuprofen versus no ibuprofen: 12.6±4.1 vs. 12.5±2.9 ml/min/1.73 m^2, $P=0.35$). Frequency of vasoactive, diuretic, and nephrotoxic drugs was similar in both groups on day 7 (respectively, in ibuprofen versus no ibuprofen: vasoactive $n=4$ vs. 0, $P=0.12$; diuretic $n=2$ vs. 0, $P=0.16$; nephrotoxic $n=7$ vs. 2, $P=0.17$). The proportion of infants exposed to amikacin or vancomycin during the first 7 days of life was similar in both groups (Ibuprofen versus no ibuprofen; amikacin 33 (44.6%) vs. 26 (35.1%), $P=0.24$; vancomycin 13 (17.6%) vs. 7 (9.5%), $P=0.15$). Factors associated with lower GFR on day 7 in bivariate analysis were ibuprofen treatment and gestational age <29 weeks (Table 2). HMD, which was more frequent in the ibuprofen group, was not associated with a significantly lower GFR on day 7. There was no interaction between HMD and ibuprofen treatment on GFR on day 7. The regression analysis performed determined a significant effect of ibuprofen treatment ($\beta=-13.2\pm6.3$, $P=0.04$), whereas HMD and the interaction HMD × ibuprofen was not significant ($\beta=-2.7\pm2.3$, $P=0.83$ and $\beta=-6.5\pm5.4$, $P=0.23$, respectively). The amplitude of GFR reduction associated with ibuprofen treatment in very preterm infants was the same in infants with or without HMD.

Factors significantly associated with decreased GFR on day 7 in the generalized linear regression model were

Table 1 Study population's general characteristics before ibuprofen treatment

		All (n=148)	Ibuprofen (n=74)	No ibuprofen (n=74)	P value
Antenatal steroids	Yes	58.1%	54.0%	62.2%	0.33
Prenatal exposure to nephrotoxic drugs	Yes	2.7%	2.7%	2.7%	1.00
Preeclampsia	Yes	14.2%	18.9%	9.5%	0.10
Gestational age	Weeks GA (mean ± SD)	28.3±1.2	28.3±1.2	28.3±1.2	0.89
Gender	Male	51.3%	54.0%	48.6%	0.48
Delivery	Caesarean	72.3%	77.0%	67.6%	0.18
Birth weight	Grams (mean ± SD)	1,114.3±281.2	1,120.5±277.1	1,108.1±287.0	0.79
CRIB score	0–4	74.3%	74.3%	74.3%	1.00
	5–10	24.3%	24.3%	24.3%	
	>10	1.4%	1.4%	1.4%	
Apgar score at 5 minutes	Median (q1; q3)	8 (6;9)	8 (6;9)	8 (5;9)	0.53
HMD	Yes	76.3%	89.2%	63.5%	<0.001

GA gestational age, *SD* standard deviation, *CRIB* Clinical Risk Index for Babies, *HMD* hyaline membrane disease defined as requirement of intratracheal instillation of surfactant on day 0

ibuprofen treatment (β=−5.8; P=0.001) and low gestational age (β=−5.9; P<0.001). Results were similar if analysis was performed excluding infants having received more than three doses of ibuprofen, indomethacin, or having undergone surgery. We could determine no additional effect on GFR of more than three doses of ibuprofen versus three doses on day 7 (12.9±3.4 vs. 12.9±6.7, respectively, P=0.59).

Secondary outcomes

Urine output was significantly decreased in the ibuprofen group during the first days of life (P=0.002), though hydroelectrolytic intake was similar in both groups. Differences disappeared after ibuprofen withdrawal (Fig. 2). When leaks occurred, the occurrence was similar in both groups (data not shown).

GFR did not change from day 2 to day 7 in the ibuprofen group, whereas an increase in GFR was observed in the no ibuprofen group (Fig. 3).

Repeated measures analysis, adjusted on the matching criteria, determined ibuprofen treatment as a significant risk factor for low GFR during the first month of life (overall difference P<0.001). GFR significantly increased over time (P<0.001). In study-group infants, the increase in GFR over time was delayed and significantly smaller than in the control group. CRIB score >4 and intrauterine growth restriction (IUGR) were also associated with a significantly lower GFR. FENa was significantly increased in study-group infants up to day 21 (bivariate analysis, ibuprofen versus no ibuprofen group, FENa (%) day 7: 3.9±3.5 vs. 2.6±1.7, P<0.001; day 14: 2.3±1.9 vs. 1.4±1.3, P<0.001; day 21: 1.6±1.8 vs. 1.1±0.9 %, P=0.04; day 28: 1.4±1.6

Table 2 Glomerular filtration rate (GFR) on day 7 according to major perinatal factors

Perinatal factor		Yes	No	P value
Ibuprofen		12.8±6.2	18.5±12.0	<0.001
Antenatal steroids		15.7±10.5	15.7±9.3	0.97
Preeclampsia		14.4±7.0	15.9±10.4	0.43
Gestational age	<29 weeks	13.5±9.2	19.9±10.0	<0.001
Gender	Male	15.1±8.2	16.4±11.7	0.44
Delivery	Caesarean	14.7±8.1	18.2±13.4	0.12
Apgar 5 min	<7	15.6±11.5	15.8±9.2	0.93
CRIB score	0–4	16.2±10.7		0.71
	5–10	14.5±7.8		
	>10	11.9±4.4		
IUGR		12.5±7.1	16.0±10.2	0.25
HMD		15.6±10.8	16.8±6.0	0.43
Nephrotoxic drugs		14.6±10.9	16.9±8.9	0.19

Nephrotoxic drugs were amino glycosides and glycopeptides. GFR (ml/min/1.73 m^2; mean ± standard deviation), Student's t test

CRIB Clinical Risk Index for Babies, *IUGR* Intrauterine growth restriction, *HMD* hyaline membrane disease

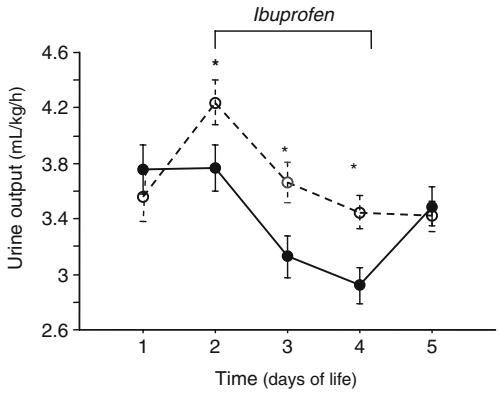

Fig. 2 Urine output during treatment period in infants receiving ibuprofen (*filled circles*) and control infants (*open circles*); 74 pairs. Values are means ± standard error of the mean (SEM). * $P<0.05$. Overall adjusted difference (determined with repeated measure analysis): $P=0.002$

vs. 0.9±0.9, $P=0.19$). Electrolyte and fluid intakes were similar in both groups from day 0 to day 28 (data not shown). In repeated measures analysis, ibuprofen significantly increased FENa during the first month of life (overall adjusted difference $P=0.003$). These results are presented Fig. 4.

The ratio microalbuminuria/creatininuria was also significantly increased in infants receiving ibuprofen up to day 14 (ibuprofen versus no ibuprofen, day 7: 0.21±0.4 vs. 0.19±0.2; day 14: 0.26±0.4 vs. 0.17±0.1 mg/mg, $P<0.001$). By day 28, the ibuprofen group had significantly more oxygen requirement (ibuprofen versus no ibuprofen, 50.8% vs. 36.1%, $P=0.02$) and higher death rate (ibuprofen versus no ibuprofen, 9.5% vs. 1.3%, $P=0.03$). In the group receiving ibuprofen, six infants died in the second week of life and two in the fourth week. However, none of these deaths had a definite relationship to ibuprofen treatment. NEC and IVH did not differ between groups (ibuprofen versus no ibuprofen: NEC 14.7% vs. 8.2%, $P=0.37$; IVH 23.5% vs. 24.6%, $P=0.96$).

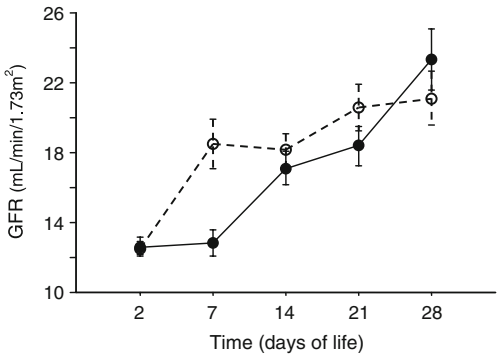

Fig. 3 Glomerular filtration rate (GFR) in infants receiving ibuprofen (*filled circles*) and control infants (*open circles*) during the first month of life; 148 infants, 74 pairs on day 7. Values are means ± standard error of the mean (SEM). Overall adjusted difference $P=0.003$

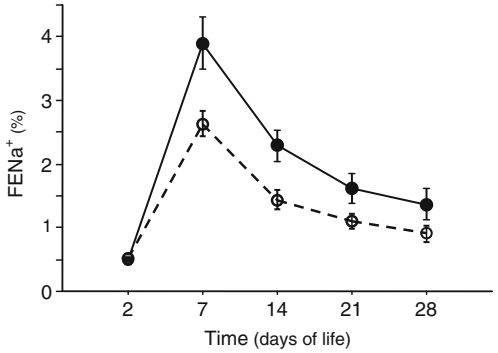

Fig. 4 Fractional excretion of sodium (FENa) from day 7 to day 28 in infants receiving ibuprofen (*filled circles*) and control infants (*open circles*); 148 infants, 74 pairs on day 7. Values are means ± standard error of the mean (SEM). Overall adjusted difference $P<0.001$

Discussion

This study showed an almost 30% significantly lower GFR on day 7 in infants exposed to ibuprofen infusion for PDA treatment compared with infants who were not. Indeed, GFR did not increase from day 2 to day 7 in study-group infants, whereas it did in control-group infants. The effect of ibuprofen on GFR lasted up to day 28. Urine output was significantly decreased during ibuprofen treatment, though not to the point of oliguria. Interestingly, tubular function was also altered during the first month of life in the ibuprofen group.

In previous studies, ibuprofen has proven to have significantly fewer side effects than indomethacin on GFR, urine output, and renal vascular resistance [7, 8]. Furthermore, Pezzati et al. reported no increase in plasma creatinine after ibuprofen treatment in preterm neonates <33 weeks gestation [11]. Yet, this conclusion was based upon the observation of no change in plasma creatinine level in ibuprofen-treated infants during and after treatment, though plasma creatinine should have decreased. At birth, plasma creatinine reflects the mother's creatinine level, and neonatal creatinine very briefly increases [26] before decreasing within the first week of life [27], as seen in the infants receiving ibuprofen in our study. Our findings of decreased GFR after treatment withdrawal is consistent with the higher plasma creatinine levels measured in observational studies or randomized controlled trials on prophylactic use of ibuprofen [28] and confirmed by a recent updated meta-analysis [15]. The magnitude of decrease in GFR is also consistent with the 21% lowered amikacin clearance after prophylactic ibuprofen reported by Allegaert et al. [14]. These studies, however, focused on ibuprofen's immediate renal impact. We note that our results emphasize the duration of GFR decrease. This is of high importance in these preterm infants, who may receive several other nephrotoxic drugs such as amikacin

and vancomycin during their first month of life, thus requiring dosing adaptation. Another important feature enhanced by our results is tubular function impairment. With regards to tubular function, ibuprofen significantly increased $FENa^+$ during the first month of life. Ibuprofen has previously been reported to have a near-significant tendency for a lower FENa [29]. This decrease can be explained by preglomerular arteriole vasoconstriction. As our results show a significantly higher FENa in infants receiving ibuprofen and a higher microalbuminuria/creatininuria ratio after treatment, we hypothesize that ibuprofen may not only induce preglomerular arteriole vasoconstriction but also tubular injury.

Study limitations

The gold standard to determine GFR is inulin clearance [30]. The need for volunteer bladder voiding renders it impossible in newborns. Creatinine clearance is an accepted feasible measurement in the preterm infant [26]. This measurement method was independent of treatment group. No differential bias can therefore be due to the measurement method. Also, infants in our study were not randomized into the two groups, as it is unethical to infuse a potentially nephrotoxic drug to preterm infants when no beneficial effect on PDA is expected. The study design hence reflects clinical practice in which ibuprofen treatment is decided upon according to PDA criteria. Furthermore, the early onset of ibuprofen treatment, relying upon echocardiographic prediction of no spontaneous closure capabilities, allowed treatment to be initiated before hemodynamic changes occurred and before PDA could affect renal function [4, 13, 31]. Comparison of creatinine clearance in the two groups was performed on day 2, before initiation of treatment. No difference was observed, suggesting that GFR was similar among study and control infants prior to treatment. Ibuprofen was initiated before the onset of hemodynamic disturbances caused by PDA.

Study and control infants were paired on GA, CRIB score, and birth weight, which are known risk factors for renal-function impairment [32]. Other potential confounding factors such as HMD, IUGR [33], or exposure to nephrotoxic drugs were not significantly associated with GFR on day 7, between the two groups. There was a significant expected correlation with gestational age, but renal function alterations observed in the exposed group remained strongly associated with ibuprofen treatment, even after adjustment for gestational age. As this was a multicenter study, to reduce any potential center effect, infants were matched on inclusion center, and analysis was adjusted on the center.

In conclusion, this study showed that treating PDA with ibuprofen was associated with renal alterations sustained up to 1 month of life. This is an important fact to take into account when other drugs primarily eliminated by glomerular filtration are considered, during or after ibuprofen treatment, in such infants. Dosing needs to be checked and adjusted to plasma levels. Long-term follow-up is required to ensure that the observed alterations are the result of maturation delay and not of subtle lesions that could impact these infants' renal function later in life.

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