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ORIGINAL ARTICLE

Dose-finding study of ibuprofen in patent ductus arteriosus using the continual reassessment method

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SUMMARY

Objective: **Intravenous ibuprofen (IBU) has been found to be as effective as indomethacin for the treatment of patent ductus arteriosus (PDA) in preterm infants and has been associated with fewer adverse effects in comparative phase III studies. The dose regimen used (10–5–5 mg/kg/day) was based on limited pharmacokinetic data and no phase II study was available to determine the optimal dose of IBU for this indication. The present study was designed to determine the minimum effective dose regimen (MEDR) of IBU (one course) required to close ductus arteriosus in preterm infants.**

Method: **A double-blind dose-finding study was conducted using the continual reassessment method, a Bayesian sequential design. Two distinct target closure rates were initially chosen according to postmenstrual age (PMA) at birth: 80% in infants with a PMA of 27–29 weeks, and 50% in infants with a PMA <27 weeks. Forty neonates (20 in each PMA group) with PDA were treated between days 3 and 5 of life. Four different dose regimens were tested: loading doses of 5, 10, 15 or 20 mg/kg, followed by two doses (1/2 loading dose) at 24-h intervals. Efficacy was evaluated by echocardiography 24 h after the third infusion.**

Results: **In infants with a PMA of 27–29 weeks, the estimated MEDR was 10–5–5 mg/kg with a final estimated probability of success of 77% (95% credibility interval: 56–92%). The 15–7·5–7·5 mg/kg dose regimen had a better estimated probability of success (88%, 95% credibility interval: 68–97%), but resulted in more minor renal adverse effects. In contrast, in infants with a PMA <27 weeks, the estimated MEDR was 20–10–10 mg/kg with an estimated probability of success of 54·8% (95% credibility interval: 22–84%), whereas the conventional dose regimen resulted in a low estimated probability of success (30·6%, 95% credibility interval: 13–56%). In these infants, compared with those with a PMA of 27–29 weeks, minor renal adverse effects were more frequent from the 10–5–5 mg/kg/day dose regimen and did not appear to be clearly dose related.**

Conclusion: **This study confirms that the currently recommended dose regimen (10–5–5 mg/kg) of IBU is associated with a high closure rate (80%) and few adverse effects in premature infants with a PMA of 27–29 weeks. The failure rate was much higher below 27 weeks. A higher dose regimen (20–10–10 mg/kg) might achieve a higher closure rate. However, tolerability and safety of this dose regimen should be assessed in a larger population before considering the use of these doses for ductus arteriosus closure.**

Keywords: **Bayesian design, continual reassessment method, dose-ranging study, ductus arteriosus, ibuprofen, premature neonate.**

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INTRODUCTION

Persistent patent ductus arteriosus (PDA) remains a frequent complication in very low birthweight premature infants with a reported incidence of about 40% on the third day of life (1–3). Haemodynamically significant PDA may increase the risks of bronchopulmonary dysplasia (BPD) (4), intracranial haemorrhage (ICH) (5), necrotizing enterocolitis (NEC) (6), and death (7). Since 1976 (8), inhibition of prostaglandin synthesis with indomethacin has been widely used in the prophylaxis and symptomatic treatment of PDA with a reported efficacy of 66–80% (9–12). However, this efficacy decreases with decreasing postmenstrual age (PMA), as reported rates of ductus ligation are more than 40% below 28 weeks (13). In addition, indomethacin affects renal, mesenteric and cerebral perfusion, and may lead to transient renal dysfunction (14, 15), NEC and gastrointestinal haemorrhage (16), and may reduce cerebral intracellular oxygenation (17, 18). These adverse effects have prompted the search for safer pharmacological strategies for PDA closure. Since the initial study by Aranda *et al.* (19), ibuprofen (IBU) appears to be as effective as indomethacin for the treatment of PDA (11, 12, 20), with fewer consequences on renal, mesenteric and cerebral perfusion (21–24). However, IBU trials have included only small numbers of very immature infants who are at greatest risk for PDA. The efficacy of IBU has therefore not yet been adequately addressed in extremely immature infants. Moreover, the dose regime used in most studies (10–5–5 mg/kg for 3 days) is based on very sparse pharmacokinetic data (25, 26). The effectiveness and safety of IBU treatment of PDA would be improved by determining the optimal dose regimen and by establishing the dose–effect relationship. However, the usual design of dose-ranging studies raises ethical, statistical and practical problems (27). An alternative trial design consists of using adaptive rules that select drug levels for successive cohorts of patients based on outcomes of patients treated previously in the trial (28). The main objective of the present study was to determine the minimum effective dose regimen (MEDR) of one course of IBU required to close PDA in premature neonates belonging to two PMA categories, and to evaluate the safety of treatment. A secondary objective was to determine the relationship between plasma IBU concentrations and PDA closure.

METHODS

Subjects

The study was conducted in two neonatal intensive care units between June 2000 and May 2002. Neonates admitted to the two units were eligible for the trial when they satisfied the following criteria: PMA between 24 and 29 weeks and 6 days, postnatal age between 72 and 120 h, haemodynamically significant PDA, dependence on mechanical ventilation or nasal continuous positive airway pressure. Exclusion criteria were: congenital heart malformation, life-threatening infection, clinical or radiographic evidence of NEC, evidence of bleeding diathesis, platelet count $<50 \times 10^9$/L, hepatic insufficiency, urine output below 1 mL/kg of birthweight per hour during the last 12 h, serum creatinine concentration $>120\ \mu$mol L^{-1}, severe ICH (grade 3 or 4), severe hyperbilirubineamia. Cases in which the mother or newborn infant were treated with either a non-steroidal anti-inflammatory drug or a drug influencing IBU metabolism, were also excluded. The protocol was approved by the Cochin Hospital Ethics Committee and written informed consent was obtained from all parents.

Study protocol

A dose-finding study was conducted according to the continual reassessment method (CRM; see experimental design). Forty patients with persistent PDA were included in two groups ($n = 20$ per group), based on their PMA. Four different loading doses (5, 10, 15 or 20 mg/kg), administered on inclusion (T0), followed by two doses representing 50% of the loading dose administered after 24 and 48 h, were tested. In each group, cohorts of three consecutive patients received the same dose regimen, as determined by the statistician on the basis of the preceding cohort results. The drug was infused continuously over 15 min. To prevent identification of the IBU dose allocated, a solution was prepared in the hospital pharmacy according to the statistician's instructions. IBU concentration was calculated to enable all infants to receive a solution volume of 4 mL/kg per injection. Orphan Europe I.V. IBU formulation (IBU-trometamol), supplied in 5 mg/mL vials, was used. A syringe containing 7 mL of the solution was delivered in the unit for each injection. An aliquot of 1 mL of each preparation was stored at −20 °C to measure IBU concentrations.

The primary efficacy endpoint was closure of the PDA, as assessed by echocardiography 72 h (T72) after treatment initiation. The statistician was informed about the therapeutic response observed and the safety of treatment for re-estimation of the posterior probability of success after each cohort of three patients.

When the ductus arteriosus was still patent 4 days after the last dose of randomly assigned treatment, another course of three IBU doses was given as a non-randomized rescue treatment (10–5–5 mg/kg/day). When this therapy also failed to induce ductus closure, standard indomethacin back-up treatment and/or surgical ligation were considered.

Patent ductus arteriosus evaluation

Before inclusion, the ductus arteriosus was evaluated by detailed colour and pulsed Doppler echocardiography (EUB 415 (Hitachi Corp., Tokyo, Japan) and Acuson scanner (Siemens Corp., Malvern, PA, USA)). PDA was diagnosed on visualization of left to right shunt through the ductus arteriosus and diastolic backflow in the main pulmonary artery on colour flow mapping or pulsed Doppler from the high left parasternal view. The diagnosis of haemodynamically significant PDA was based on at least one of the following criteria: left atrium/aortic root ratio >1·4, diastolic backflow in the descending aorta immediately beneath the ductus arteriosus or decreased diastolic flow in the anterior cerebral artery with pulsatility index >0·8. The efficacy of therapy was evaluated on a second echocardiography performed 24 h after the last dose of IBU (T72). PDA was considered to be closed when, in addition to improved clinical condition, an image of the PDA could not be obtained, no diastolic backflow could be recorded in the main pulmonary artery and all criteria of haemodynamically significant PDA disappeared.

Concomitant treatment

Infants were nursed in humidified incubators. Fluid intakes, which were initially 60–80 mL/kg, increased by 10–20 mL/kg/day, according to body weight loss and serum sodium concentration. Weight losses of 10–15% were allowed in the first days of life. Respiratory distress syndrome was treated by respiratory support (conventional mechanical ventilation or high-frequency oscillatory ventilation), supplemental oxygen and early rescue therapy with natural surfactant (Curosurf®, Chiesi S.A., Palma, Italy; 200 mg/kg initially). Inotropic agents (dopamine or dobutamine) and/or fluid replacement therapy were used at the discretion of the attending neonatologist.

Clinical course and outcome

Laboratory data, demographic data and clinical outcome were recorded prospectively. Maternal treatments during pregnancy, antenatal glucocorticoid use, premature rupture of membranes, PMA, birthweight and sex were noted. The safety of IBU was carefully assessed during the 120-h duration of the study. Renal adverse effects were detected using daily recordings of weight, fluid and sodium intakes, urine output based on weighing the nappies, and serum levels of creatinine, sodium and urea nitrogen. Gastrointestinal safety was assessed clinically. Cases of NEC were recorded until 30 days after IBU treatment, based on the usually accepted criteria (29).

Possible adverse effects on the pulmonary or cerebral circulation were monitored. The mode of respiratory support, the parameters of mechanical ventilation, and the level of supplemental oxygen were recorded. Three cranial ultrasound scans were performed in all infants, before inclusion, within 3 h after the loading dose, and at T72 with a measurement of peak systolic, end-diastolic and mean velocity in the anterior cerebral artery. ICH were graded according to the Papile classification (30). BPD was defined as the need for supplemental oxygen at 36 weeks of PMA.

Ibuprofen assay

Plasma IBU concentrations were measured on 0·4 mL blood samples, using high-pressure liquid chromatography, as previously published (31). IBU concentrations were measured in each patient twice: 5 min after the end of the loading dose infusion, and at the time of assessment of the primary efficacy endpoint (T72). Plasma (200 μL) was obtained after centrifugation and stored at −20 °C.

Statistical analysis

The design of this phase II, double-blind, dose-finding study was chosen in order to assess the MEDR of IBU for the closure of PDA. The CRM was used (32). The CRM is an iterative Bayesian method based on a one-parameter model, designed to estimate the targeted percentile of response among k dose levels, denoted d_i ($i = 1,\ldots,k$, with k dose levels), i.e. determination of the MEDR of IBU required to close PDA. Based on previous reports demonstrating lower PDA closure rates with decreasing PMA (13), the PDA closure rate used to define the MEDR was 80% for neonates with a PMA of 27–29 weeks, and 50% for neonates with a PMA <27 weeks. Each of the four dose levels was arbitrarily associated by the investigator with the following prior guesses of success probability, p_i ($i = 1,\ldots,4$), e.g. 60, 80, 90 and 95% in the ≥27-week PMA group and 30, 50, 60 and 80% in the <27-week PMA group for the loading dose levels 5, 10, 15 and 20 mg/kg respectively. We then chose the one-parameter logistic model (with scale parameter fixed at 3) in order to fit the dose–response curve. We assumed an exponential distribution with a mean equal to 0·5 for the model parameter. The posterior estimated probabilities of success were re-estimated after each new cohort of three patients on the basis of updated data. The dose allocated to each new cohort of patients was the dose level with the updated response probability closest to the target closure rate (80% for ≥27-week group and 50% for <27-week group) unless adverse effects were observed. In practice, the development of weight increase >30 g/kg/day with oliguria (urine output <1 mL/kg/h during an 8-h collection period) or increased plasma creatinine (>120 μmol/L), or gastrointestinal haemorrhage or NEC in at least two patients of a cohort, within 72 h after the loading dose, required a reduction of the dose regimen of the subsequent cohort by one dose level.

In the present study, the first cohort of patients received a loading dose of 10 mg/kg for the ≥27-week group (the dose level with associated initial guess of success probability closest to the target) and a loading dose of 5 mg/kg for the <27-week group (the lowest dose level for security reasons in the younger group). The MEDR was defined as the dose level among the four chosen doses that had a final response probability closest to the target. The decision to end the study was based on a stopping decision analysis (33). The CRM continued until one of the following discontinuation criteria was met: (i) the planned number of 20 subjects per subgroup was reached; (ii) estimated efficacy was too low for all dose levels; (iii) suitable estimation of the MEDR was obtained, based on the predictive gains (mean and maximum) of further patients inclusions on the response probability and on the width of its credibility interval lower than 5%.

Sequential statistical analysis was performed using BPCT software (Bayesian Phase I or II Clinical Trials) for Windows NT 4 (34). Descriptive analysis, logistic regression analysis and calculation of odds ratios were performed using SAS (version 8·2 for Windows). Qualitative and quantitative results were expressed as percentage and median (interquartile range) respectively. Non-parametric tests (Mann–Whitney *U*-test or Kruskal–Wallis test, as appropriate) were used to compare continuous data between groups.

RESULTS

Demographic data

Forty-six patients were included in the study. The results could not be evaluated in six cases. IBU preparation could not be provided on time in two cases. Severe pulmonary haemorrhage and sepsis occurred after inclusion, but before IBU administration, in one case. In addition to these three patients, who did not receive any study drug, three patients received IBU, but were not evaluable at T72 and had to be excluded from the sequential analysis, due to violation of the drug administration protocol in two cases, and sepsis-related death before T72 in the third case.

Twenty patients were evaluated in each PMA group. The characteristics of these infants before treatment are shown in Table 1. The two groups of infants with a PMA ≥27 weeks and <27 weeks received the first IBU dose at the median (inter-

Table 1. Baseline characteristics of the study groups

	≥27-week PMA group (n = 20)	<27-week PMA group (n = 20)
Birth weight (g)	1040 (900–1135)	830 (615–950)
Postmenstrual age (weeks)	28·0 (28·0–29·0)	25·9 (24·9–26·4)
Small for gestational age[a]	3 (15)	0
Male	9 (45)	13 (65)
Pre-eclampsia	8 (40)	2 (11)
Premature rupture of membrane	3 (15)	3 (15)
Antenatal steroids	17 (85)	14 (70)
Surfactant therapy	19 (95)	20 (100)
Ventilatory support at inclusion:		
CMV	12 (65)	15 (75)
HFOV	2 (10)	4 (20)
N-CPAP	5 (25)	1 (5)
Inspired oxygen (%) at inclusion	21·0 (21·0–26·5)	21·0 (21·0–29·0)
Mean airway pressure at inclusion	6·5 (5·0–7·2)	6 (4·2–8·7)
Intracranial haemorrhage		
Grade 1	0	3 (15)
Grade 2	2 (10)	7 (35)
Grade 3	0	1 (5)
Fluid intake at inclusion (mL/kg/day)	120 (109–133)	138 (122–153)
Weight loss at inclusion (% of birthweight)	10·1 (4·7–14·9)	13·9 (10·8–18·6)

Values are given as median (interquartile range) or number (%). CMV, conventional mechanical ventilation; HFOV, high frequency oscillatory ventilation; N-CPAP, nasal continuous positive airway pressure.
[a]Birth weight below the 10th percentile of Lubchenco's weight curves.

quartile range) age of 3 (3–4) and 4 (3–5) days respectively.

Dose-efficacy study

Infants with PMA ≥27 weeks. Loading doses of 5, 10 or 15 mg/kg were assigned to one (5%), eight (40%) and 11 (55%) patients respectively (Table 2). Failures were recorded in four (20%) patients. Minimal shunting was observed in two patients who did not require respiratory support and in whom the PDA closed spontaneously. The remaining two patients received rescue doses of IBU, which was not effective, and subsequently required surgery.

After treatment of the planned 20 patients, the posterior estimated probabilities of success for the four loading doses 5, 10, 15 and 20 mg/kg were 56·7, 77·1, 88 and 93·8% respectively. The 10–5–5 mg/kg/day dose regimen corresponded to the MEDR, as this dose regimen was associated with the closest probability to the target of 80% of PDA closure (estimated probability of success: 77·1%; 95% credibility interval: 56·1–92·3%). The sequential estimated probabilities of success associated with the MEDR after each cohort of patients and its 95% credibility intervals are represented in Fig. 1. In agreement with the study design, inclusions were stopped after 20 patients, after obtaining a suitable MEDR estimation, as three of the four pre-established stopping criteria gave a probability lower than 5% that new inclusions would improve the MEDR estimate (Fig. 2).

Infants with PMA <27 weeks. Loading doses of 5, 10, 15 and 20 mg/kg were assigned to seven (35%), six (30%), six (30%) and one (5%) patient respectively (Table 3). Failures were recorded in 14 (70%) cases. These failures were observed in six, four and four patients who received loading doses of 5, 10 and 15 mg/kg respectively. Eleven patients received a second rescue IBU course, and two patients received the alternative indomethacin treatment. IBU rescue treatments achieved closure in three cases. Surgery was subsequently required in eight patients (40%).

Table 2. Sequential posterior estimated probabilities of success of the four tested doses, updated after each new cohort of patients in the ≥27-week PMA group

Cohort no.	Patients (n)	Allocated dose	Success/ failures	Ibuprofen loading dose (mg/kg)			
				5	10	15	20
				Prior estimated probabilities of success			
				0·60	**0·80**	0·90	0·95
1	3	10	2/1	0·481	0·683	**0·812**	0·891
2[a]	1	5	0/1	0·370	0·544	0·682	**0·787**
3[b]	3	15	3/0	0·539	**0·744**	0·861	0·925
4	3	10	2/1	0·512	0·717	**0·840**	0·915
5	3	15	2/1	0·467	0·667	**0·799**	0·882
6	2	15	2/0	0·500	0·703	**0·829**	0·903
7[c]	1	10	1/0	0·519	0·723	**0·845**	0·914
8	3	15	3/0	0·553	**0·757**	0·870	0·931
9	1	10	1/0	0·567	**0·771**	0·880	0·938

In bold the dose associated with the posterior estimated probability of success closest to the target probability of 80%. This was the dose that had to be administered to the subsequent cohort.

[a]15 mg/kg should have been administered to this cohort, but, as adverse effects were observed in two patients of cohort no. 1 following administration of 10 mg/kg, the dose had to be reduced to the lowest dosage (5 mg/kg). Only one patient received this dose.

[b]20 mg/kg should have been administered to this cohort, but, as adverse effects were observed in two patients of cohort no. 1 following administration of 10 mg/kg, the dosage was reduced by one dose level.

[c]The 10 mg/kg dose was administered due to incorrect declaration of PMA. This neonate was initially included in the <27-week PMA group. It was decided to consider this patient for statistical analysis but to limit this cohort to this single patient.

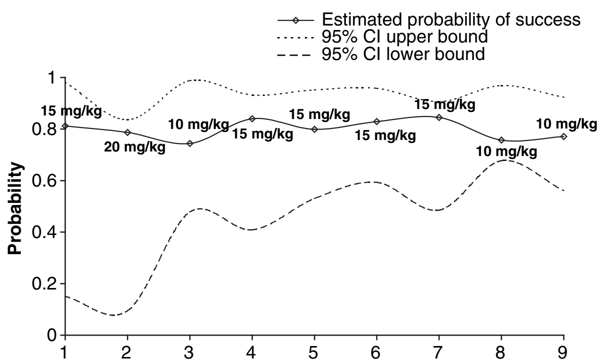

Fig. 1. Sequential estimated probability of success and 95% credibility intervals (CI) associated with the MEDR of ibuprofen (loading dose in bold characters) after each cohort of patients for the ≥27-week PMA group.

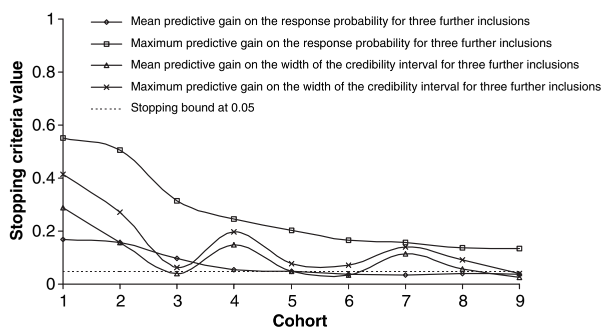

Fig. 2. Stopping criteria based on the predictive gain (mean and maximum) of further patient inclusions on the estimated response probability and the width of its 95% credibility intervals for the ≥27-week PMA group. Three criteria of four were lower than 5% by the ninth cohort.

The MEDR was 20–10–10 mg/kg/day with a posterior estimated probabilities of success of 54·8% (95% credibility interval: 22·3–83·9%). The 5, 10 and 15 mg/kg loading doses gave low posterior estimated probabilities of success, i.e. 19·2, 30·6 and 31·2% respectively. The 95% credibility intervals of the probabilities of success associated with the MEDR remained very large

Table 3. Sequential posterior estimated probabilities of success of the four tested doses, updated after each new cohort of patients in the <27-week PMA group

				Ibuprofen dose range studied (mg/kg)			
				5	10	15	20
				Prior estimated probability of success			
Cohort no.	Patients (n)	Allocated dose	Success/ failures	0·30	**0·50**	0·60	0·80
1[b]	4	5	1/3	0·210	0·339	**0·412**	0·601
2	3	15	2/1	0·292	**0·487**	0·586	0·787
3	3	10	2/1	0·335	**0·557**	0·660	0·848
4	3	10	0/3	0·242	0·390	**0·485**	0·687
5[a]	3	5	0/3	0·218	0·354	**0·431**	0·624
6	3	15	0/3	0·170	0·264	0·319	**0·472**
7[b]	1	20	1/0	0·192	0·306	0·312	**0·548**

In bold the dose level associated with the posterior estimated probability of success closest to the target probability of 50%. This was the dose that had to be administered to the subsequent cohort.

[a]A loading dose of 15 mg/kg of ibuprofen should have been administered to this cohort, but, as adverse events were observed in three patients of cohort 4 following administration of 10 mg/kg, the dose had to be reduced to the lowest dosage (5 mg/kg).

[b]Cohort 1 is composed of four patients because two patients were included on the same day in the two centres and cohort 7 is composed of only one patient because the maximum number of patients was reached.

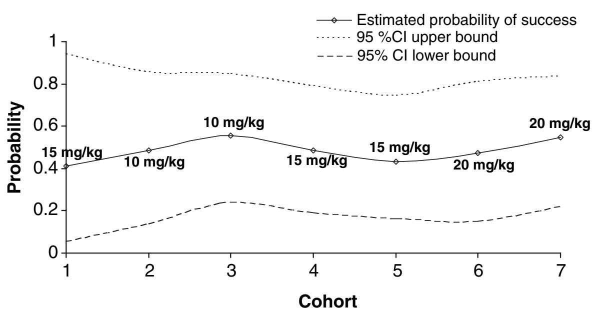

Fig. 3. Sequential estimated probability of success and 95% credibility intervals (CI) associated with the MEDR of ibuprofen (loading dose in bold characters) after each cohort of patients for the <27-week PMA group.

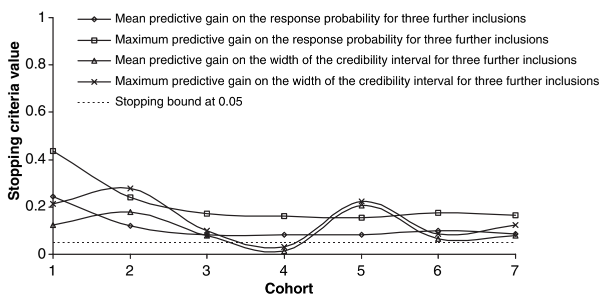

Fig. 4. Stopping criteria based on the predictive gain (mean and maximum) of further patient inclusions on the estimated response probability and the width of its 95% credibility intervals for the <27-week PMA group. None of the four criteria was lower than 5%.

during the study (Fig. 3). Inclusions were stopped after 20 patients, as initially planned, but none of the four stopping criteria had been reached (Fig. 4).

Multiple logistic regression models were used to study the effect of the dose administered on the probability of success. The model was adjusted to the patient group (<27 and ≥27 weeks), and a linear relation between the dose levels and the probability of success was found (OR: 1·24 by dose level; 95% confidence interval: 1·01–1·52; $P = 0·042$).

Safety of treatment

Renal function. Renal adverse effects related to the IBU dose regimen are shown in Table 4. No major adverse effects of IBU on renal function were recorded with any dose. The data collected in the

Table 4. Renal adverse effects during ibuprofen treatment according to dose subgroups

	≥27-week PMA group			<27-week PMA group			
Ibuprofen loading dose (mg/kg)	5 (n = 1)	10 (n = 8)	15 (n = 11)	5 (n = 7)	10 (n = 6)	15 (n = 6)	20 (n = 1)
Serum creatinine (μmol/L)							
Pre-treatment	92	77 (72–94)	90 (83–93)	85 (78–92)	99 (95–111)	100 (73–109)	76
Post-treatment	91	80 (69–93)	88 (82–100)	98 (79–105)	119 (99–139)	85 (79–93)	85
Diuresis (mL/kg/h)							
Pretreatment	3·4	3·7 (2·8–4·2)	3·4 (3–3·6)	3·9 (3·0–4·3)	3·1 (2·4–3·6)	2·9 (2·8–3·9)	4·2
During treatment[a]	4·5	3·1 (2·4–3·9)	3·1 (2·4–3·9)	2·2 (2·1–2·7)	2·4 (2·2–2·6)	2·4 (2·1–2·7)	4·7
Oliguria[b]	0	0	2	0	1	0	0
Weight gain >30 g/kg/day	0	4	6	3	6	4	1
Increased creatinine >140 (μmol/L)	0	0	0	0	2	0	0
Decreased sodium <130 (mmol/L)	0	0	3	1	1	3	1

Values are given as median (interquartile range) or number.
[a]Mean urine output during the 3 days of treatment.
[b]Urine output <1 mL/kg/h during an 8-h collection.

various dose subgroups, before, during, and after the treatment were compared in each PMA group. Fluid intakes were similar. The median urine output and median serum creatinine levels were not significantly different.

However, in the ≥27-week group mild renal adverse effects were associated with increasing IBU doses, as two patients developed oliguria (urine output <1 mL/kg over 8 h), both with the 15 mg/kg loading dose. Urine output returned to normal in <24 h. Signs of renal adverse effects (weight increase >30 g/kg/day, oliguria, increased serum creatinine >140 μmol/L, and decreased serum sodium <130 mmol/L) were more frequent with the 15 mg/kg IBU loading dose, as nine of 11 infants (82%) who received this dose presented at least one of these elements (one infant received diuretics), compared with four of eight infants (50%) who received an IBU loading dose of 10 mg/kg (one infant received diuretics).

In the <27-week group, compared with the less premature group, renal adverse effects were more frequent for all doses tested. Signs of renal adverse effects were observed in three of seven (43%), six of six (100%), five of six (83%) and one of one patients with the 5, 10, 15 and 20 mg/kg loading doses respectively. These renal adverse effects were mild and transient. One patient receiving the 10–5–5 mg/kg/day regimen developed oliguria, and two patients (receiving the same dose) required diuretics.

Outcome. No case of severe hypoxemia was observed after IBU administration. Eight of the 33 infants who required mechanical ventilation were extubated during the trial period. Eleven patients (27%) developed BPD. Four patients developed NEC (two in the 5 mg/kg dose subgroup and in the 10 mg/kg dose subgroup). Three cases of ICH were observed (grade 2 ICH before and grade 4 ICH after IBU treatment with 5–2·5–2·5 mg/kg, one case; grade 2 ICH after IBU 5–2·5–2·5 mg/kg, one case; and grade 2 ICH after IBU 10–5–5 mg/kg, one case). Three patients (10%) died in the <27-week group (sepsis, two cases; grade 4 ICH, one case). The cranial ultrasound scans performed before the inclusion and within 3 h after the loading dose showed no significant reduction of the peak systolic, end-diastolic and mean velocity in the anterior cerebral artery whatever the dose (data not shown).

Plasma IBU levels and relationships to response. Because of technical problems, blood samples at T0 (5 min after the loading dose), and T72 (24 h after the last dose) were both available in only 28 neonates. One of two samples was available in 11 infants, and none in one patient. IBU concentrations at T0 increased significantly according to the dose. The median concentrations were 27·8 mg/L (24–32·8), 40·6 mg/L (34·4–44·5), 55·3 mg/L (49·6–64) and 68 mg/L in the 5, 10, 15 and 20 mg/kg dose subgroups respectively ($P < 0{\cdot}001$). The median concentrations at T72 did not follow any pattern with 22·1 (9·2–30·4), 16·2 mg/L (8·5–26·25) and 18·6 mg/L (7·4–27·7) in the 5, 10 and 15 mg/kg dose subgroups, respectively (NS). There was a great dispersion in the observed values. The median IBU concentrations obtained with each dose regimen at T0 and T72 were similar in the ≥27-week and <27-week PMA groups (data not shown).

The IBU concentrations in relation to treatment response are shown in Fig. 5. At T0, plasma IBU levels were not significantly different in the cases of success (closure) or failure (Fig. 5a). The median (range) values were 49 mg/L (40·6–55·5) vs. 34·8 mg/L (27–43·2), and 58·2 mg/L (39–68) vs. 44·2 mg/L (34·2–52·4), in the two PMA groups respectively. The same comparison of IBU concentrations at T72 according to the treatment response gave a similar result [17 mg/L (12·6–21·9) vs. 10·6 mg/L (6·2–10·6), and 34·8 mg/L (25·8–36·1) vs. 20 mg/L (6·4–27·8) (Fig. 5b)]. No statistically significant differences in plasma IBU concentrations were observed between the neonates with and without renal adverse effects.

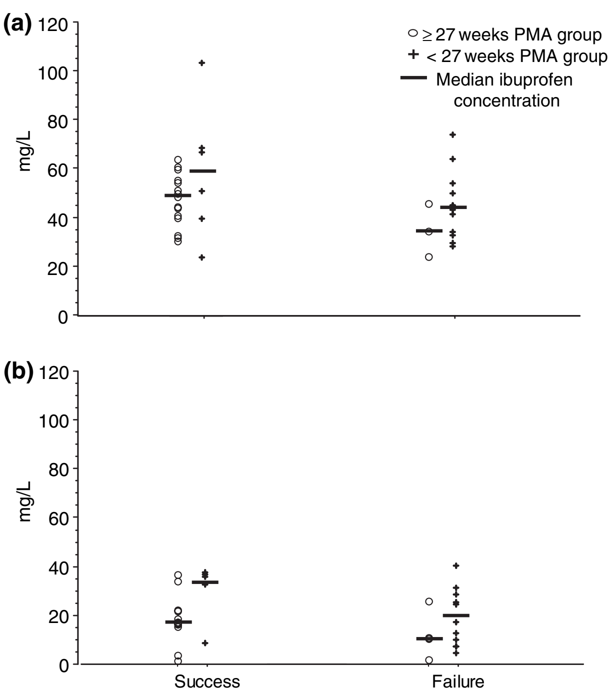

Fig. 5. Ibuprofen concentrations according to response (success or failure). (a) Ibuprofen concentrations 5 min after the end of the loading dose. (b) Ibuprofen concentrations 24 h after the last dose (T72).

DISCUSSION

The dose regimen of intravenous IBU used in premature neonates (loading dose of 10 mg/kg followed by a maintenance dose of 5 mg/kg/day for 2 days) is based on limited pharmacokinetic data (25, 26). Although this IBU dose regimen has been associated with a similar efficacy to that of the usual indomethacin treatment of PDA (11, 12, 20), additional studies are essential to determine whether this is the optimal IBU dose regimen, before the drug can be more widely used.

In this study, the CRM (27, 32) was preferred to a parallel group design because of the potential advantages of this type of design in paediatric trials: fewer patients are needed to determine the MEDR, double-blind evaluation is possible, a placebo group is not necessary, a suboptimal range of IBU doses with unacceptable probabilities of failure can be detected earlier, and the dose allocated to each subsequent patient is supposedly closer to the optimal dose. This study is the first to attempt to examine the efficacy and side-effects of different doses in two separate PMA categories. Two target probabilities of success according to PMA had to be selected, as the efficacy of cyclo-oxygenase inhibitors in closing PDA is related to PMA (2, 10, 11, 13). We targeted an IBU dose regimen (one course) that would close PDA in 80% of premature neonates with a PMA of 27–29 weeks based on the data of the literature on the efficacy of IBU (11, 12). As the efficacy of IBU has not yet been adequately addressed in extremely premature infants (<27 weeks) and as a high ligation rate (>40%) has been reported with indomethacin (13), we chose a lower target probability of success of 50%. This is a preliminary study designed to use the minimum number of patients to predict efficacy among a predetermined empirical choice of dose range that can either be underestimated or overestimated at the beginning of the study and which may not include the most effective dose. In addition, the power of this study was not sufficient to detect significant differences in adverse effects between groups.

The main result of this study is that the neonatal IBU dose regimen recommended in previous studies (19, 25, 26) seems to be the optimal dose regimen in infants with PMA of 27–29 weeks, but appears to be inadequate to treat more immature infants (<27 weeks) with a low efficacy (posterior estimated probability of success of 30·6%, 95% credibility interval: 13–56%).

In infants with PMA of 27–29 weeks, the MEDR was estimated to be 10–5–5 mg/kg/day with a posterior estimated probability of success of 77·1% (95% credibility interval: 56·1–92·3%), as the higher probability of closure (88%, 95% credibility interval: 68–97%) observed with the next dose level tested (15–7·5–7·5 mg/kg/day) appears to be associated with more frequent minor renal adverse effects. The standard dose regimen therefore appears to be associated with the best risk/benefit ratio in this PMA group.

In the <27-week group, the MEDR was estimated to be 20–10–10 mg/kg/day with a posterior estimated probability of success of 54·8% (95% credibility interval: 22·3–83·9%). Minor renal adverse effects were more frequent in this younger gestational age population than in older infants. They were observed from the 10–5–5-mg/kg/day dose regimen and did not appear to be clearly dose related. Increasing the dose did not appear to increase the incidence of other adverse effects (NEC, ICH), but the small number of patients could limit the power of the study to detect significant differences in dose-related clinical effects. In line with previous reports on IBU (22, 24), we did not observe any significant reduction of cerebral perfusion after any of the loading doses tested. In one study, a severe adverse effect, pulmonary hypertension, occurred after administration of IBU within the first 6 h of life (35). No case of severe hypoxaemia was observed in our curative study, using the same IBU formulation administered later, after assessment of pulmonary blood flow.

Lastly, another possible adverse effect of IBU is also a subject of concern, namely its potential to increase the free fraction of bilirubin (36), and thereby increase the risk of kernicterus. In a recent study, no significant bilirubin displacement was observed after intravenous administration of the currently used IBU dose regimen for the treatment of PDA in preterm infants during the first week of life (37). However, Ahlfors, in an *in vitro* study (38), showed that IBU induced significant displacement of bilirubin from albumin at serum IBU levels >100 μg/mL, the peak level achieved in one patient with a loading dose of 15 mg/kg in our study.

Finally, the main limitation of this study is that this estimation was based on the efficacy data of a single patient for the 20–10–10 mg/kg dose regimen. The tolerability and safety of this high dose regimen may therefore have not been correctly assessed. However, this study should encourage other larger phase II trials comparing the two dose regimens that are necessary to evaluate the safety of the 20–10–10 mg/kg dose regimen in this population of very immature preterm infants.

A very marked variability of plasma IBU concentrations was observed between subjects 5 min after the same loading dose, as plasma levels varied over a threefold range. Similar findings have been previously reported by Van Overmeire (25), who showed that inter-individual variability may change with postnatal age. He found age-related differences in IBU pharmacokinetics with half-lives of 43 ± 7·8 h and 28·6 ± 6·5 h on the third day and fifth day of life, respectively, a period which corresponds to our inclusion period. The inter-patient variability observed in our study suggests that the use of higher doses may expose some patients to a higher risk of adverse effects. However, no adverse effects were reported by Aranda in association with plasma levels higher than those observed in our study, in premature infants receiving IBU within 3 h after birth (26). Similarly, IBU concentrations 24 h after the last dose varied considerably.

No relationship was demonstrated in our study between plasma IBU concentrations and ductus closure, as the plasma IBU levels measured 5 min after the loading dose and 24 h after the last dose were higher in infants in whom ductus closure was obtained than in those in whom the ductus remained open, but the differences were not statistically significant. Further studies are needed to identify the plasma IBU level/ductus response relationship.

In conclusion, the currently used dose regimen of intravenous IBU (10–5–5 mg/kg/day) appears to be associated with the best risk/benefit ratio in premature infants with PMA of 27 weeks and more. This dose regimen results in <30% success in more immature infants with PMA <27 weeks. Higher doses improve the efficacy of IBU in both PMA groups, which would be particularly useful in the most immature infants. However, tolerability and safety should be carefully assessed in other studies before considering the possibility of using doses higher than the currently recommended doses.

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