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Population pharmacokinetics of nalbuphine after surgery in children

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Editor's key points

- This study reveals paediatric population data for nalbuphine, an opioid analgesic agent widely used for control of mild-to-severe pain.
- A two-compartment allometric power model developed in this study best described the data.
- Allometric models in children well described the relationships between clearances, volumes of distribution, and weight and might be useful for dose adjustments.

Background. Nalbuphine is an opioid analgesic agent widely used for control of mild-to-severe pain. However, limited data are available on the pharmacokinetics of this drug in children. The aim of this study was to characterize the population pharmacokinetics of nalbuphine in patients with ages ranging from 1 to 11 yr and to identify patient characteristics partially explaining inter-individual variability in nalbuphine pharmacokinetic parameters.

Methods. Twenty-two children were included in this study. They received nalbuphine after surgery by continuous infusion (loading dose, 0.2 mg kg^{-1} over 10 min followed by continuous infusion of 0.8 mg kg^{-1} over 24 h). If pain relief was not adequate, 0.1 mg kg^{-1} bolus doses were allowed in 10 min. Eleven blood samples were collected per patient. The data were analysed by non-linear mixed-effect modelling with the use of a two-compartment structural model.

Results. Twenty patients completed the study. In the final model, the parameter values were standardized for a body weight of 70 kg using an allometric model. Population parameter estimates were: clearance 130 litre h^{-1} 70 kg^{-1}, inter-compartment clearance 75.6 litre h^{-1} 70 kg^{-1}, central volume of distribution 210 litre 70 kg^{-1}, and peripheral volume of distribution 151 litre 70 kg^{-1}. In the children of this study, total clearance expressed in litre h^{-1} kg^{-1} decreased significantly with increasing age and the elimination half-life significantly increased.

Conclusions. The allometric power model developed in this study best reflected the data and may be useful for dose adjustment.

Keywords: population pharmacokinetics; surgery, laparoscopy; children

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Nalbuphine hydrochloride [(−)-17(cyclobutylmethyl)-4,5α-epoxymorphinan-3,6α,14-triol hydrochloride] is a synthetic narcotic agonist–antagonist analgesic of the phenanthrene series with a duration of analgesia of 4–5 h.[1] It is structurally related to narcotic antagonist, naloxone, and to the potent narcotic analgesic, oxymorphone. Nalbuphine is used to treat and prevent moderate to severe pain; it can also be used for pain relief before and after surgery and during childbirth. In adults with acute pain, its analgesic potency is equivalent to that of morphine on a milligram basis.[2] In regard to morphine, nalbuphine could induce less respiratory depression at high doses and less effect on arterial pressure.[3] This drug undergoes an important hepatic metabolism in humans giving *N*-hydroxycetocyclobutylmethyl nornalbuphine, the major metabolite, and hydroxylated derivatives.[1] The estimated hepatic extraction ratio of nalbuphine is 0.5–0.7; thus, its hepatic clearance will be mainly dependent on hepatic blood flow.[4 5] Pharmacokinetic data of this drug are limited; studies have been carried out in adults, children, and neonates.[4 6–8] It is well known that the pharmacokinetics of most drugs are age-dependent.[9–11] Maturation of metabolic pathways takes place at a different rate; the metabolic clearance of drugs is usually very low at birth and then increases to reach a maximum at about the age of 1 yr when it can exceed that of adults. Simultaneously, water compartments are significantly larger in children than in adults. Thus, the treatment of postoperative pain by drugs extensively metabolized in the liver raises a challenge to the clinician who takes care of them.

Although nalbuphine has been approved for clinical use in children, pharmacokinetic data of the drug remain very limited. Nicolle and colleagues[7] reported data for a few

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neonates whose mothers had received nalbuphine during labour. Jacqz-Aigrain and colleagues[8] have reported data of a population pharmacokinetic study carried out in neonates. These authors found that birth weight is a major determinant of variability in nalbuphine disposition. Jaillon and colleagues[4] have shown that the elimination half-life of nalbuphine is shorter in infants of 1.5–5 yr of age than in those of 5–8.5 yr and that systemic clearance per kilogram of body weight decreased with age. However, only seven infants have been included in each group. The present study was designed to provide data on pharmacokinetics of nalbuphine in a paediatric population aged 1–11 yr old. The purpose of this study was (i) to determine accurate population pharmacokinetic parameters by using a two-compartment open model; this model was parameterized in terms of total clearance, central volume of distribution, inter-compartment clearance, and peripheral volume of distribution, (ii) to accurately estimate both inter- and residual variability in pharmacokinetic parameters, and (iii) to identify which of the patient physiological parameters could have influenced drug disposition. These data provide further valuable information regarding appropriate paediatric dosing.

Methods

Study design

The study protocol was reviewed and approved by the institutional review board. It was performed in accordance with the legal requirements and the Declaration of Helsinki, and with current European Community and US Food and Drug Administration guidelines for good clinical practice. Written informed consent was obtained from the parents or legal guardians.

Twenty-two infants undergoing laparoscopic fundoplication for gastro-oesophageal reflux aged 1–11 yr were included in this study. They were admitted in the department of paediatric surgery of the Lapeyronie Hospital (Montpellier, France). For all children, pre-anaesthetic data, anamnestic data, physical examination, and standard laboratory tests which included haematological and biochemical tests were performed before and at the end of the study. Each subject's measurements of alanine aminotransferase, aspartate aminotransferase, bilirubin (direct bilirubinaemia <2 mg dl^{-1}), creatinine (creatininaemia <1 mg dl^{-1}), red blood cell count, white blood cell count, platelet count, haematocrit, and haemoglobin were within normal ranges. Also children receiving analgesics or anti-inflammatory drugs the week before surgery were excluded. Anaesthesia was standardized for all patients. Patients were fasting for 6 h. One hour before surgery, they received midazolam (0.4 mg kg^{-1}) as rectal premedication. Upon arrival in the operating theatre, standard monitoring equipment was applied, an i.v. line was established, and anaesthesia was started with propofol (4 mg kg^{-1}) and remifentanil (1 mg kg^{-1}). After tracheal intubation, anaesthesia was maintained with sevoflurane (1 MAC end-tidal concentration in 50% oxygen and air) and remifentanil (0.4 μg kg^{-1} min^{-1}). Neuromuscular block was obtained with atracurium (0.5 mg kg^{-1} to maintain a train-of-four count of 1) at the beginning of surgery. A second i.v. line was inserted into a femoral vein to facilitate subsequent blood sampling. Central temperature was carefully maintained above 35.5°C using a forced air system. Ventilation was adjusted to maintain end-tidal CO_2 between 30 and 35 mm Hg at the beginning of surgery. No further change in ventilation was allowed during the study period. At skin closure, remifentanil and sevoflurane were stopped, end of neuromuscular block was assessed, and children were allowed to breathe 100% O_2 spontaneously. After surgery, children received niflumic acid, a selective inhibitor of cyclooxygenase 2, by rectal route (20 mg kg^{-1} twice a day), acetaminophen i.v. (30 mg kg^{-1}, four times a day), and nalbuphine i.v. according to the following protocol: the loading dose, 0.2 mg kg^{-1}, over 10 min was given at wound closure followed by continuous infusion of 0.8 mg kg^{-1} over 24 h. In addition, 0.1 mg kg^{-1} bolus doses were allowed in 10 min if pain relief was not adequate, but no more than twice within 1 h and no more than five times for the 24 h study period. If pain remained unacceptable, nalbuphine would be stopped and rescue analgesia would be provided using i.v. morphine. Pain, evaluated every hour and 30 min after each additional dose of nalbuphine, was considered unacceptable when the Children and Infants Postoperative Pain Score (CHIPPS)[12] exceeded 2 on a maximum of 10.

Blood sampling

It was planned to collect heparinized blood samples (2.5 ml) from each patient at the following times: (i) immediately before and (ii) at the end of the loading dose, (iii) 12 and 24 h after the beginning of i.v. infusion, and (iv) 0.25, 0.5, 1, 2, 4, 6, and 12 h after the end of infusion. Immediately after collection, plasma was separated by centrifugation (1500*g*) within 10 min and was frozen at −30°C until assayed.

Nalbuphine assay

Nalbuphine was quantified in human plasma by high-performance liquid chromatography using tandem-mass spectrometry detection (LC-MS/MS). The internal standard used was morphine. The LC system equipped with an autosampler set at 4°C was coupled to a PE Sciex API 365 quadrupole MS (Applied Biosystem MDS Sciex, Courtaboeuf, France) with a turbo electrospray ion source that was operated in a positive ionization mode with the nebulizer and TurboIonSpray gases (nitrogen) set at 12 and 30 pounds per square inch (psi), respectively. The voltage and temperature were maintained at 4500 V and 250°C, respectively. Nitrogen gas was used in a collision-induced dissociation at a back pressure of approximately level 6. Nalbuphine was quantified via a multiple reaction monitoring mode of the transitions at *m/z* 358.2→340.2 for nalbuphine and *m/z* 286.2→286.2 for morphine, with a dwell time of 500 ms per transition. Optimized collision energy of 10 eV was used for nalbuphine and 14 eV for

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morphine. The chromatographic separation was carried out on a 30×5 mm (5 μm) reversed-phase Lichrospher ODS2 LC column operating at room temperature (~21°C). An isocratic mobile phase consisting of ammonium formate (1 mM)–acetonitrile (80:20, v/v) containing 1% formic acid was used at a flow rate of 0.3 ml min^{-1}. A 10 μl sample was injected onto the column. Samples were extracted using the solid-phase extraction (SPE) automate Aspec XL4 on Bond Elut C18 (100 mg) cartridges. SPE cartridges were first conditioned with 1 ml of methanol, 1 ml of distilled water, and 1 ml of Tris-buffered saline solution (pH 7.5) and then plasma samples were loaded onto the cartridges. The column was then rinsed with 1 ml of distilled water. The elution was carried out with 1 ml of a mixture of acetonitrile–water (80:20, v/v) containing 1% formic acid. The organic phase was evaporated under a stream of nitrogen at 40°C. The peak area ratios (nalbuphine/internal standard) varied linearly with concentration over the range of 1–100 μg $litre^{-1}$. All calibration curves were weighted according to the $1/x^2$ weighting scheme. The method was precise (precision, ≤12%) and accurate (recovery, 91–100%). Mean extraction efficiencies >80% for each analyte were obtained. No significant matrix effects occurred. Dilution has no influence on the performance of the method. The lower limit of quantitation (LLOQ) was 1 μg $litre^{-1}$.

Pharmacokinetic analysis

Pharmacokinetic model-building analyses were performed using the non-linear mixed-effects modelling (NONMEM) software (version 5.1.1, Globomax LLC, Hanover, MD, USA)[13] through the Visual-NM graphical interface.[14] The following covariates were considered pertinent to this study: patients' age, body surface area, weight, height, gender, and the ASA score (physical status classification system before surgery). A two-compartment model fitted data better than a one- or a three-compartment pharmacokinetic model. This model was parameterized in terms of total clearance (CL), central volume of distribution (V_1), inter-compartment clearance (Q), and peripheral volume of distribution (V_2). First-order conditional estimation was used to fit the models because individual data sets were extensive.[13] The structural model was chosen on the basis of changes in −2 log-likelihood and on graphical analyses of the goodness of fit. Because −2 log-likelihood is approximately χ^2 distributed and the addition of one compartment increases the degree of freedom by a factor of 4, a change of 9.49 in −2 log-likelihood was required at the 5% significance level to select the more complex model. Several error models were compared: additive, exponential, or combined (additive+exponential). It was found that residual variability was best described by an exponential error model given below:

$$C_{ij}(t) = f(P_j, D_{ij}, t_{ij}) \times \exp(\varepsilon_{ij}) \quad (1)$$

where P_j is the pharmacokinetic parameter of the subject j, t_{ij} the time of the ith measurement, D_j the dosing history of the subject j, f the pharmacokinetic model, and ε_{ij} the residual deviation of the model from the observations and contains contributions from intra-individual variability, assay error, and model misspecification for the dependent variable. ε is assumed to be a random Gaussian variable with mean zero and variance of ω_ε^2. Inter-individual variability in pharmacokinetic parameters was assessed according to an exponential error model; the P_j parameter of the jth subject was described by the relationship:

$$P_j = P_{\text{mean}} \times \exp(\eta_P) \quad (2)$$

where P_j is the pharmacokinetic parameter of subject j, P_{mean} the population pharmacokinetic parameter, and η_P a Gaussian random variable with mean zero and variance of $\omega_{\eta P}^2$.

Individual parameters were calculated as empirical Bayes estimates using the POSTHOC option in NONMEM. Several secondary pharmacokinetic parameters were calculated from the individual primary pharmacokinetic parameters: the volume of distribution at steady-state (V_{ss}) and the half-life ($t_{1/2}$) of the terminal part of the curves.

After selection of the best basic pharmacostatistical model, both a traditional approach and an allometric scaling were used to test the influence of covariates. In a first step, the relationships between the individual pharmacokinetic parameters and the above-mentioned covariates were investigated graphically. Covariates showing a strong correlation with a pharmacokinetic parameter were then separately incorporated in the population model and tested for statistical significance. Both linear functions and power models were tested (covariates being centred or not around the mean values). The effect of each covariate was assessed by the likelihood ratio test, based on the difference in the objective function values between hierarchical models. The forward inclusion and backward elimination method was applied for covariate model development.

In a second step, allometric scaling[15–17] was also tested to assess the influence of weight on CL, Q, V_1, and V_2:

$$\text{Param}_j = \text{Param}_{\text{std}} \times \left[\frac{\text{WT}_j}{\text{WT}_{70\ \text{kg}}}\right]^{\gamma} \quad (3)$$

with γ=0.75 for clearances and γ=1 for volumes of distribution. In this equation, Param_j is the parameter in the jth individual with a weight of WT_j and $\text{Param}_{\text{std}}$ the parameter in an individual with a weight of 70 kg ($\text{WT}_{70\ \text{kg}}$).

Quality of fit

Criteria for model selection included visual inspection of goodness-of-fit plots [i.e. measured concentrations (DV) *vs* population (PRED) and individual predictions (IPRED); weighted residuals (WRES) *vs* PRED; and WRES *vs* time after administration]. The performance of Bayesian estimation was assessed by examining the prediction error (PE); PE was defined as [(DV–IPRED or PRED)/IPRED or PRED]×100%. Both MDPE (median of all PEs) and MDAPE (median of all absolute PEs) were calculated.

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Using the final covariate model, the visual predictive checks (VPCs) were carried out by simulating 1000 virtual data sets to assess the performance of the model. This analysis was performed using the R program. The 5th, 50th (population median response), and 95th percentile concentrations were plotted against time post-dose and the patients' data were superimposed.

Simulations

We selected an average concentration of 12 μg litre^{-1} as the therapeutic concentration for the design of an effective dosing regimen for nalbuphine. This concentration corresponds to the mean steady-state plasma concentration observed in this study. Simulations were performed using parameters of the final model to determine the optimal treatment schedule of nalbuphine needed to maintain this concentration. Typical patients of weight 10 kg (1–2 yr old), 13 kg (2–5 yr old), and 24 kg (5–11 yr old) were assumed for simulation purposes. Moreover, we have characterized the pharmacokinetics of elimination of nalbuphine in terms of the 20%, 50%, and 80% context-sensitive decrement times.

Validation of the final model

The bootstrap resampling procedure was used for evaluating the stability and robustness of the final model.[18] The bootstrap resampling was repeated 1000 times to evaluate whether an appreciable discrepancy existed between the parameter values estimated from the original data and the estimated bootstrap mean values. Final population parameters were compared with those obtained from the 1000 bootstrap analyses.

Results

All patients received planned continuous analgesia and no therapeutic failure (i.e. shift to morphine) was observed. There were 14 patients (63.6%) who required at least one additional bolus of nalbuphine. This first bolus was given at a mean time of 2.2 h after surgery (SD: 2.3 h). Nine patients (41.0%) received a second bolus at 7.4 h, seven received a third bolus at 10.0 h, three a fourth bolus at 12.6 h, and one a fifth bolus at 19.8 h. All resulted in a decrease in CHIPPS from 6.5 down to 0.7 within 30 min. Drowsiness was observed in seven patients (31.8%), nausea in three (13.6%), and urinary retention in three. Out of 22 children enrolled in the study, two were excluded for lack of blood samples. Baseline patient characteristics of the 20 children (six girls and 14 boys) who completed the study are presented in Table 1. Eight children had an ASA score of I, 10 had an ASA score of II, and two had an ASA score of III. Depending on the patient, 4–6 h after the end of infusion, nalbuphine concentrations were below the LLOQ of the analytical method. Therefore, a total of 157 plasma concentration measurements were included in the analysis.

A decrease in the objective function of 60.6 is associated with the use of a two-compartment model compared with a one-compartment model. The use of a three-compartment model led to failure in model convergence. Before covariate inclusion (Step 1), population pharmacokinetic parameters are summarized in Table 2. During covariate analysis, two models gave good results: (i) the addition of weight and age on CL [$CL = weight \times (-age \times \theta_1 + \theta_2)$] and age on V_1 [$V_1 = \theta_3 \times (age/4.2)^{\theta_4}$] to the base model produced a decrease in objective function of 44.6 units; and (ii) the use of allometric scaling results in an improvement of the objective function of 39.3 units. For both models, the fits to the data were excellent and the differences were relatively small. As the first model has two more parameters than the allometric model, it is not statistically better. Moreover, criteria on the quality of fit were slightly better for the allometric model. Thus, this model was selected as the final model.

Table 1 Patient characteristics. CI, confidence interval

	Age (yr)	Weight (kg)	Height (cm)	Body surface area (m^2)
Mean	4.2	15.6	97.6	0.64
95% CI	3.0–5.4	12.4–18.7	90.3–104.9	0.56–0.72
Maximum	11	34.0	137	1.0
Minimum	1	7.2	74	0.39

The estimated population parameters of nalbuphine in the final model are shown in Table 2. It was not possible to estimate population parameter variability on V_2. The ratios of the between-subject variance predictable from covariates to the total population parameter variance obtained without covariate analysis are presented in Table 3. Inclusion of body weight decreased the variance of CL and V_1, but increased the variance of Q. A reason may be that there is no ω for V_2 (having a large variance of 0.473 in the basic model) in the allometric model, so that the high variance of Q may in part be attributable to V_2. Results presented in Table 3 indicate that 39% and 65% of the overall variability in V_1 and CL are predictable from covariate information, respectively.[19] Mean pharmacokinetic parameters of nalbuphine in the 20 children who completed this study are presented in Table 4. The elimination half-life of nalbuphine increased with age (from 1.7 h in 1- to 2-yr-old children to 3.5 h in 7–11 yr old) and the CL in litre h^{-1} kg^{-1} decreased (from 3.3 to 2.2 litre h^{-1} kg^{-1}, in the two groups, respectively; Fig. 1).

The goodness of fit has been evaluated by comparing the regression line estimated on the DV *vs* IPRED values [slope: 1.04, 95% confidence interval (CI): 0.99–1.06; intercept: −0.57 μg litre^{-1}, 95% CI: −1.4 to 0.023] to the reference line of slope=1 and intercept=0, and no significant difference occurred (Supplementary Fig. S1A). Likewise, the slope of the regression line DV *vs* PRED was not statistically different from 1 and the intercept was not statistically different from 0 (slope: 1.04, 95% CI: 0.97–1.10; intercept: −0.20 μg litre^{-1}, 95% CI: −1.63 to 1.22) (Supplementary Fig. S1B). Moreover, adequate plots were observed in the final model

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Table 2 Population pharmacokinetic parameters of nalbuphine. IIV, inter-individual variability; SE, standard error of estimate expressed as coefficient of variation; σ, residual variability; CL, total clearance; V_1, initial volume of distribution; V_2, peripheral volume of distribution; Q, inter-compartment clearance; PEs, prediction errors; MDPE, median of all PEs; MDAPE, median of all absolute PEs; DV, observed concentrations; IPRED, individual predicted concentrations; PRED, population predicted concentrations

	Basic model		Final covariate model (allometric model)	
	Mean (SE, %)	IIV, % (SE, %), shrinkage, %	Mean (SE, %)	IIV, % (SE, %), shrinkage, %
Population parameters				
CL (litre h^{-1})	41.6 (9.4)	31.2 (39.9), 13.6		
CL (litre h^{-1} 70 kg^{-1})			130 (5.1)	18.4 (36.7), 7.86
V_1 (litre)	39.9 (8.5)	39.1 (38.3), 37.0		
V_1 (litre 70 kg^{-1})			210 (8.7)	30.7 (53.1), 28.5
V_2 (litre)	27.9 (19.7)	68.8 (57.5), 28.6		
V_2 (litre 70 kg^{-1})			151 (14.0)	Not estimated
Q (litre h^{-1})	15.7 (36.6)	22.4 (28.7), 44.7		
Q (litre h^{-1} 70 kg^{-1})			75.6 (35.2)	34.8 (53.5), 34.4
σ (%)	24.7 (18.0)		24.1 (21.4)	
MDPE (%)				
(DV *vs* IPRED)	−1.78		0.17	
(DV *vs* PRED)	3.70		−0.40	
MDAPE (%)				
(DV *vs* IPRED)	10.7		11.3	
(DV *vs* PRED)	28.3		22.8	

Table 3 Effect of covariate analysis on variance (ω^2). PPV2, total population parameter variance obtained without covariate analysis; BSVP2, between subject variance predictable from covariates; BSVR, random between subject variance estimated when covariate analysis is included; CL, total clearance; V_1, initial volume of distribution; V_2, peripheral volume of distribution; Q, inter-compartment clearance

	PPV2	BSVP2	BSVR	BSVP2/PPV2
CL	0.0979	0.0641	0.0338	0.65
V_1	0.153	0.059	0.0941	0.39
V_2	0.473	Not estimated		
Q	0.050	−0.071	0.121	−1.42

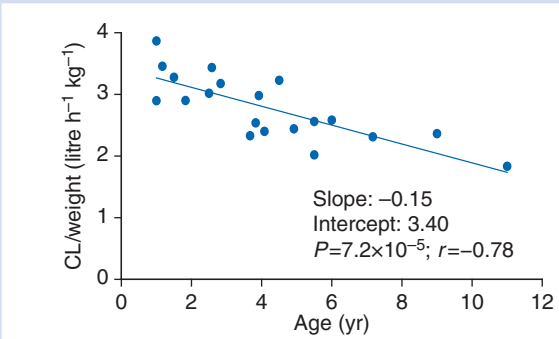


Fig 1 Scatter plots showing the relationship between individual weight-normalized CL values and age.

Table 4 Mean pharmacokinetic parameters of nalbuphine in the 20 children of this study undergoing laparoscopic fundoplication. IIV, inter-individual variability; CL, total clearance; V_1, initial volume of distribution; V_2, peripheral volume of distribution; Q, inter-compartment clearance; V_{ss}, steady-state volume of distribution; $t_{1/2}$, half-life of the terminal part of the curve

	Mean	IIV (%)
CL (litre h^{-1})	41.0	35.1
V_1 (litre)	47.3	51.1
V_2 (litre)	34.0	48.3
Q (litre h^{-1})	24.1	33.5
V_{ss} (litre)	81.3	48.0
$t_{1/2}$ (h)	2.7	18.3

between weighted residuals and predicted concentrations (Supplementary Fig. S1C). The vast majority of the weighted residuals lay within 2 units of perfect agreement and were symmetrically distributed around the zero ordinate; no systematic deviations were observed. For the final model, the MDPE and MDAPE of the population predictions PRED were −0.40% and 22.8%, respectively (Table 2). These values were in a typical range for pharmacokinetic models. The plot of PEs *vs* time shows random distribution around the zero ordinate (data not shown). The VPC plot (Fig. 2) confirms the adequacy of model predictions, showing no apparent deviations between model and data. About 95% of the data fit well within the 5th–95th percentiles band and the

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data were symmetrically distributed around the median. The time–concentration profile (with 90% CI) for a 4-yr-old child weighing 16 kg is presented in Figure 3.

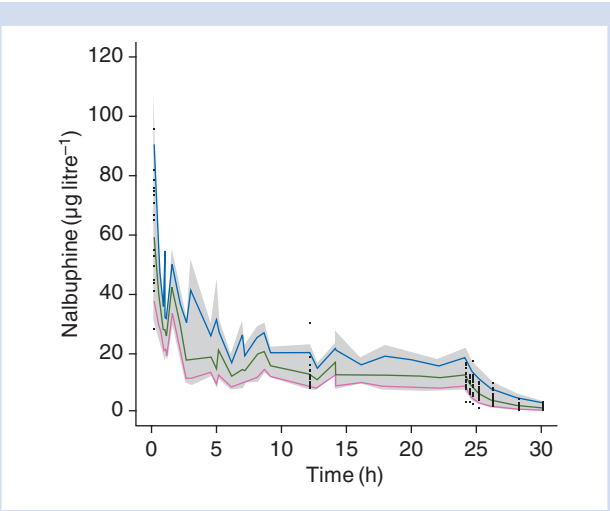


Fig 2 VPC plot for the studied population. The middle line depicts the model predicted median. The other lines (above and below the median) present the 5th and 95th percentiles. The grey area depicts the range between the 1th and 99th percentiles. Black dots are observations.

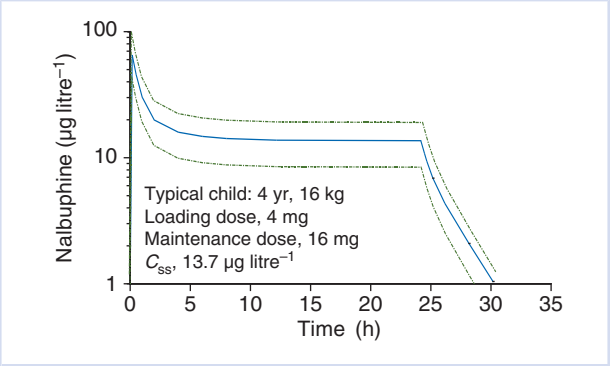


Fig 3 Time–concentration profile for a child aged of 5 yr and weighing 20 kg. The dashed lines represent the 90% CIs. C_{ss}, steady-state plasma concentration

Table 5 presents (i) the simulation results for different ages and weights to obtain a target concentration of 12 μg litre^{-1} and (ii) context-sensitive decrement times for 20%, 50%, and 80% concentration decrement. These dosing schedules result in 85% of simulated subjects having concentrations above 12 μg litre^{-1} at steady state (between 12 and 15 μg litre^{-1}). Three children of 1, 1.5, and 7.2 yr have steady-state nalbuphine concentrations of 9.7, 8.8, and 8.3 μg litre^{-1}, respectively.

The final model was fitted repeatedly to 1000 bootstrap-resampled data sets. Less than 6% of bootstrap runs were unsuccessful. The average parameter values obtained from the bootstrap analyses and the final estimates from the original data set are compared in Table 6. These results indicated that the reliability and robustness of the parameter estimates and thus the population pharmacokinetic model was acceptable.

Discussion

The present study was undertaken in the light of the limited information regarding pharmacokinetics of nalbuphine in children.[4 7 8] With the exception of neonates,[8] these published studies have been performed in a limited number of subjects.[4 7] Both NONMEM and non-parametric expectation maximization methods have been used for population pharmacokinetic modelling in children. In this study, nalbuphine population characteristics were estimated using NONMEM. This population modelling method described nalbuphine data well. Different pharmacokinetic models were tested; the structural model was chosen on the basis of the changes in −2 log-likelihood and qualitative assessment of diagnostic plots. Contrary to the findings reported by Jacqz-Aigrain and colleagues,[8] a two-compartment model was found to fit the data satisfactorily. This model was in agreement with that published by Jaillon and colleagues.[4]

The number of patients finally included in this study was 20. In infants having about the same age, there are marked inter-patient variations in weight (e.g. in patients between 3 and 4 yr of age, the body weight ranged from 8 to 15 kg). These results were in agreement with those reported by Jacqz-Aigrain and colleagues[8] in neonates. It has been suggested that the use of allometric models in

Table 5 Dosing regimens that attain a target concentration of 12 μg litre^{-1} at steady-state and context-sensitive decrement times

Age (yr)	Mean weight (kg)	Loading dose over 10 min (mg)	Maintenance dose over 24 h (mg)	Context-sensitive decrement times (min)		
				% concentration decrement		
				20	50	80
Range, 1–2; mean, 1.5	10	0.40 (0.040 mg kg^{-1})	9.6 (0.960 mg kg^{-1})	19	54	168
Range, >2–5; mean, 3.5	13	0.65 (0.050 mg kg^{-1})	12.1 (0.931 mg kg^{-1})	22	62	193
Range, >5–11; mean, 7.5	24	1.10 (0.046 mg kg^{-1})	16.0 (0.666 mg kg^{-1})	25	80	246

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Table 6 Bootstrap validation of the estimated population pharmacokinetic parameters in the final model

Parameters	Original data		1000 bootstrap replicates	
	Mean estimate	2.5% quantile, 97.5% quantile	Mean estimate	2.5% quantile, 97.5% quantile
CL (litre h^{-1})	130	115, 145	131	118, 144
V_1 (litre)	210	166, 255	208	164, 251
V_2 (litre)	151	129, 173	153	128, 180
Q (litre h^{-1})	75.6	55.0, 96.2	75.8	54.6, 96.9
Inter-individual variability				
ω^2CL	0.0338	0.0140, 0.0536	0.0324	0.0128, 0.0613
ω^2V_1	0.0941	0.0405, 0.148	0.0929	0.0436, 0.142
ω^2V_2	Not estimated			
ω^2Q	0.121	0.0280, 0.215	0.123	0.0272, 0.218
Residual variability, σ^2	0.0580	0.0353, 0.0807	0.0563	0.0340, 0.0841

children well described the relationships between clearances and weight and volumes of distribution and weight.[15–17 19] In the current study, different covariate models were examined: the traditional approach using a linear or power model and the allometric model. The best results were obtained using the allometric model. Such a parameterization avoids additional parameters in the model and allows a comparison of children parameter estimates with those reported in adults and neonates. A large proportion of the parameter variability (39% and 65% of the overall variability in V_1 and CL, respectively) can be attributable to the inclusion of weight in the model. In our population of children, the mean CL was 41.0 litre h^{-1}, mean V_{ss} was 81.3 litre, and mean $t_{1/2}$ elimination was 2.7 h. After weight adjustment, CL was 2.78 litre h^{-1} kg^{-1} and V_{ss} was 5.5 litre kg^{-1}. Similar CL values were found by Jaillon and colleagues[4] in infants (1.5–8.5 yr). As reported by these authors, systemic clearance of nalbuphine expressed in litre h^{-1} kg^{-1} decreased significantly with age (Fig. 1) and the elimination half-life significantly increased. At the age of 11 yr, children have a CL about two times lower than at the age of 1 yr. In the present study, V_{ss} and the elimination half-life were 1.5–2 times higher than that reported by Jaillon and colleagues.[4]

The population model developed in this study predicts nalbuphine plasma concentrations accurately and with good precision as evidenced by small MDPE and MDAPE values (−0.4% and 22.8%, respectively) and the results of the VPC plots. The result of bootstrap analysis validation indicated that the reliability and robustness of the parameter estimates and thus the population pharmacokinetic model was acceptable.

Patients who completed the study received administered doses of nalbuphine ranging from 1 to 1.4 mg kg^{-1} day^{-1} (mean, 1.12 mg kg^{-1} day^{-1}) including one to four additional bolus doses required in 14 children to maintain adequate pain relief. The bolus dose at the initiation of treatment ranged between 0.18 and 0.21 mg kg^{-1} (mean, 0.2 mg kg^{-1}), reaching a mean nalbuphine plasma concentration of 63.3 μg $litre^{-1}$. The maintenance dose ranged between 0.73 and 0.83 mg kg^{-1} (mean, 0.8 mg kg^{-1}). The maximum dose of 1.4 mg kg^{-1} day^{-1} was administered to two children of 4.1 and 5.5 yr old. For simulations, we have selected an average concentration of 12 μg $litre^{-1}$ as the therapeutic concentration for nalbuphine. It is remarkable that in most of the patients who required additional bolus doses, the nalbuphine concentrations were lower than 10 μg $litre^{-1}$. Moreover, the majority of these patients had maintenance doses lower than those predicted from simulated data. For a typical 3.5-yr-old child, weighing 13 kg, an initial bolus dose of 0.050 mg kg^{-1} nalbuphine and a maintenance dose of 0.931 mg kg^{-1} over 24 h achieve and maintain the steady-state plasma concentration of 12 μg $litre^{-1}$. Overall, the treatment was well tolerated by the children and none of them required morphine rescue analgesia.

Patients of this study received co-administration of midazolam, propofol, remifentanil, sevoflurane, and acetaminophen. Nalbuphine is metabolized via cytochrome P-450 3A4 (CYP3A4) and 2C19.[20] CYP3A4 is responsible for the metabolism of numerous therapeutic drugs including midazolam and acetaminophen.[21 22] Anaesthetic agents—remifentanil, propofol, and sevoflurane—were selected to avoid clinical interference with pain evaluation and proved rapid elimination. Midazolam also had a short elimination half-life, between 1.5 and 2.5 h and was given at least 3 h before nalbuphine.[23] Acetaminophen was administered after surgery, four times a day; it is likely that therapeutic blood levels are much higher than those of nalbuphine. Thus, a risk of non-competitive inhibition of the metabolism of nalbuphine by acetaminophen, as previously reported for fentanyl,[24] might occur. However, in clinical practice, acetaminophen is routinely associated with opioid analgesics as part of multimodal analgesic procedures; nalbuphine–acetaminophen drug interactions have never been reported. Concerning the other co-administered drugs, there is no risk of pharmacokinetic interactions.

In conclusion, we reported for the first time the results of a population pharmacokinetic analysis carried out in children to estimate individual pharmacokinetic parameters of nalbuphine. This study demonstrates the importance of considering and incorporating weight as a covariate in order to adequately describe the drug behaviour. The allometric power model developed in this study best reflected the data and may be useful for dose adjustment.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Conflict of interest

None declared.

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