BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2008.03118.x

An optimized ibuprofen dosing scheme for preterm neonates with patent ductus arteriosus, based on a population pharmacokinetic and pharmacodynamic study

Déborah Hirt,[1] Bart Van Overmeire,[2] Jean-Marc Treluyer,[1,3] Jean-Paul Langhendries,[4] Arnaud Marguglio,[4] Mark J. Eisinger,[2] Paul Schepens[5] & Saïk Urien[1,6]

[1]EA3620, Université Paris – Descartes, Paris [3]Pharmacologie Clinique, Assistance publique- Hôpitaux de Paris, Hôpital Cochin-Saint-Vincent-de-Paul, Université Paris – Descartes, Paris [6]Unité de Recherche Clinique, Paris-Centre, France, [2]Neonatology, Antwerp University Hospital, Antwerp [4]Neonatology CHC, Saint Vincent Rocourt, Liège and [5]Center for Toxicology, University of Antwerp, Antwerp, Belgium

Correspondence
Dr Déborah Hirt, Unité de Recherche clinique, Hôpital Tarnier, 89 rue d'Assas, 75006 Paris, France.
Tel.: + 33 158412884
Fax: + 33 1584 11183
E-mail: deborah.hirt@univ-paris5.fr

Keywords
ibuprofen, patent ductus arteriosus, population pharmacokinetics, threshold AUC

Received
25 June 2007

Accepted
28 November 2007

Published *OnlineEarly*
27 February 2008

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Ibuprofen is a nonsteroidal anti-inflammatory agent that induces closure of the patent ductus arteriosus in neonates.
- Few studies of ibuprofen pharmacokinetics have been performed and were limited to small groups of preterm infants, showing a large intersubject variability and an increase in clearance with either postnatal or gestational age.

WHAT THIS STUDY ADDS

- A population pharmacokinetic study was performed on 66 neonates to characterize the concentration-time courses of ibuprofen.
- Ibuprofen clearance significantly increased from postnatal age day 1 to day 8, but not with gestational age.
- A relationship was shown between ibuprofen area under the curve (AUC) and patent ductus arteriosus closure rate, and an effective threshold AUC was evidenced.
- Dosing schemes were proposed as a function of postnatal age, to achieve this AUC and to improve the efficacy of treatment for patent ductus arteriosus in neonates.

AIMS

To describe ibuprofen pharmacokinetics in preterm neonates with patent ductus arteriosus (PDA) and to establish relationships between doses, plasma concentrations and ibuprofen efficacy and safety.

METHODS

Sixty-six neonates were treated with median daily doses of 10, 5 and 5 mg kg^{-1} of ibuprofen-lysine by intravenous infusion on 3 consecutive days. A population pharmacokinetic model was developed with NONMEM. Bayesian individual pharmacokinetic estimates were used to calculate areas under the curve (AUC) and to simulate doses. A logistic regression was performed on PDA closure.

RESULTS

Ibuprofen pharmacokinetics were described by a one-compartment model with linear elimination. Mean population pharmacokinetic estimates with corresponding intersubject variabilities (%) were: elimination clearance CL = 9.49 ml h^{-1} (62%) and volume of distribution V = 375 ml (72%). Ibuprofen CL significantly increased with postnatal age (PNA): CL = 9.49*(PNA/96.3)$^{1.49}$. AUC after the first dose (AUC1D), the sum of AUC after the three doses (AUC3D) and gestational age were significantly higher in 57 neonates with closing PDA than in nine neonates without PDA closure (P = 0.02). PDA closure was observed in 50% of the neonates when AUC1D < 600 mg l^{-1} h (or AUC3D < 900 mg l^{-1} h) and in 91% when AUC1D > 600 mg l^{-1} h (or AUC3D > 900 mg l^{-1} h) (P = 0.006). No correlation between AUC and side-effects could be demonstrated.

CONCLUSIONS

To achieve these optimal AUCs, irrespective of gestational age, three administrations at 24 h intervals are recommended of 10, 5, 5 mg kg^{-1} for neonates younger than 70 h, 14, 7, 7 mg kg^{-1} for neonates between 70 and 108 h and 18, 9, 9 mg kg^{-1} for neonates between 108 and 180 h.

Introduction

The ductus arteriosus closes spontaneously in most healthy full term neonates. The closure may be delayed in premature infants suffering from respiratory distress syndrome. The significant left to right shunt arising from the persistency of a patent ductus arteriosus (PDA) may lead to increased neonatal morbidity and mortality [1, 2].

Ibuprofen is a nonselective nonsteroidal anti-inflammatory agent that induces closure of the patent ductus arteriosus by inhibiting cyclo-oxygenase [3, 4]. So far, few studies of ibuprofen pharmacokinetics have been performed, and only in small groups of premature infants [5–8], showing a very large variability in drug pharmacokinetic parameters. The aim of the present study was to characterize ibuprofen pharmacokinetics more extensively in a larger group of neonates and to optimize an individualized dosage schedule in neonates of variable gestational and postnatal age suffering from PDA. This was achieved by (i) developing a population pharmacokinetic model to describe the mean ibuprofen pharmacokinetics, (ii) using a pharmacostatistic model to identify infant characteristics that could influence the pharmacokinetics, the intersubject and residual variabilities and (iii) investigating relationships between AUC and ibuprofen efficacy and side-effects for PDA closure. The most relevant toleration parameter for ibuprofen is known to be potential renal toxicity, so in the study, renal side-effects were assessed using creatinine clearance and urine output.

Methods

Patients

Sixty-six very low-birth-weight infants with gestational age from 25 to 34 weeks, and postnatal age ranging from 14 to 262 h (1–11 days) (Table 1) with respiratory distress syndrome and haemodynamically significant PDA were enrolled. The patency of the ductus was evaluated by colour Doppler echography. Patients with congenital malformations, hydrops fetalis, intraventricular haemorrhage as evaluated by cranial ultrasonography, renal insufficiency, or documented infection were excluded. Clinical history since birth, daily 24 h urine production, respiratory support and concomitant treatment were carefully recorded, allowing us to analyze potential adverse effects linked to this treatment. The study protocol was approved by the Independent Medical Ethics Committee at both participating hospitals (Antwerp University Hospital and CHC St Vincent Hospital Liège, Belgium). Informed consent was obtained from parents.

Ibuprofen administration

Three daily doses of ibuprofen-lysine (Table 1) were given, the first was 10 mg kg^{-1}, the second and third each 5 mg kg^{-1}. The amount was calculated using the birthweight rounded to the nearest 100 g. The doses were given intravenously on 3 consecutive days at 24 h intervals. Ibuprofen-lysine was infused during a 15 min period with a syringe pump via a peripheral vein. The line was flushed afterwards with saline. Timing of ibuprofen administration and each end of associated flushing procedures were carefully recorded in hours and minutes. Time between the end of each administration and sampling was also carefully noted.

Table 1

Patient characteristics

	Median	Min	Max
At baseline			
Age (h) at first dose	69	14	262
Bodyweight (g) at first dose	1015	490	1986
Apgar score 1 min	6	0	9
Apgar score 5 min	8	4	10
Apgar score 10 min	8	1	10
Gestational age (weeks)	28	25	34
Serum creatinine before treatment (mg dl^{-1})	1.0	0.6	1.3
Albumin before treatment (g dl^{-1})	1.9	1.2	3
Urine output before treatment (ml kg^{-1} h^{-1})	3.4	0.9	7.7
Serum sodium before treatment (mEq l^{-1})	141	124	155
During treatment			
Dose at first administration (mg kg^{-1}*) (n = 66)	10	5.9	50
Dose at second administration (mg kg^{-1}*) (n = 63)	5	2	10.7
Dose at third administration (mg kg^{-1}*) (n = 49)	5	2	6.4
Serum creatinine change† (%)	–6.2	–38.8	121
Urine output change† (%)	–3.0	–76.9	142
Bodyweight change† (%)	–2.8	–18.8	25.0

*mg kg^{-1} at birth weight, dose was calculated to the nearest 100 g of birthweight.
†Relative change between day 0 and day 3 calculated from the formula: 100 × (value at day 3–value at day 0)/value at day 3.

Sampling

Blood samples were taken from an arterial line, at various times after the 15 min intravenous administration of ibuprofen, on days 1, 2 and 3.

Ibuprofen assay

Analysis of plasma ibuprofen concentration was performed at the Center for Toxicology at the University of Antwerp as described previously [6]. The analytical procedure from human plasma was shown to be linear from 1 to 100 mg l^{-1}, and the limit of quantification was validated at 1 mg l^{-1}. The overall imprecision (expressed as coefficient of variation) on ibuprofen concentrations was 5%.

Population pharmacokinetic modelling of ibuprofen

Data were analyzed using the nonlinear mixed effect modelling software program NONMEM (version V, level 1.1,

double precision) with the DIGITAL FORTRAN compiler [9]. The first-order conditional estimation (FOCE) method was used. Ibuprofen data were analyzed according to a one compartment, two compartment, or with a non linear (Michaelis Menten) pharmacokinetic model.

Several error models were investigated (i.e. exponential, proportional and additive error models) to describe intersubject and residual variabilities.

A generalized additive modelling was used to test systematically the influence of each covariate (bodyweight, gestational age, postnatal age, Apgar score, creatinine and albumin, serum sodium and urine output before treatment) on pharmacokinetic parameters, according to the following equation.

For example, using CL:

$$CL = TV(CL) \times [BW/\text{median}(BW)]^{\theta BW}$$

where TV(CL) is the typical value of clearance for a patient with the median covariate value and θ_{BW} is the estimated influential factor for bodyweight (BW).

The influence of previous administration of ibuprofen on its CL and *V* was studied using occasion as a covariate, independent of the age and weight effect. For example, IF(DAY.EQ.1) DD = 0, IF(DAY.GT.1) DD = 1, and CL = TV(CL) × (1 + θ(4) × DD).

All the covariates were tested via an upward model building. A covariate was selected if (i) its effect was biologically plausible; (ii) it produced a minimum decrease of 10.82 units (chi^2, 1 degree of freedom, $P < 0.001$) in the objective function value; (iii) it produced a reduction in the variability of the pharmacokinetic parameter, assessed by the associated intersubject variability; and (iv) the 95% confidence interval of the estimated influential factor should not include zero. Among the covariates tested on the base model, the most significant was added in an intermediate model. Then the other covariates were tested on this intermediate model and the most significant covariate was retained. This process was repeated until no more covariates were significant (i.e. $P > 0.001$)

For evaluation of the goodness-of-fit, the following graphs were compared: observed and predicted concentrations *vs.* time (Figure 1), population and individual predicted concentrations *vs.* observed concentrations, population weighted residuals *vs.* population predicted concentrations and population weighted residuals *vs.* time (Figure 2). Diagnostic graphics and distribution statistics were obtained using the R program (Rfn, https://sourceforge.net/project/showfiles.php?group_id=29501&package_id=140129&release_id=538680) [10].

Bootstrap evaluation

The accuracy and robustness of the final population model were assessed using a bootstrap method, as previously described in detail [11]. Briefly, this includes the following steps,

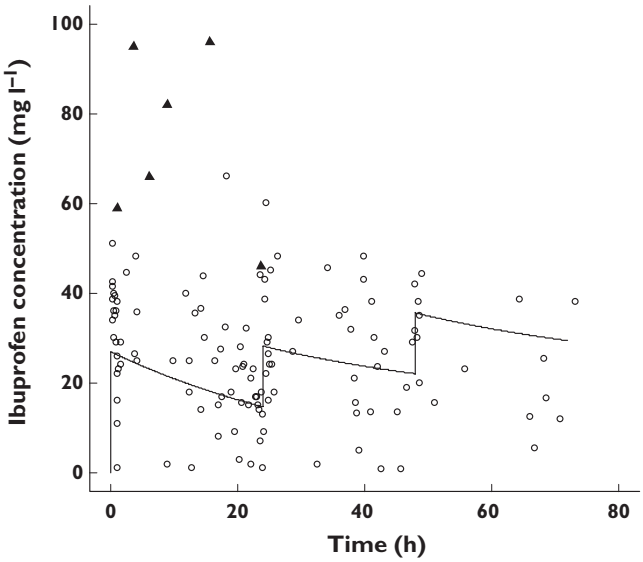

Figure 1

Observed concentrations (points) and population predicted concentrations (line) for a neonate with median postnatal age (69 h) and bodyweight (1015 g) as a function of time. Full triangles represent values of the six samples from the patient who had an overdose

1) from the original data set of *n* individuals, B bootstrap sets (B = 1000) of *n* individuals are drawn with replacement (resampling),
2) for each of the B bootstrap sets, the population pharmacokinetic parameters are estimated,
3) with the B estimates of each population pharmacokinetic parameter, the corresponding mean and SD are estimated,
4) to validate the model, the parameters estimated from the bootstrap must be close to estimates obtained from the original population set.

The entire procedure was performed in an automated fashion using Wings for NONMEM (http://wfn.sourceforge.net/wfninst.htm). This procedure also provided statistics of the population parameters.

Visual predictive check validation

Ibuprofen concentration profiles were simulated and compared with the observed data to evaluate the predictive performance of the model. More precisely, the vector of pharmacokinetic parameters from 1000 simulations of 66 patients was simulated using the final population model. Each vector parameter was drawn in a normal distribution with a variance corresponding to the intersubject variability previously estimated. A simulated residual error was added to each simulated concentration. The simulations were performed using NONMEM. The 10th, 50th and 90th percentiles of the simulated concentrations at each time were then overlaid on the observed concentration data using R program and a visual inspection was performed.

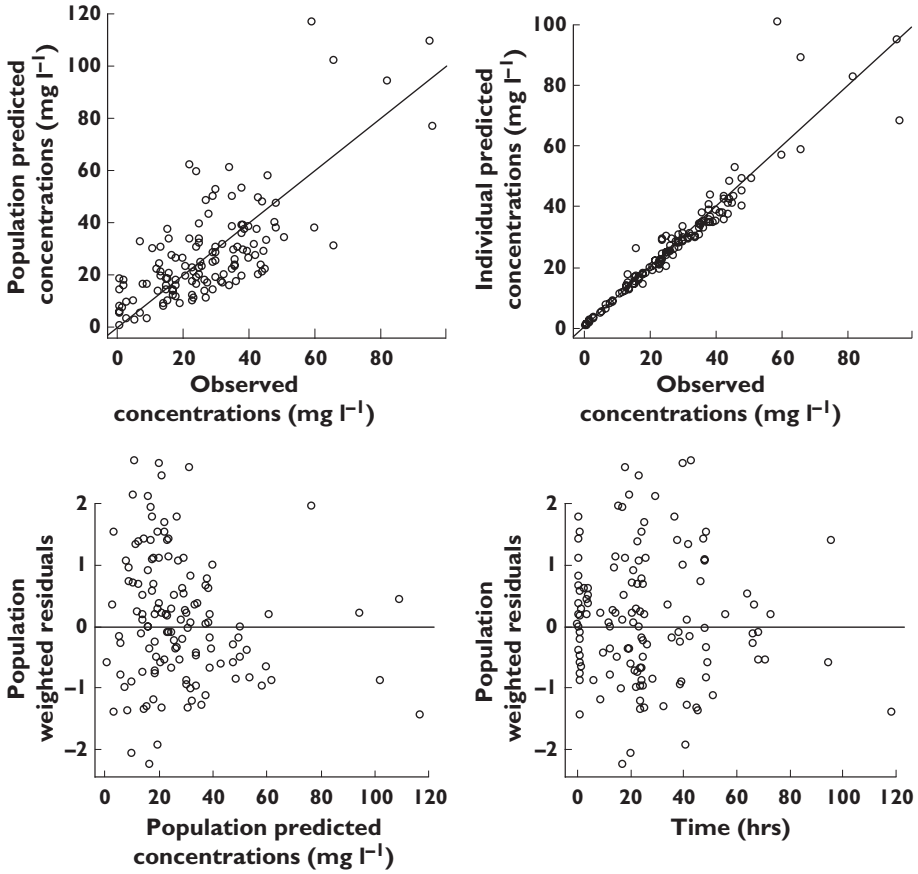

Figure 2

Goodness of fit plots based on final model for ibuprofen: population predicted concentrations *vs.* observed concentrations (top left), individual predicted concentrations *vs.* observed concentrations (top right), population weighted residuals *vs.* predicted concentrations (lower left) and population weighted residuals *vs.* time (lower right)

Statistics for pharmacokinetic-pharmacodynamic study

Individual pharmacokinetic parameters obtained from the POSTHOC option of NONMEM were used to estimate individual pharmacokinetic parameters, providing area under the curve (AUC) after the first administration (AUC1D, from 0 to 24 h) and the cumulated AUC for all the administrations (AUC3D, from 0 to 72 h). Differences between AUC values in the group of neonates with or without PDA closure were assessed by a Mann–Whitney test. The threshold AUC at which the probability of PDA closure was increased was determined by the use of a Fisher exact test performed for every 50 mg l^{-1} h increase in ibuprofen AUC. Then different doses kg^{-1} were simulated in each patient with individual parameters in order to achieve the threshold AUC. The proposed dose-adjustments were then evaluated, calculating the probability of success in 66 000 neonates, obtained from 1000 simulations of the 66 neonates of the database. A logistic regression was performed on PDA closure with AUC and covariates which significantly differed between groups with and without PDA closure. For side-effects, the relative difference in serum creatinine concentration (CRE0-3), urine output (UR0-3) and bodyweight (BW0-3) before the first dose (at baseline) and after the third administration were correlated with AUC1D and AUC3D by the use of Spearman regression.

Results

Demographic data

Sixty-six neonates (129 samples) were available for pharmacokinetic evaluation. Table 1 summarizes patient characteristics. Median age at first dose and gestational age were, respectively, 66 h (from 14 to 262) and 29 weeks of gestation (from 25 to 34) in neonates with PDA closure, 75 h (from 30 to 178) and 27 weeks of gestation (from 26 to 28) in neonates without PDA closure. One infant had an accidental overdose for the first dose (50 mg kg^{-1}). In 49 infants three samples were taken, in 14 infants two, and in three infants one sample was taken. Median sampling time was 13.2 h after the preceding infusion of ibuprofen, ranging from 8 min to 24 h 50 min. Ibuprofen concentration–time courses are depicted in Figure 1.

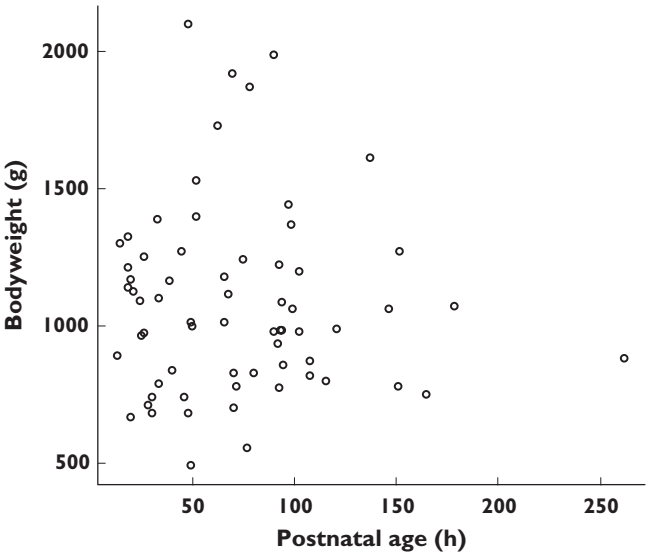

Figure 3

Plot of bodyweight *vs.* postnatal age for the 66 neonates

Population pharmacokinetics

Model building A one-compartment model adequately described the data. The NONMEM subroutine ADVAN1 TRANS2 was used to describe the one compartment model and the parameters of the model were the volume of distribution (*V*) and elimination clearance (CL). Intersubject and residual variabilities were best described by exponential and proportional error models, respectively. The effect of bodyweight, postnatal age, gestational age, apgar scores at 1, at 5 and at 10 min, and serum Na, serum creatinine, serum albumin and urine output before treatment were tested on elimination clearance and volume of distribution. Finally, ibuprofen elimination clearance significantly increased with postnatal age (from 1 to 8 days) resulting in a 55 units decrease in objective function value with a reduction in the intersubject variability of clearance. None of the other covariates reduced objective function value by more than 10.82 units. Figure 3 represents bodyweight as a function of postnatal age (median bodyweight = 1039 g, median postnatal age = 96.3 h); there was no significant link between these two covariates ($r^2 = 0.003$, $P = 0.66$). On the second and third day, clearance and volume of distribution were not significantly influenced by previous administrations of ibuprofen.

The following equation describes the final covariate model for ibuprofen:

$$CL = 9.49 \times (PNA/96.3)^{1.49} (ml\,h^{-1})$$

When postnatal age increased, clearance increased and volume of distribution did not change, leading to a decrease in half-life. By replacing PNA in the equations, half-lives were 42.2 h at 3 days, 19.7 h at 5 days, and 9.8 h at 8 days. As only one child was older than 8 days, this relationship was accurate only between 1 and 8 days. Table 2 summarizes base and final population pharmacokinetic estimates.

Table 2

Population pharmacokinetic parameters and bootstrap evaluation

Parameter	Base model Original dataset Mean (CV%)	Final model Original dataset Mean (CV%)	Bootstrap* Mean (CV%)
Structural model			
CL (ml h^{-1})	9.55 (14)	9.49 (10)	9.61 (12)
CL, θ_{AGE}	/	1.49 (17)	1.41 (21)
V (ml)	403 (19)	375 (10)	368 (11)
Statistical model			
σ (%)	26 (34)	18 (27)	18 (24)
ω (CL) (%)	98 (33)	62 (28)	62 (19)
ω (V) (%)	77 (45)	75 (44)	66 (35)

*Statistics from 1000 bootstrap analyses; Key: CV%, coefficient of variation (standard error of estimate/estimate × 100); σ residual variability estimates (CV of residual variability, %) and ω, interindividual variability estimates (CV of intersubject variability, %).

Model performance Final model performance can be seen in Figure 2.

Bootstrap assessment of the final population model The final model obtained with the original dataset was subjected to a bootstrap analysis. As shown in Table 2, the bootstrap means and coefficients of variation of parameter estimates obtained from the bootstrap process, 1000 runs, were close to the estimates previously obtained with the original dataset.

Validation The data are presented in Figure 4. The visual predictive check confirmed that the average prediction matched the observed concentration–time courses for the three different doses. The variability is reasonably estimated, since the 80% confidence interval for the proportion of observed data outside the bounds included the theoretical value of 20% for each dose.

Pharmacokinetic-pharmacodynamic study

In 57 of 66 (86%) neonates, the PDA was closed at the end of treatment, although all neonates received the same ibuprofen dose kg^{-1} bodyweight. AUC after the first dose of ibuprofen (AUC1D) and cumulated AUC for the three daily doses (AUC3D) were significantly higher in the 57 neonates with PDA closure than in the nine neonates without ($P = 0.02$) (Table 3, Figure 5). To increase significantly the probability of PDA closure, most discriminating AUC values were determined. PDA closure was observed for 50% (4/8) of the neonates when AUC1D < 600 mg l^{-1} h (or

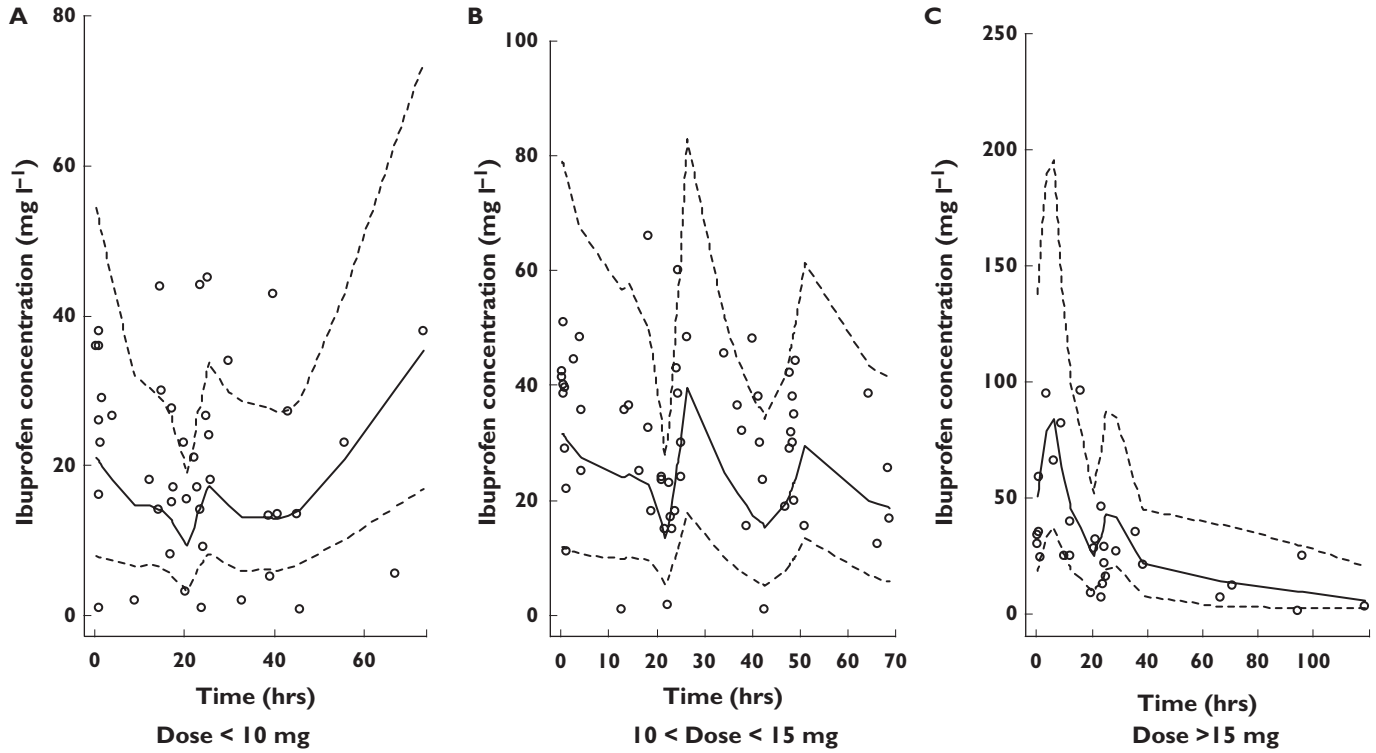

Figure 4

Evaluation of the final model: comparison between the 10th (dash line), 50th (full line) and 90th (dash line) percentile obtained from 1000 simulations, stratified by three dose groups of which the first dose was either (a) < 10 mg, (b) > 10 mg to < 15 mg and (c) >15 mg, and the observed data (points) for ibuprofen concentrations

Table 3

Pharmacodynamic results

	PDA closure ($n = 57$)		Non PDA closure ($n = 9$)		
	Mean	SD	Mean	SD	*P*
Concentrations comparisons					
AUC1D (mg l^{-1} h)	4620	5232	1581	1352	0.02
AUC3D (mg l^{-1} h)	5883	5865	2244	1724	0.02
Target concentrations					
AUC1D < 600 mg l^{-1} h or AUC3D < 900 mg l^{-1} h	4		4		0.006
AUC1D > 600 mg l^{-1} h or AUC3D > 900 mg l^{-1} h	53		5		

AUC1D, AUC after the first dose; AUC3D, cumulated AUC for the three doses.

AUC3D < 900 mg l^{-1} h) and 91% (53/58) when AUC1D > 600 mg l^{-1} h (or AUC3D > 900 mg l^{-1} h) ($P = 0.006$) (Table 3). AUC1D could be as well related to efficacy as AUC3D.

Gestational age did not influence significantly ibuprofen pharmacokinetics. However, a significant difference in gestational age was observed between neonates with and without PDA closure (28.6 *vs.* 27 gestation weeks, $P = 0.04$). Using logistic regression, an AUC value > 600 mg l^{-1} h significantly increased the probability for PDA closure ($P = 0.0054$) and a trend was found for gestational age ($P = 0.07$).

For side-effects, AUC1D and AUC3D were not significantly correlated with relative changes of serum creatinine and urine output during the 3 days of treatment. After 3 days of treatment, bodyweight significantly decreased with AUC1D ($P < 10^{-4}$) and with AUC3D ($P < 10^{-4}$). However postnatal age was highly correlated to both AUC1D and AUC3D ($P < 10^{-4}$) and to bodyweight decrease ($P < 10^{-4}$): infants younger than 30 h lost an average of 13.6% of their weight and their AUC was approximately five times higher than that of other infants. Comparable relationships were obtained for AUC1D or AUC3D.

In order to achieve an AUC1D above 600 mg l^{-1} h for all the neonates at the first dose, children younger than 70 h should receive 10 mg kg^{-1} as recommended, children between 70 and 108 h should receive a minimum of 14 mg kg^{-1} and children between 108 and 180 h should receive a minimum dose of 18 mg kg^{-1}. Accordingly, AUC values would range between 616 and 2790 mg l^{-1} h. To achieve an AUC3D higher than 900 mg l^{-1} h, the second and third doses should be increased proportionally to the first one. The ibuprofen administration scheme would be 10-5-5 mg kg^{-1} for children younger than 70 h, 14-7-7 mg kg^{-1} for children between 70 and 108 h and 18-9-9 mg kg^{-1} for children between 108 and 180 h. The

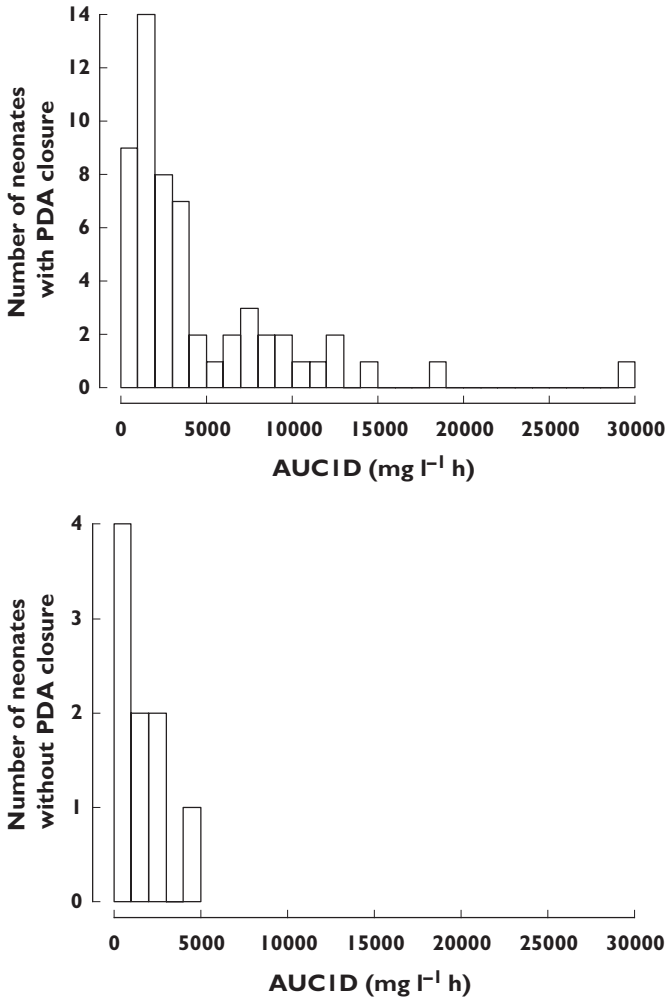

Figure 5
Histograms of AUC(0,24 h) as a function of treatment success

Table 4
Probability of success in the 66 000 simulated neonates

	Actual dosage	Proposed dosage
All neonates	88%	94%
Age <70 h	97.7%	97.7%
Age 70–108 h	83.5%	93%
Age >108 h	50%	80%

probability of success in 66 000 neonates (1000 simulations of our 66 neonates) was compared between the actual dosage of 10-5-5 mg kg^{-1} for all the neonates and the proposed dose-adjustments which depended on postnatal age (Table 4). In our study population, with the standard dosing scheme of 10-5-5 mg, older neonates are less successful: 100% of the neonates younger than 30 h, 91% of the neonates younger than 70 h, 87% of the 70–108 h old neonates and only 70% of the neonates older than 108 h had a PDA closure.

Discussion

This paper provides data on the pharmacokinetics of intravenously administered ibuprofen-lysine during treatment for PDA in premature infants with respiratory distress syndrome. We found that neonates who had an AUC1D > 600 mg l^{-1} h or an AUC3D > 900 mg l^{-1} h had a much higher percentage of PDA closure (91%) than neonates with a value below these thresholds (50%) (P = 0.006). Gestational age was significantly lower in neonates without PDA closure than in neonates in whom the ductus did close (P = 0.04). However, as assessed by logistic regression, AUC1D > 600 mg l^{-1} h was more predictive for ductal closure than gestational age. Gestational age did not significantly influence ibuprofen pharmacokinetics. We could not evidence any correlation between AUC and side-effects of ibuprofen use.

Ibuprofen pharmacokinetics were satisfactorily described by a one compartment model. Ibuprofen disposition has already been described by a two compartment model, but the sparse data (a median of two concentration–time samples per neonate) did not allow the identification of both volume of distribution of the peripheral compartment and intercompartmental clearance. Nevertheless, the following observations support the use of the proposed one compartment pharmacokinetic model:

1) ibuprofen mean plasma clearance CL = 9.49 ml h^{-1} or 9.13 ml h^{-1} kg^{-1} was consistent with a previously reported value: 9.49 ml h^{-1} kg^{-1} in 13 neonates [6]
2) ibuprofen mean volume of distribution V = 360 ml kg^{-1} was also consistent with this previous study: 357 ml kg^{-1} in 13 neonates on day 3 and 349 ml kg^{-1} on day 5 [6].
3) when postnatal age increased from 1 to 8 days, ibuprofen plasma clearance increased but volume of distribution did not change, leading to a decrease in half-lives: 42.2 h at 3 days and 19.7 h at 5 days. Previous studies reported half-lives of 43.0 h on day 3 and 26.8 h on day 5 [6].
4) goodness-of-fit depicted in Figure 2.

Ibuprofen is metabolized by the cytochrome P450 complex and more specifically by the CYP2C9 and CYP2C8 subfamily. It has been shown that the CYP2C protein content is barely detectable in newborns aged less than 24 h, increases steadily in the first week of life and reaches about one third of the adult value at the end of the first month [12]. In foetuses, the low amount of RNA is constituted by equal amounts of CYP2C8, 2C9, 2C18 RNA, and after birth the rise of total 2C RNA is essentially caused by an increase in CYP2C9 RNA, which represents a 10 fold

greater increase as compared with other subfamilies. These important maturational effects could explain the significant increase in ibuprofen clearance with postnatal age.

Age has already been shown to be related to the increase in ibuprofen clearance; however, Gregoire *et al.* [8] found gestational age whereas Van Overmeire *et al.* [6] and Aranda *et al.* [5] found postnatal age. In our final model, postnatal age had a much more important effect on clearance ($P < 10^{-4}$) than gestational age. This is in agreement with the findings of Treluyer *et al.* [12] showing that no relationship between the CYP2C content and the gestational age at birth could be detected in infants, so maturation of CYP2Cs depended only on postnatal age.

As clearance kg^{-1} increased with postnatal age, when the same dose kg^{-1} was administered to all neonates, exposure will decrease with age. In our study population, the oldest subjects were less successful on the standard regimen. All the children younger than 30 h had PDA closure, 91% of the neonates younger than 70 h, 87% of the 70–108 h old neonates and only 70% of the neonates older than 108 h had a PDA closure with the three recommended administrations of 10, 5 and 5 mg kg^{-1}. In order to improve the rate of PDA closure for all the neonates, minimal AUC1D and AUC3D needed and minimal doses to reach these AUCs were determined, comparing the nine neonates without PDA closure with the 57 neonates with PDA closure; however, there is a relative imbalance between the number of responders and non responders. The threshold AUC was found to be 600 mg l^{-1} h, after the first administration of ibuprofen for all the neonates. It was assumed that age did not influence the threshold AUC for PDA closure, as no proof of change in prostaglandin receptor types, subtypes, affinity to PGs and expression was given over a wide range of gestational or postnatal ages in preterm ductal tissue.

The results of this study suggest the following schedule for ibuprofen administration in the first days of life: to achieve threshold AUC values in all the patients, neonates younger than 70 h of postnatal age should receive at the first, second and third administrations, respectively, 10, 5 and 5 mg kg^{-1} as previously recommended; neonates between 70 and 108 h of postnatal age should receive a minimum of 14, 7 and 7 mg kg^{-1}; neonates between 108 and 180 h of postnatal age should receive a minimum dose of 18, 9 and 9 mg kg^{-1}. These proposed dose adjustments were confirmed by simulations. Using these schedules in infants older than 70 h would lead to similar AUC values to infants younger than 70 h. We did not consider keeping the same doses and reducing the time between administrations. For this reason and as there is no relationship between ibuprofen AUC increase and serum creatinine variation, it is unlikely that these new schedules would lead to ibuprofen toxicity. However these assumptions about efficacy and toxicity need to be tested prospectively.

REFERENCES

1 Hermes-DeSantis ER, Clymann RI. Patent ductus arteriosus: pathophysiology and management. J Perinatol 2006; 26: S14–8, S22–3.

2 Van Overmeire B, Chemtob S. The pharmacologic closure of the patent ductus arteriosus. Semin Fetal Neonatal Med 2005; 10: 177–84.

3 Adams SS, Bresloff P, Mason CG. Pharmacological differences between the optical isomers of ibuprofen: evidence for metabolic inversion of the (-) -isomer. J Pharm Pharmacol 1976; 28: 256–7.

4 Van Overmeire B, Smets K, Lecoutere D, Van de Broek H, Weyler J, Degroote K, Langhendries JP. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. N Engl J Med 2000; 343: 674–81.

5 Aranda JV, Varvarigou A, Beharry K, Bansal R, Bardin C, Modanlou H, Papageorgiou A, Chemtob S. Pharmacokinetics and protein binding of intravenous ibuprofen in the premature newborn infant. Acta Paediatr 1997; 86: 289–93.

6 Van Overmeire B, Touw D, Schepens PJ, Kearns GL, van den Anker JN. Ibuprofen pharmacokinetics in preterm infants with patent ductus arteriosus. Clin Pharmacol Ther 2001; 70: 336–43.

7 Sharma PK, Garg SK, Narang A. Pharmacokinetics of oral ibuprofen in premature infants. J Clin Pharmacol 2003; 43: 968–73.

8 Gregoire N, Gualano V, Geneteau A, Millerioux L, Brault M, Mignot A, Roze JC. Population pharmacokinetics of ibuprofen enantiomers in very premature neonates. J Clin Pharmacol 2004; 44: 1114–24.

9 Beal SL, Sheiner LB. NONMEM User's Guide; NONMEM Project Group. San Francisco: University of California, 1998.

10 Ihaka R, Gentleman R. R: a language for data analysis and graphics. J Comput Graph Stat 1996; 5: 299.

11 Parke J, Holford NH, Charles BG. A procedure for generating bootstrap samples for the validation of nonlinear mixed-effects population models. Comput Methods Programs Biomed 1999; 59: 19–29.

12 Treluyer JM, Gueret G, Cheron G, Sonnier M, Cresteil T. Developmental expression of CYP2C and CYP2C-dependent activities in the human liver: in-vivo/in-vitro correlation and inducibility. Pharmacogenetics 1997; 7: 441–52.