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Population Pharmacokinetics of Nalbuphine in Neonates

Evelyne Jacqz-Aigrain[1], Thierry Debillon[2], Patrick Daoud[2], Claire Boithias[2], Isabelle Hamon[2], Isabelle Rayet[2], Michel Popon[1] and France Mentré[3]

[1]*Department of Paediatrics and Pharmacology, Robert Debré Hospital, Paris*

[2]*Population Pharmacokinetic Network*

[3]*Department of Epidemiology, Biostatistics and Clinical Research, INSERM E0357, Bichat-Claude Bernard Hospital, Paris*

Corresponding Author

Professor Evelyne Jacqz-Aigrain, Pharmacologie Pédiatrique et Pharmacogénétique, Hopital Robert Debré, 48 Boulevard Sérurier, 75019, Paris, France Email: evelyne.jacqz-aigrain@rdb.ap-hop-paris.fr

Aim: **Nalbuphine is an opioid analgesic agent administered intravenously in critically ill neonates undergoing invasive procedures. Differences in the maturation of hepatic and renal function affect the disposition of drugs in neonates. As nalbuphine is primarily eliminated by metabolism, the aim was to characterise the disposition of nalbuphine in neonates and to identify the factors associated with inter-individual variability.**

Methods: **A pharmacokinetic population study was conducted in 71 neonates (40 boys) requiring intravenous analgesia for painful procedures associated with intensive care and artificial ventilation. They received nalbuphine as bolus doses of 50 to 270 microg/kg with repeated doses in some cases. Blood samples were collected 30 minutes and 3 hours after the first and fifth administrations when nalbuphine was given as repeated doses. Data were collected after the 5th administration in only 3 centres. Nalbuphine concentrations (n=170) were analysed by use of NONMEM and a one compartment model with two parameters: clearance (CL) and volume of distribution (V). The influence of birth weight, gestational age, postnatal age, other disease and co-medications were investigated.**

Results: **Both CL and V were found to be significantly related to birth weight. Using the concentrations measured after the first administration, the estimates of the population means and inter-individual coefficients of variations in the model including body weight were 0.40 L/kg/h (CV 61%) for CL and 2.44 L/kg (CV 30%) for V. In the final model including all significant covariates, it was found that CL and V were respectively 1.21 and 1.56 times higher in boys than in girls, and that V was 1.32 times higher in the presence of respiratory distress syndrome and 0.62 lower if other pulmonary disease was present. The analysis of the global data set showed that the inter-occasion variability was higher than the inter-individual variability and were respectively 92% and 61% for CL, and 51% and 30% for V in the model with birth weight only.**

Conclusions: **In the neonates studied, CL was lower than the values reported in older infants, children and adults. Birth weight was a major determinant of variability in nalbuphine disposition. Although the therapeutic interval remains to be determined, it is clear that the mean nalbuphine doses required for critically ill neonates are lower than those required for older infants.**

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Introduction

The management of pain is important in all neonates[1,2] but particularly during neonatal intensive care where invasive procedures are more frequent. A few pharmacological agents have been evaluated, such as lidocaine- pilocarpine for use in pre-emptive analgesia[3,4] and paracetamol, morphine and fentanyl for the treatment of ongoing pain[5-9] in these patients. Nalbuphine is currently administered intravenously in critically ill neonates under mechanical ventilation and undergoing invasive procedures but with an empirical dosing regimen.

Nalbuphine is an agonist-antagonist opiate with a duration of analgesia of 4–5 hours. In adults, nalbuphine is equipotent to or slightly less potent than morphine in acute pain[10]. Possible advantages over morphine are less respiratory depression at high doses and less effect on blood pressure[11]. After parenteral administration, it is metabolised by the liver to an inactive glucuronide congujate[12]. Pharmacokinetic data are available for adults and children over 18 months of age[13,14]. One study has reported data for a few neonates whose mothers had received nalbuphine for obstetric analgesia[15]. Differences in the maturation of hepatic and renal function[16] modify the disposition of drugs in neonates. The clearance of most drugs is slower in preterm than in term neonates and increases rapidly with age[7,17]. The use of inappropriate doses may reduce efficacy and be associated with toxicity. Therefore, the aim of the present study was to characterise the disposition of nalbuphine in neonates and to identify the factors associated with inter-individual variability.

Methods

Patients and data collection

The study, performed in six centres in France, was approved by the Ethics Committee of Paris – Bichat – Claude Bernard Hospital. Informed consent was obtained from the parents of the neonates. The population pharmacokinetic study was conducted in 71 neonates (40 boys) requiring intravenous analgesia for painful procedures associated with intensive care and artificial ventilation. Nalbuphine was administered as bolus doses of 50–270 microg/kg (mean 150 microg/kg). A few patients received repeated bolus doses every 6 hours.

It was planned to collect samples around 30 minutes and 3 hours after the first administration of nalbuphine and, when nalbuphine was given as repeated doses, again two samples at the same times after the fifth administration. Data after the fifth administration were only collected in three centres. Blood samples were drawn after the first administration in 70 neonates (137 samples). Among these 70 neonates, 16 neonates had blood samples collected after the fifth administration (31 samples). One patient had samples drawn after the fifth administration only (two samples). Therefore, a total of 170 plasma concentration measurements were included in the analysis.

Nalbuphine assay

All samples were assayed in the same laboratory. Nalbuphine plasma concentrations were determined by HPLC using electrochemical detection as previously described[18]. Briefly, 50µl of internal standard (naltrexone 100µg/ml) was added to 500 µl of plasma and 1.5 ml of 0.1 M ammonia in a 12 ml pyrex tube fitted with a PTFE lined screw cap. Samples were extracted with 8 ml hexane-dichloromethan-n-propylic alcohol (69:30:1 v/v) and centrifuged for 10 minutes at 4°C (3500 RPM). The upper organic layer was transferred and evaporated at 45°C under nitrogen flux. The residue was dissolved by 300 µl 17 mM phosphoric acid and 100 µl was injected in the HPLC system. The mobile phase was ammonium citrate 0.01 M pH 4.5 and the column was a LC8 (Supelco) 150 x 4.6 mm 5µm. The limit of quantification was 2.5 ng/ml. Calibration curves were linear over the range 5 to 200 ng/ml. The inter-assay variability was 8% for 40 ng/ml and 4% for 150 ng/ml. The intra-assay variability was 7% for 40 ng/ml and 2% for 150 ng/ml.

Table 1. Characteristics of the 71 neonates included in the population analysis (mean± SD)		
Parameter	***n***	**Value**
Nalbuphine dose (microg/kg)	71	150 ± 60
Birth weight (g)	71	1537 ± 739
Apgar score (5 min)	69	7.9 ± 1.9
Gestational age (weeks)	71	30.6 ± 3.7
Delay between birth and drug administration (days)	71	4.1 ± 3.7
Length of hospitalisation (days)	71	37.4 ± 30.4
Biochemistry		
Serum creatinine (µmol/L)	56	87.5 ± 22.8
Hematocrit (%)	67	43 ± 9
Serum protein (g/L)	57	45 ± 8
Serum bilirubin (µmol/L)	53	124 ± 48
Gender (boys / girls)	41 / 30	
Delivery (vaginal / Caesarean section)	26 / 45	
Diseases		
Acute fetal distress	8	
Respiratory distress syndrome	40	
Other pulmonary diseases	7	
Bacterial infection	17	
Surgery	11	
Other	15	
Comedications		
Aminoglycosides	47	
Other antibiotics	57	
Analgesics	37	
Vasoactive drugs	23	
Enzyme inducers	25	
Death	6	

Data analysis

The concentrations were analysed by a population approach using NONMEM (version 5.0, double precision) with the FOCE method for all runs[19]. The NONMEM output was analysed using Xpose for Splus[20] and standard statistical analyses were performed using SAS.

The unitary dose given to each neonate was used. Model development was performed along the following steps. The concentrations measured after the first administration of nalbuphine only were analysed to select the pharmacostatistical model and to build the model with covariates. There were no changes in covariates between the 1st and 5th administration; indeed data in most patients were available after the 1st administration only. In addition, concentration data after the first administration were more reliable because the timing of the first drug administration was recorded more precisely.

A basic pharmacostatistical model with data after the first administration and no covariates was first defined. It is composed of the pharmacokinetic model, the residual error model and the model of between patient variability. One and two compartment open pharmacokinetic models with IV bolus administration were compared (NONMEM, ADVAN1 TRANS2 and ADVAN3 TRANS3, respectively). Several error models were compared: additive, proportional or combined (additive + proportional). Inter-individual variability (IIV), which describes variability between patients, was modelled with exponential random effects on the pharmacokinetic parameters. The influence of birth weight on this basic model was also tested. The adequacy of the basic model was checked using the several goodness-of-fit plots proposed in Xpose[20].

With the best basic pharmacostatistical model, an exploratory analysis of the influence of several covariates was performed using empirical Bayes

Table 2. Construction of the population model and corresponding objective function (OBJ)		
Data set	**Model description**	**OBJ**
First administration		
	No adjustment for body weight, no covariates	–796.8
	Adjustment for body weight, no correlation between CL and V, no covariates	–922.2
	Adjustment for body weight, correlation between CL and V, no covariates	–942.3 [a]
	Adjustment for body weight, correlation between CL and V, gender effect on CL and V	–952.5 [b]
	Adjustment for body weight, correlation between CL and V, all four significant covariates	–962.6 [b]
Global data set		
	Adjustment for body weight, correlation between CL and V, all four covariates, no IOV	–1073
	Adjustment for body weight, correlation between CL and V, all four covariates, IOV on CL and V	–1126
	Adjustment for body weight, no IIV on V and no correlation between CL and V, all four covariates, IOV on CL and V	–1120 [b]
	Adjustment for body weight, correlation between CL and V, no covariates, IOV on CL and V	–1104
	Adjustment for body weight, no correlation between CL and V, no covariates, IOV on CL and V	–1096 [a]

[a] Detailed results reported in Table 3.
[b] Detailed results reported in Table 4.

estimates of the random effects of the pharmacokinetic parameters (post hoc). More precisely, the influence of the covariates on each individual random effect were first tested by a *t*-test (for categorical covariates) or by correlation test (for continuous covariates). The following covariates, in addition to birth weight, were tested: gestational age, APGAR score, delay between birth and first administration of nabulphine, serum creatinine and protein levels, haematocrit, gender, mode of delivery (vaginal/Caesarean section), assisted ventilation (yes/no), acute fetal distress (yes/no), respiratory distress syndrome (yes/no) or other pulmonary diseases (yes/no), co-medication with an enzyme inducer (clofibrate, yes/no), analgesic/sedative drugs (midazolam, yes/no), aminoglycosides (yes/no) or vasoactive agents (dopamine and/or dobutamine, yes/no). As several of these covariates are highly correlated, a stepwise multivariate linear regression for each random effect was then performed using the covariates found to be significant ($P < 0.05$) in the univariate analyses. The covariates that remained significant in these multiple analyses were then incorporated one by one in the population model and tested using a likelihood ratio test with a type I error of 5%, i.e., an increase of 3.84 in the objective function for one covariate was considered significant.

Finally, the complete set of data was analysed adding the concentrations measured after the fifth administration. Inter-occasion variability (IOV) was tested on each pharmacokinetic parameter with an exponential random-effect model. IOV describes intra-patient variability from one administration to the other. The model using all data was estimated with and without the covariates identified from the analysis of data from the first administration only. Model adequacy was checked by several goodness-of-fit plots.

Results

All neonates received nalbuphine for analgesia during intensive care procedures. The characteristics of the patients are presented in Table 1.

The one compartment model described the data adequately with satisfactory goodness-of-fit plots and standard errors of estimates. The population parameters of the two compartment model could not be estimated adequately and this model led to no improvement in the objective function. A one

Table 3. Population parameter estimates (and standard errors expressed in CV%) of the model adjusted by birth weight for the data after first administration only and for the global data set

	First administration	Global data set
CL (L/kg/h)	0.498 (11%)	0.401 (4%)
V (L/kg)	2.24 (8%)	2.44 (7%)
CL		
CV of IIV[a]	76.3% (27%)	61.5% (54%)
CV of IOV[b]	–	92.2% (31%)
V		
CV of IIV	58.4% (24%)	30.1% (103%)
CV of IOV	–	50.7% (43%)
Correlation (CL,V)	0.62 (32%)	–
σ(mg/L)	0.056 (89%)	0.090 (23%)
Objective function	–942.3	–1096

[a] IIV = inter-individual patient variability.
[b] IOV = inter-occasion or intra-patient variability.

compartment model was therefore chosen; it involved two parameters: clearance (CL) and volume of distribution (V). The best error model was an additive error model, which corresponds to a constant error model, and it was therefore chosen for the subsequent analyses. Exponential random effects were estimated for both V and CL.

The estimates of the population values (and inter-individual variability expressed as coefficients of variation) for this population model were 0.48 L /h (CV = 131%) for CL and 2.58 L (CV = 86%) for V. When a model, where both CL and V were corrected by body weight, was tested, an important decrease of the objective function (OBJ) from –796.8 to –922.2 was found (Table 2). This standardisation by body weight was kept in all subsequent analyses. A covariance between CL and V was tested and led to a further improvement (OBJ fell from –922.2 to –942.3). The population parameters of this basic model are given in Table 3; the mean (and interpatient variability expressed as a CV) values were 0.50 L/kg/h (CV = 76%) for CL and 2.24 L/kg (CV = 58%) for V; these results illustrated the decrease in interpatient variability (IIV) compared to a model with no adjustment for birth weight. The goodness-of-fit plots for this model were satisfactory.

The relationships with the other covariates were then tested using this model. The multivariate analysis using the empirical Bayes estimates of the random effects of CL and V found significant effects of gender on CL; of gender, serum creatinine, respiratory distress syndrome (RDS), other pulmonary diseases and acute fetal distress on V. These covariates were then included one by one in the population model using the likelihood ratio test. When serum creatinine values were missing (14 patients) the mean value of 87.69 μmol/L was used. In the population model a significant effect of gender on both CL and V ($P<0.006$) was found; then a significant effect of RDS on V ($P<0.04$) and then a significant effect of other pulmonary diseases on V ($P<0.02$). The model describing the influence of these covariates on V and CL was as follows:

$$V = \theta_V \quad (\beta_{V,gender})^{gender} \quad (\beta_{V,RDS})^{RDS} \quad (\beta_{V,OPULM})^{OPULM}$$

$$CL = \theta_{CL} \quad (\beta_{CL,gender})^{gender}$$

where θV and θCL are the mean V and CL for girls with no RDS or other pulmonary diseases and the parameters β quantify the effects of male gender, presence of RDS and presence of other pulmonary diseases on V and CL.

The population parameter estimates with only gender in the model and with all these covariates are given in Table 4. The effect of gender on both CL and V was the most important with a fall of 10.6 in the objective function. This factor led to an increase of 64% and 54% in mean CL and V, respectively, in boys compared to girls, but only a slight decrease in inter-individual variability (from 76.3% to 71.2% for CL and from 58.4 % to 54.2% for V). The addition of the two other covariates

Table 4. Population parameter estimates (and standard errors expressed in CV) of the final model with covariates for the data after first administration only and for the global data set

	First administration		Global data set
	Gender only	All covariates	All covariates
CL (L/kg/h)	0.375 (17%)	0.371 (17%)	0.386 (5%)
V (L/kg)	1.78 (12%)	1.56 (15%)	1.69 (13%)
CL			
CV of IIV [a]	71.2% (27%)	73.0% (27%)	45.6% (113%)
CV of IOV [b]	–	–	102.0% (27%)
V			
CV of IIV [a]	54.2% (24%)	50.5% (23%)	0
CV of IOV [b]	–	–	50.3% (19%)
Correlation (CL,V)	0.60 (30%)	0.58 (25%)	–
σ (mg/L)	0.060 (68%)	0.056 (68%)	0.090 (27%)
Effects of			
Gender on CL	1.66 (21%)	1.64 (21%)	1.21 (7%)
Gender on V	1.52 (15%)	1.54 (13%)	1.56 (13%)
RDS on V	–	1.32 (14%)	1.35 (12%)
Pulmonary disease on V	–	0.62 (15%)	0.56 (20%)
Objective function	–952.5	–962.6	–1120

[a] IIV = inter-individual patient variability.
[b] IOV = inter-occasion or intra-patient variability.

to V led to a fall of 10.1 in the objective function and represented an increase of 30% in V for neonates with respiratory distress syndrome and a decrease of 62% in V when other pulmonary diseases are present. However, the variability on V only fell to 50.5%, which is again a small decrease compared to the variability observed when only gender was included in the model (54.2%).

The next step focused on the analysis of the global data set with all concentrations (170) obtained after the first and fifth administrations of nalbuphine. The final model adjusted for body weight and containing all the covariates was used to analyse all the data. Without the addition of inter-occasion variability (IOV) on CL or V, all estimated population parameters were similar to those obtained with data from the first administration only. However, there was an increase in the estimate of the standard deviation of the residual error from 0.056 mg/L with data of the first administration only to 0.16 mg/L for all data. When random effects for inter-occasion variability were added both for CL and for V, the objective function decreased from –1073 to –1126 (Table 2). Unfortunately, all the variance parameters could not be estimated precisely in that model; furthermore it was found that inter-patient variability on V was only 25% and was lower than IOV. Therefore, in the final model, IIV for V and the covariance between CL and V were set to 0. The objective function was –1120. The estimated population parameters of this model are given in Table 4, which shows that the fixed effects parameters are similar to those estimated with data after the first administration only. The inter-occasion variability is higher than the inter-individual variability for CL (102 % for IOV and 46 % for IIV) and for V (50 % of IOV, IIV fixed to 0), which suggests a high variation between the two days of administration. We also estimated IIV and IOV with the global data set when covariates were not included to check whether similar results were observed regarding variability. The best model included IIV and IOV for both CL and V, and the population parameters are given in Table 3. Again, IIV was higher than IOV for CL (92 % for IOV, 61 % for IIV) and for V (51 % for IOV and 30% for IIV). The value for IIV on V was not estimated with good accuracy but was needed in the model but the covariance between CL and V could be fixed to 0.

Discussion

In premature and term neonates, individual pharmacokinetic studies are considerably limited by the amount of blood that can reasonably be

Table 5. Mean pharmacokinetic parameters (and coefficient of variation) of intravenous nalbuphine according to age

	CL (L/kg/h)	Volume (L/kg) of distribution
Neonates[a] (25 to 42 weeks of gestational age)	0.40 (61%)	2.44 (30%)
Children[b] (1.5 – 5 years)	2.89 (43%)	3.62 (49%)
Children[b] (5 – 8.5 years)	2.51 (41%)	3.63 (51%)
Adults[b] (23 – 32 years)	1.78 (1%)	5.45 (26%)
Elderly patients[b] (65 – 90 years)	1.41 (39%)	4.30 (46%)

[a] Present study.
[b] From reference 14.

obtained. The population approach, which allows pooling of data, is now used[21,22]. In the past decade, population pharmacokinetic parameters for neonatal patients have been determined for many drugs, such as antibiotics and sedative drugs[23,24] but population data on analgesics are only available for paracetamol[25]. However, administration of analgesics is an important component of the management of pain in neonatal intensive care units[2], as important adverse effects of pain and stress have been shown in these patients[26].

Nalbuphine is used as an analgesic drug for neonates receiving mechanical ventilation in the NICU. The pharmacokinetics of nalbuphine are usually described by a two compartment model with a rapid distribution phase and a slower elimination phase. The distribution half-life in young children of 1.5 to 5 years was estimated to be 5.4 minutes[14] whereas it was estimated to be 53 minutes in healthy volunteers[13]. In the present study, the first samples were supposed to be drawn about 30 minutes after the injection so that distribution should have been complete and consequently a one compartment model was adequate. In addition, the number of early samples was limited and did not allow characterisation of the rapid distribution phase.

Neonates are a very heterogeneous population and in our study, gestational age ranged from 25 to 42 weeks and birth weight ranged from 0.5 to 4.5 kg. In the studied population, birth weight significantly influenced both CL and V and the analysis was therefore performed with parameters adjusted by birth weight. In the final model, the mean CL was 0.401 L/kg/h and V was 2.44 L/kg. The main additional determinant of CL and V was gender: CL and V were respectively 1.21 and 1.56 times higher in boys. This rather unusual effect of gender on both parameters might be related to the linear adjustment by birth weight, which is perhaps not strictly linear. It has been suggested in a population pharmacokinetic analysis of paracetamol in neonates, infants and children, based on allometric models, that a correction to body weight by a power less than one is perhaps more appropriate[23]. They used a factor of 0.75 for CL but a factor of 1 for volume. Mean birth weight was higher in the 41 boys (1612± 822 g) than in the 30 girls (1434 ±604 g). However, the ratio of body weights is only 1.12, and the ratio of body weight to the power 0.7 is 1.08, which are both lower than the estimated effects of gender, especially for V. This does not explain the increased V in boys found in the present study. The other mildly significant effects on V were related to respiratory distress syndrome (V 1.35 times higher) and other pulmonary diseases (0.56 times lower). The inter-patient variability in the model with covariates (Table 4) after the first administration was large for both parameters (CV of 73% and 50 % for CL and V). When inter-occasion variability was estimated, IIV decreased and main variability was explained by IOV. These results suggested high changes in the neonates from one administration to the other, whereas no general trend was found, i.e. no bias in the prediction.

The present population study was undertaken as data in the literature are very limited in adults and children and no data were available in neonates. Table 4 summarises the results found in the present study and those estimated from 7 young infants, 7 older infants, 9 adults and 9 elderly patients using extensive sampling after

single administration of nalbuphine[14]. In the neonates studied, CL was lower than the values reported in older infants, children and adults. Birth weight was a major determinant among the factors of variability of nalbuphine disposition. Although the therapeutic interval remains to be determined, the mean nalbuphine doses required for critically ill neonates are much lower than those required for older infants.

Differences between countries and centres in the management of pain in neonates and in the drugs chosen are important, although a consensus statement for the management of pain in neonates has been published[2]. This pharmacokinetic study of nalbuphine demonstrates the reduced clearance in neonates in comparison with young children[14]. The next step will be to perform a pharmacokinetic-pharmacodynamic study, using a pain score validated for neonates, evaluating lower and standardised doses of nalbuphine.

Appendix

The following members of the "Population Pharmacokinetic Network" took part in the present study:

Clamart	Hopital Antoine Béclère, **C. Boithias**
Montreuil	Centre hospitalier intercommunal, **P. Daoud**
Nancy	Maternité régionale A. Pinard, **I. Hamon**
Nantes.	Centre Hospitalier Universitaire Hotel Dieu, **Th. Debillon**
Paris	Hôpital Robert Debré, Paris, **E. Jacqz-Aigrain.**
Saint-Etienne	Centre hospitalier Régional Universitaire, **I. Rayet**

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