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Population pharmacokinetics of nefopam in elderly, with or without renal impairment, and its link to treatment response

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Nefopam is a centrally acting non-opioid analgesic indicated for treatment of postoperative pain after abdominal, urological or orthopaedic surgery, either alone or in combination with other drugs.
- There is limited knowledge about nefopam pharmacology in the elderly. This is a challenging patient group to study.

WHAT THIS STUDY ADDS

- This study describes nefopam pharmacology in the elderly to propose guidelines for practical use. Nefopam pharmacokinetic predictors of morphine requirement and side effects were determined.
- A single dose of nefopam (20 mg) should be infused over a period >45 min in aged patients with or without renal impairment.

AIMS

Nefopam is a nonmorphinic central analgesic, for which no recommendation exists concerning adaptation of regimen in aged patients with or without renal impairment. The objective was to describe the pharmacology of nefopam in aged patients to obtain guidelines for practical use.

METHODS

Elderly patients ($n = 48$), 65–99 years old, with severe or moderate renal impairment or with normal renal function, were recruited. Nefopam (20 mg) was administered as a 30 min infusion postoperatively. Simultaneously, a 1 min intravenous infusion of iohexol was performed, in order to calculate the glomerular filtration rate. Blood samples were drawn to determine nefopam, desmethyl-nefopam and iohexol plasma concentrations. Nefopam and desmethyl-nefopam concentrations were analysed using a nonlinear mixed-effects modelling approach with Monolix version 4.1.3. The association between pharmacokinetic parameters and treatment response was assessed using logistic regression.

RESULTS

A two-compartment open model was selected to describe the pharmacokinetics of nefopam. The typical population estimates (between-subject variability) for clearance, volume of distribution, intercompartmental clearance and peripheral volume were, respectively, 17.3 l h^{-1} (53.2%), 114 l (121%), 80.7 l h^{-1} (79%) and 208 l (63.6%). Morphine requirement was related to exposure of nefopam. Tachycardia and postoperative nausea and vomiting were best associated with maximal concentration and the rate of increase in nefopam plasma concentration.

CONCLUSIONS

We identified the nefopam pharmacokinetic predictors for morphine requirement and side-effects, such as tachycardia and postoperative nausea and vomiting. In order to maintain morphine sparing and decrease side-effects following a single dose of nefopam (20 mg), simulations suggest an infusion time of >45 min in elderly patients with or without renal impairment.

Introduction

Elderly people undergo more surgical procedures than younger individuals [1, 2], and pain in the elderly is poorly controlled [3–5]; therefore, providing adequate postoperative analgesia is critical and essential. Several pharmacological agents combined according to different strategies, as in multimodal analgesia, can be used for pain management [4, 6, 7]. Nefopam (nef) is a centrally acting non-opioid analgesic indicated for treatment of postoperative pain after abdominal, urological or orthopaedic surgery, either alone or in combination with other drugs [8–10]. In contrast to opioid analgesics, nefopam has no respiratory-depressive effect [11, 12] and provides a better quality of analgesia [10, 13–15]. After administration, nefopam is mainly metabolized by the liver; seven metabolites have been described, with only one, desmethyl-nefopam (dnef), denoting pharmacological activity and found at very low concentrations [16]. The main route of elimination of the metabolites is renal [17]. Nevertheless, only one study focused on nefopam pharmacokinetics in patients with end-stage renal disease [18]. Furthermore, interpatient variability in pharmacokinetics and pharmacodynamics consequent to physiological age-related impairments and pathological changes in cardiac, renal and hepatic function must be taken into account in order to adjust the analgesic treatment regimen [4–7]. Aged patients more frequently experience cardiovascular and respiratory side-effects from drugs [5]. However, due to the lack of studies focusing on the link between pharmacokinetics and treatment response, no scientific rationale is available to date for the optimal administration schedule of nefopam in the aged patient. Indeed, no therapeutic monitoring guidelines for nefopam are available. In the present work, the objective was to explore the relationships between nefopam and desmethyl-nefopam pharmacokinetic parameters in aged patients, with or without renal impairment, and morphine requirement and side-effects (nausea and tachycardia).

Patients and Methods

After approval by the Reims Ethics Committee (protocol: PHRC-2004-R11-07; registered at agence française de sécurité sanitaire des produits de santé AFSSAPS: 060493), this single-centre, open prospective study was conducted in the University Hospital of Reims (France). After obtaining written informed consent, patients between 65 and 99 years of age scheduled for repair of a fractured hip were enrolled in this study between June 2006 and August 2011. Renal function was characterized as normal [Cockroft–Gault glomerular filtration rate (GFR) >60 ml min^{-1} (1.73 m)$^{-2}$], moderate impairment [Cockroft–Gault GFR <60 ml min^{-1} (1.73 m)$^{-2}$] or severe impairment [Cockroft–Gault GFR ≤30 ml min^{-1} (1.73 m)$^{-2}$]. Exclusion criteria were nonsigned consent form, nefopam contraindication (hepatic insufficiency defined as a prothrombin level below 70% or haemostasis impairments, epilepsy, glaucoma and prostate adenoma), hypersensitivity to nefopam or to iodinated contrast media, congestive heart failure, unstable angina, sequelae of cardiac infarction, uncontrolled arrhythmia and haemodialysis.

Before surgery, patients received sedative premedication with hydroxyzine. The surgical procedure was performed under general or regional anaesthesia at the discretion of the anaesthesiologist in charge of the patient. In the postanaesthetic care unit, when patients had fully recovered from general anaesthesia (tracheal tube removed) or when the anaesthetic level of spinal anaesthesia was below T10, 20 mg of nefopam hydrochloride (Acupan® injectable; Biocodex, Montrouge, France; IUPAC name, 5-methyl-1-phenyl-1,3,4,6-tetrahydro-2,5-benzoxazocine) diluted with 0.9% of saline solution was infused over a 30 min period using an infusion pump. Twenty-nine minutes after beginning nefopam infusion, a 1 min intravenous infusion of 5 ml iohexol (Omnipaque 180®, GE HEALTHCARE SAS, Vélizy-Villacoublay, France) was performed, in order to estimate the GFR. Iohexol clearance has been described as a gold standard that reflects the GFR in the elderly (GFRio) [19]. Blood samples for the determination of nefopam, desmethyl-nefopam and iohexol were drawn 0, 5, 10, 15, 30, 60, 120, 180, 240, 480 and 1440 min after nefopam and iohexol administration. Plasma nefopam, desmethyl-nefopam and iohexol concentrations were determined as previously described [19, 20].

Population pharmacokinetics

A population approach, with the nonlinear mixed-effect modelling implemented in Monolix (version 4.1; http://www.lixoft.eu), was used to study the pharmacokinetic profile of nefopam and desmethyl-nefopam [21]. Parameters were estimated by computing the maximum likelihood estimator without any approximation of the model, using the stochastic approximation expectation maximization (SAEM) algorithm combined with an MCMC (Markov Chain Monte Carlo: 2 for the number of chain) procedure [21–25]. All runs were carried out more than six times to ensure that estimated parameters and likelihood remained stable.

Separate structural model nefopam and desmethyl-nefopam concentrations were described using compartmental pharmacokinetic modelling (Figure 1). For nefopam concentrations, one, two and three mammillary compartment models, included in the Monolix (version 4.1) software library, with first-order distribution constants were tested (see Supporting Information). For desmethyl-nefopam, the MLXTRAN language included in Monolix (version 4.1) was used. One, two and three mammillary compartment models, with zero- or first-order input, meta-

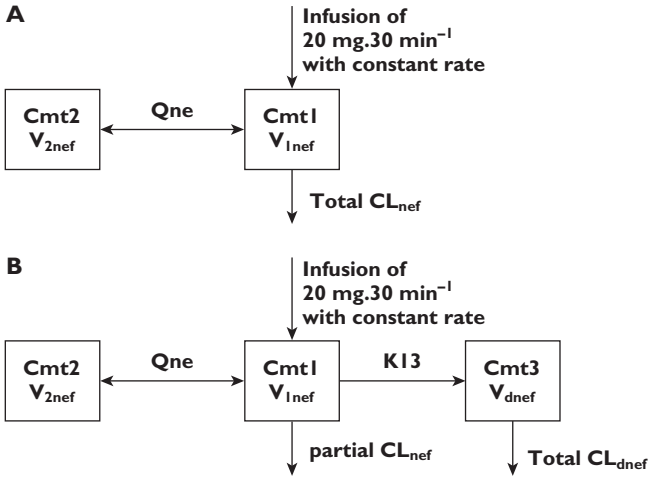

Figure 1

Schematic representation of structural pharmacokinetic models for nefopam (A) and desmethyl-nefopam (B). Abbreviations are as follows: *CL*, clearance; Cmt, compartment; dnef, desmethyl-nefopam; *K*13, apparent clearance of metabolization of nefopam to desmethyl-nefopam; Q, intercompartmental clearance; nef, nefopam; *V*, volume of compartment

bolic clearance of nefopam with a lag time or a lag time before enterohepatic circulation, and first-order elimination were tested to describe observed desmethyl-nefopam concentrations (see Supporting Information). All individual parameters are defined as log-normally distributed.

Several error models (constant, proportional, additive or mixed, exponential and logit error model) were studied to describe the residual variability (ε). The between-subject variability (BSV) of pharmacokinetic parameters was described using an exponential model, as follows: $\theta_i = \theta_{TV} \times \exp(\eta_i)$,where θ_i is the estimated individual parameter, θ_{TV} the typical value of the parameter and η_i the random effect for the *i*th patient. The values of θ_i were assumed to be normally distributed, with mean 0 and variance (ω^2) which were parameterized as a diagonal matrix. Correlations between random effects were tested.

The model best describing individual data was selected and evaluated based on the usual diagnostic plot, precision and information criteria with a minimum of pharmacokinetic parameters (to prevent overfitting) [21–27]. The likelihood ratio test (LRT), including the −2 log-likelihood, the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), was used to test different hypotheses regarding the final model [23, 25, 26]: covariate effect on pharmacokinetic parameter(s), residual variability model (proportional *vs.* proportional plus additive error model), and the structure of the variance–covariance matrix for the interindividual variability parameters. As covariate search method, stepwise covariate modelling was used [26]. We evaluated the following covariates: age, sex (1, male; 2, female), weight, size, body mass index [26], lean body weight [26], fat free mass [26], ideal body weight [26], body surface area [26], glomerular filtration rate using iohexol clearance (GFRio) [19] or the four-variable Modification of Diet in Renal Disease (MDRD) [26] or the Cockroft–Gault glomerular filtration rate. Covariates were selected in the model if their effect was biologically suspected, using a forward selection (LRT, $P = 0.05$) followed by backward elimination process (LRT, $P = 0.01$), they reduced the between-subject variability of the corresponding pharmacokinetic parameter, and the relative standard error of the covariate parameter was lower than 20%.

The goodness of fit was evaluated with the following graphs produced for the final model: observed and predicted concentrations *vs.* time, observed concentrations *vs.* population predictions, weighted residuals *vs.* time and weighted residuals *vs.* predictions.

Relative standard errors (RSEs) of all estimations of <20% were accepted. To evaluate accuracy and robustness of the model appropriateness across time, prediction-corrected visual checks with 1000 simulated data sets was used [28]. The observed concentrations were overlaid on the prediction intervals and compared visually. The normal distribution of normalized prediction distribution errors (NPDE) metrics was tested [29]. As for NPDE, population or individual weighted residuals (PWRES or IWRES) *vs.* time and PWRES or IWRES *vs.* predictions should be centred on zero, without systematic bias.

Individual pharmacokinetic parameters, such as total clearance, intercompartmental clearance, volume of distribution, predicted nefopam (nef) and desmethyl-nefopam (dnef) plasma concentration as a function of time, area under the curve of plasma concentration as a function of time (in hours) for nefopam ($AUC_{nef0\rightarrow\infty}$, in micrograms hours per litre) and desmethyl-nefopam ($AUC_{dnef0\rightarrow\infty}$, in micrograms hours per litre) were derived for each patient by using the Empirical-Bayes-Estimates (EBE) of the individual parameters determined by final model (see Supporting Information).

Assessment of relationship between pharmacokinetics and outcome

The association between predictors [maximal concentration (C_{max}), rate of increase in concentration (RC_{max}), from time of the start the infusion ($t = 0$ h) to the time corresponding to C_{max}, $AUC_{0\rightarrow\infty}$ for nefopam or desmethyl-nefopam] and outcomes, such as developing the postoperative nausea and vomiting (PONV) as described [30], postoperative tachycardia with heart rate over than 100 beats min^{-1} and requirement for morphine sulfate (10 mg), were assessed by logistic regression analysis using IBM® SPSS® (version 20.0). To ensure that any observed association between a predictor and a given outcome was not confounded by the presence of reported risk factors, a multivariate model of logistic regression was

used. Therefore, we provided an adjusted odds ratio (OR), by modelling the association between predictors and outcomes, controlling the other covariates for confounding effects. We used a binary scale or score to describe PONV and tachycardia (1, presence; 0, absence) and morphine requirement (score 1, administration of at least 10 mg of morphine sulfate as requested by the patient to control the pain; score 0, for patient not requesting morphine sulfate). The assessments of the scores were done during a postoperative period of 24 h.

The omnibus test of model coefficients (OTMC) as LRT for logistic regression in SPSS® software is associated with a *P* value, which can be used to accept or reject the model. The goodness of fit and appropriateness of the logistic regression model were evaluated using the Nagelkerke r^2 values and Hosmer–Lemeshow value and, finally, by the overall correct percentage of prediction.

The covariate factors were chosen by fitting a logistic regression model using a forward selection procedure ($P < 0.05$). The covariate was retained if it did not reduce the overall correct percentage of prediction and the Hosmer–Lemeshow value of the model. For tachycardia, we assessed as covariate factors body mass index, GFR using iohexol clearance, nefopam clearance (CL_{nef}), desmethyl-nefopam clearance (CL_{dnef}) and age, and as binary covariate factors, sex, administration of drug enhancing the probability of tachycardia (drug–tachycardia) as reported in the full prescribing information [17] and the morphine requirement, reflecting the pain, and type of anaesthesia (score 1, general anaesthesia; score 0, local–regional anaesthesia). For PONV, we assessed the impact of body mass index, GFR using iohexol clearance, CL_{nef}, CL_{dnef}, age, and as binary covariate factors, sex, administration of drug enhancing the probability of PONV (drug–PONV) as reported in the full prescribing information [17], a simplified Apfel score [30] and type of anaesthesia (score 1, general anaesthesia; score 0, local–regional anaesthesia). For morphine requirement, we assessed as covariates body mass index, GFR using iohexol clearance, CL_{nef}, CL_{dnef}, age, and as dummy covariate factors, sex, the type of anaesthesia and the use of sufentanil or intravenous acetaminophen during the surgical intervention. To assess the discriminatory performance of a binary logistic model, a receiver operating curve (ROC) was created, and the area under the ROC curve (AUC) was calculated. Values of $AUC_{0\to\infty}$, C_{max}, RC_{max} of nefopam and/or desmethyl-nefopam corresponding to a predicted probability higher than 0.5 (i.e. cut-values) for development of side-effects (PONV and tachycardia) were determined using logistic regression analysis. Finally, values of $AUC_{0\to\infty}$, C_{max} and RC_{max} of nefopam and/or desmethyl-nefopam corresponding to a predicted probability lower than 0.5 for morphine requirement were also determined using logistic regression analysis. The regimens needed to achieve these targets were studied by Monte Carlo simulations using Monolix (version 4.1) software.

Results

Subject characteristics

Forty-eight patients were included in this study. Their demographic characteristics are described in Table 1. The demographic characteristics were not significantly different between groups based on their expected renal capacity.

Nefopam pharmacokinetic model

A two-compartment open model, parameterized with clearances (total CL_{nef} and intercompartmental Q_{nef}) and volumes (central V_{1nef} and peripheral V_{2nef}), with zero-order input, best described the pharmacokinetics of nefopam (Figure 1). The BSV was described by exponential terms and residual variability by a combined additive (a = 1.33 μg l^{-1}) and proportional (coefficient = 0.228) error model. Values (estimated mean ± SEM) of CL_{nef}, V_{1nef}, Q_{nef} and V_{2nef} were, respectively, 17.3 ± 1.9 l h^{-1} (BSV 53 ± 9%), 114 ± 21 l (BSV 121 ± 21%), 80.7 ± 15.0 l h^{-1} (BSV 79 ± 17%) and 208 ± 31 l (BSV 64 ± 15%). The correlation between observed and predicted concentrations (derived from EBE) of nefopam was evaluated ($P < 0.0001$, Spearman $r = 0.95$; Figure 2).

None of the covariates met the predefined inclusion criteria; however, GFRio with values ≤30 ml min^{-1} was correlated with CL_{nef} ($P < 0.05$, Spearman test). Patients with GFRio >30 ml min^{-1} had higher CL_{nef} and lower area under the curve for nefopam ($AUC_{nef0\to\infty}$) than patients with GFRio <30 ml min^{-1} ($P < 0.05$; Table 2). The values of C_{max} and RC_{max} for nefopam did not differ between patients with GFRio >30 ml min^{-1} and patients with GFRio <30 ml min^{-1} (Table 2).

Desmethyl-nefopam pharmacokinetic model

A one-compartment open model, parameterized with total clearances CL_{dnef} and volumes of distribution V_{dnef} and with first-order input ($K13$; apparent clearance of metabolization of nefopam to desmethyl-nefopam) best described the pharmacokinetics of desmethyl-nefopam (Figure 1 and Supporting Information). Between-subject variability was described by exponential terms and residual variability by a combined additive (a = 0.01 μg l^{-1}) and proportional (coefficient = 0.68) error model. Typical values for CL_{dnef}, V_{dnef} and $K13$ were, respectively, 17.81 ± 0.6 l h^{-1} (BSV 144 ± 19%), 12.5 ± 0.01 l (BSV 1 ± 0.9%) and 0.35 ± 0.022 l h^{-1} (BSV 120 ± 67%). The correlation between observed and predicted concentrations (derived from EBE) of desmethyl-nefopam was evaluated ($P < 0.0001$, Spearman $r = 0.94$; Figure 2).

As for nefopam, none of the covariates met the predefined inclusion criteria. Clearance, C_{max}, RC_{max} and $AUC_{0\to\infty}$ of desmethyl-nefopam were not different between patients with GFRio >30 ml min^{-1} and patients with GFRio <30 ml min^{-1} (Table 2).

Table 1
Characteristics of patients with severe renal impairment, moderate renal impairment and normal renal function

Characteristic	Global population (n = 48)	Severe renal impairment (n = 10)	Subdivision group as function of glomerular rate filtration Moderate renal impairment (n = 28)	 Normal renal function (n = 10)	Statistical test
GFR[a] (ml.min^{-1})	48.36 ± 24.19 [10.77–131.50]	21.83 ± 5.79†‡ [10.77–29.91]	43.89 ± 8.26*‡ [30.21–59.84]	85.20 ± 23.19*† [64.34–131.50]	[c]
Age (years)[b]	83 ± 8 [65–99]	86 ± 8 [76–99]	83 ± 7 [72–97]	78 ± 7 [65–89]	[c]
Weight (kg)[b]	63 ± 13 [40–100]	59 ± 9 [45–75]	61 ± 13 [40–90]	71 ± 13 [60–100]	[c]
Height (cm)[b]	161 ± 7 [144–183]	164 ± 3 [160–169]	160 ± 9 [144–183]	164 ± 7 [155–177]	[c]
Body mass index (kg m^{-2})[b]	23.9 ± 4.7 [15.6–39.1]	21.9 ± 2.6 [17.6–26.3]	23.8 ± 4.8 [15.6–36.3]	26.3 ± 5.3 [20.5–39.1]	[c]
Haemoglobin (g (100 ml)$^{-1}$)[b]	125.3 ± 18.7 [90.0–157.0]	116.6 ± 23.4 [94.0–156.0]	127.5 ± 16.8 [90.0–154.0]	128.2 ± 19.4 [106.0–157.0]	[c]
Fibrinogen (g l^{-1})[b]	4.2 ± 1.2 [2.0–6.8]	3.8 ± 1.5 [2.0–5.9]	3.9 ± 1.1 [2.3–6.8]	4.9 ± 0.7 [4.7–6.4]	[c]
Sex ratio (male to female)	0.45	0.66	0.40	0.43	[d]

[a]Glomerular filtration rate (GFR) estimated with Cockroft–Gault formula; [b]mean ± SD [range]; [c]comparison between groups using one-way ANOVA followed with Tukey's multiple comparison test ($P < 0.05$); and [d]comparison between groups using χ^2 test. *$P < 0.05$, compared with severe renal impairment; †$P < 0.05$, compared with moderate renal impairment; ‡$P < 0.05$, compared with normal renal function.

Evaluation and validation of pharmacokinetic models

The mean and variance of the normalized prediction distribution error (NPDE) metrics [29] for the nefopam model (Figure 3) were not significantly different from zero (P = 0.2, Student's unpaired t test; P = 0.3953, Wilcoxon signed rank test) and one (P = 0.83, Fisher variance test), respectively, and their distribution was not different from a normal distribution (P = 0.21, Shapiro–Wilk test of normality; P = 0.35, D'Agostino and Pearson omnibus normality test).

The mean and variance of the NPDE metrics for the desmethyl-nefopam model (Figure 3) were not significantly different from zero (P = 0.10, Student's unpaired t test; P = 0.12, Wilcoxon signed rank test) and one (P = 0.95, Fisher variance test), respectively, and their distribution was not different from a normal distribution (P = 0.11, Shapiro–Wilk test of normality; P = 0.62, D'Agostino and Pearson omnibus normality test).

As shown in Figure 4, PWRES or IWRES *vs.* time and PWRES or IWRES *vs.* predictions were centred around zero, without systematic bias, and most values were within ±2 SD (about 5th and 95th percentiles of a normal distribution).

The prediction-corrected visual predictive check, for nefopam and desmethyl-nefopam, showed that the 5th, 50th and 95th percentiles of observed data are within the 90% confidence interval of 5th, 50th and 95th of simulated percentiles (Figure 2). The observations were contained within prediction intervals, and the models appear adequate to describe the observed data.

Considering these above evaluations, the performance of the model would be considered appropriate and could be used for pharmacokinetic simulations of nefopam in aged patients.

Assessment of relationship between pharmacokinetics and outcome

Tachycardia and PONV were reported in ~20% of the patients but none showed signs of sweating or sedation. A logistic regression analysis of the data was carried out, considering the presence of tachycardia or PONV (binary outcome measure) and C_{max}, RC_{max} and $AUC_{0\to\infty}$ for nefopam or desmethyl-nefopam as the continuous predictors. The logistic model was found to be appropriate for prediction of tachycardia or PONV score using C_{maxnef} or RC_{maxnef} as predictors (Table 3), and inappropriate with predictors such as $AUC_{0\to\infty}$ of nefopam even when $AUC_{0\to\infty}$ of desmethyl-nefopam was added (P > 0.3, OTMC, Nagelkerke r^2 and Hosmer–Lemeshow Test).

The morphine requirement score was best predicted using $AUC_{nef0\to\infty}$ as the predictor (Table 3). Addition of $AUC_{dnef0\to\infty}$ to $AUC_{nef0\to\infty}$ as a predictor did not improve the model acceptance and goodness-of-fit criteria. Therefore, desmethyl-nefopam pharmacokinetic parameters were excluded from further logistic regression analysis.

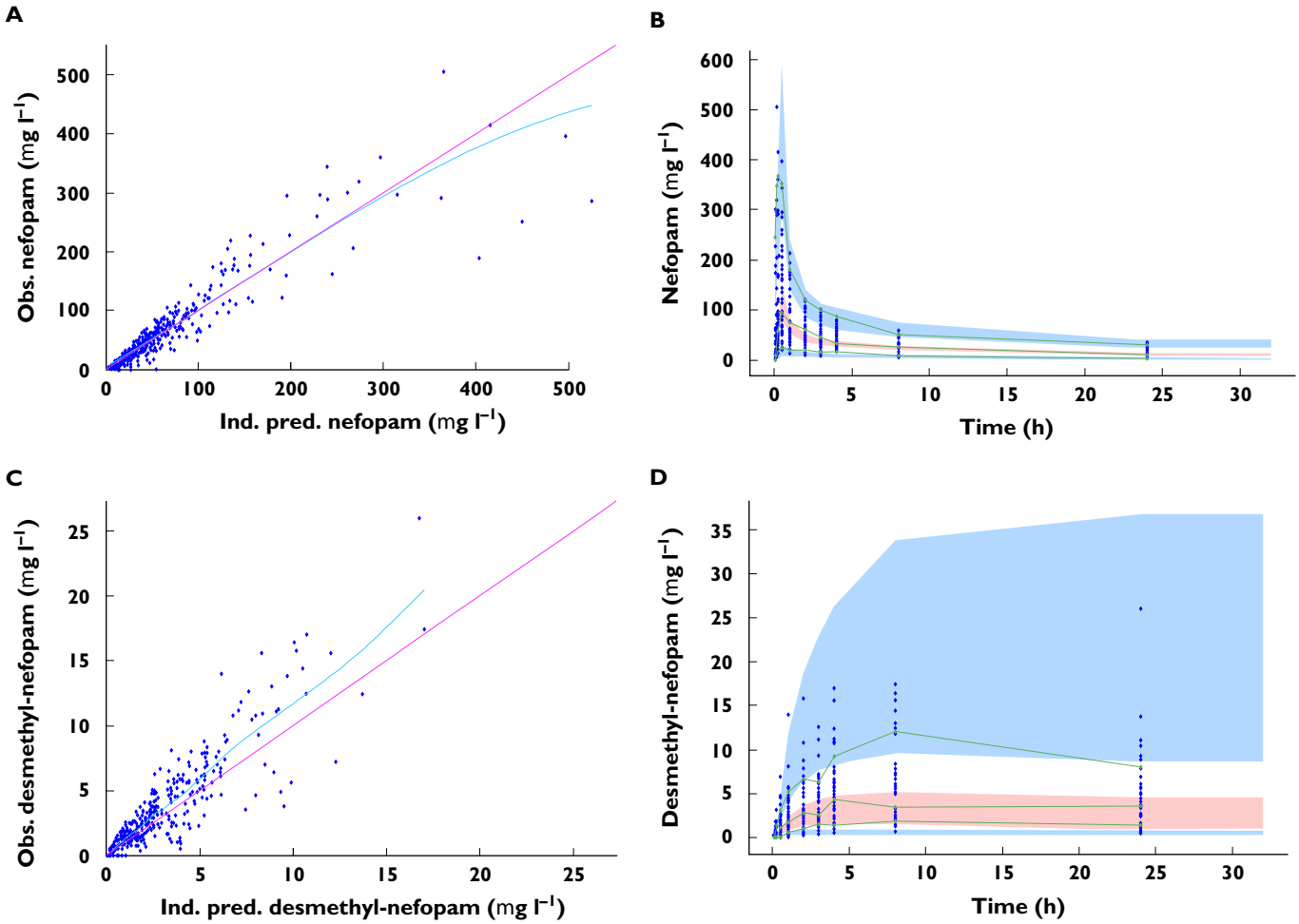

Figure 2

Goodness-of-fit plots. (A) Observed (Obs) nefopam concentrations *vs.* individual-predicted (Ind.pred) nefopam concentrations. (B) Observed (Obs) desmethyl-nefopam concentrations *vs.* individual-predicted (Ind.pred) desmethyl-nefopam concentrations. Prediction-corrected visual predictive check (PC-VPC) for nefopam concentrations (C) and desmethyl-nefopam concentrations (D). The green lines show the 5th, 50th and 95th percentiles of observed data; the areas represent the 90% confidence interval around the simulated percentiles

Table 2

Individual pharmacokinetic parameters of patients with severe renal impairment (GFRio ≤ 30 ml min^{-1}) or without severe renal impairment

	Severe renal impairment (n = 10)	Without severe renal impairment (n = 38)
Nefopam		
Clearance (l h^{-1})	13.04 ± 1.45 [8.92–13.50]	24.61 ± 13.43* [10.44–66.91]
C_{max} (µg l^{-1})	156.2 ± 122.4 [52.9–477.4]	148.2 ± 131.8 [19.2–512.8]
RC_{max} (µg l^{-1}) h^{-1})	315.10 ± 264.40 [103.90–1037.00]	290.70 ± 268.30 [37.73–1037.00]
$AUC_{0\rightarrow\infty}$ (µg l^{-1} h)	1617.0 ± 367.3 [1087.0–2585.0]	1184 ± 540.6* [382.5–3620]
Desmethyl-nefopam		
Clearance (l h^{-1})	16.82 ± 8.82 [2.92–28.93]	17.92 ± 14.88 [3.34–90.46]
C_{max} (µg l^{-1})	7.0 ± 6.1 [1.2–23.0]	4.9 ± 3.2 [1.3–12.6]
RC_{max} (µg l^{-1}) h^{-1})	0.67 ± 0.83 [0.05–2.95]	1.15 ± 1.16 [0.09–4.87]
$AUC_{0\rightarrow\infty}$ (µg l^{-1} h)	141.7 ± 127.0 [25.8–470.5]	95.1 ± 67.1 [12.0–281.5]

Abbreviation is as follows: $AUC_{0\rightarrow\infty}$, Area Under Curve of time course of plasma concentration; C_{max}, plasma maximum concentration; GFRio, glomerular filtration rate estimated by iohexol administration; RC_{max}, rate of increase of plasma concentration. *P < 0.05, compared with severe renal impairment (Mann–Whitney U test). Data are means ± SD [range].

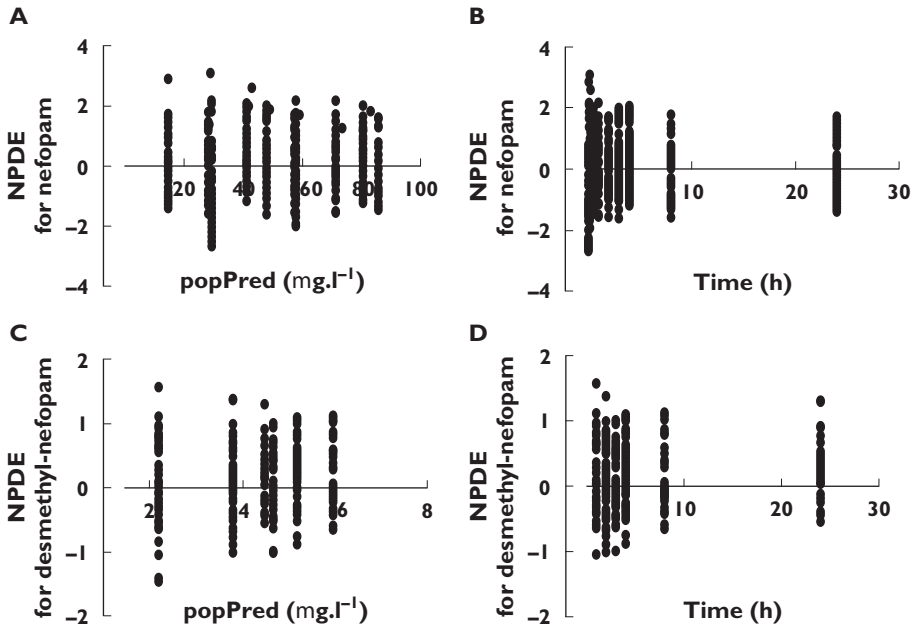

Figure 3

Diagnostic plots. Normalized prediction distribution error (NPDE) as a function of population-predicted (popPred) concentrations of nefopam (A) and desmethyl-nefopam (C), and as a function of time for nefopam (B) and for desmethyl-nefopam (D)

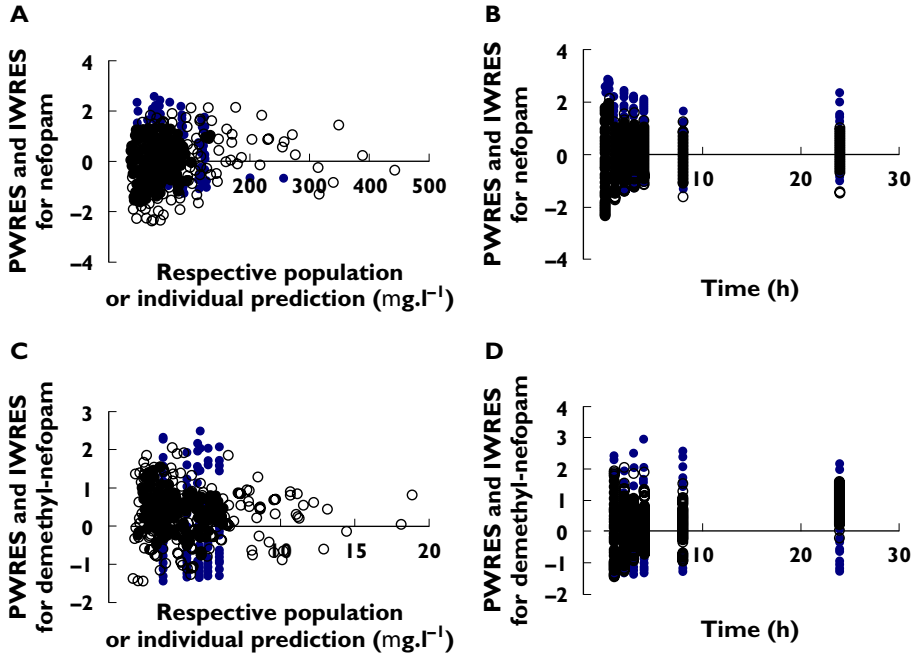

Figure 4

Diagnostic plots. Population (blue dot) or individual (black circle) weighted residuals (PWRES or IWRES) *vs.* time for nefopam (A) and desmethyl-nefopam (C), and PWRES or IWRES *vs.* respective predictions for nefopam (B) and desmethyl-nefopam (D)

The final model of logistic regression for tachycardia included the age and score of drug inducing tachycardia (1, if levobupivacaine at a dose of >75 mg or bupivacaine at a dose of >75 mg was administered; 0, if the same drugs were not administered) as covariates. For logistic regression analysis of PONV, the included covariates were the simplified Apfel score [31], age and drug inducing PONV [17] (score 1, if ropivacaine at a dose >100 mg or

Table 3

Association between pharmacokinetic parameters and pharmacological effect of nefopam analysed by logistic regression

		Model acceptance		Logistic regression Goodness of fit		OR and adjusted OR‡				Overall correct percentage of prediction*	Receiver operating curve analysis			
	Predictors	Unit increment	Final –2 log likelihood	*P* value of OTMC	Nagelkerke r^2	Hosmer–Lemeshow test	Wald test	Exp (B)	Lower 95% CI	Upper 95% CI		Area under curves	*P* value†	Cut value*	Final model status
Tachycardia	$AUC_{nef0\rightarrow\infty}$	1 μg l^{-1} h	26.390	0.128	0.250	0.867	0.049	1.001‡	1.000	1.002	80%	0.788	0.019	3280 μg l^{-1} h	
	C_{maxnef}	1 μg l^{-1}	24.338	0.05	0.330	0.770	0.025	1.010‡	1.003	1.018	83%	0.887	0.002	389 μg l^{-1}	Appropriate
		50 μg l^{-1}					0.025	1.580‡	1.060	2.355					Appropriate
	RC_{maxnef}	1 μg l^{-1} h^{-1}	24.058	0.046	0.341	0.755	0.023	1.005‡	1.001	1.009	83%	0.892	0.001	764 μg l^{-1} h^{-1}	Appropriate
		50 μg l^{-1} h^{-1}					0.023	1.261‡	1.033	1.538					Appropriate
PONV	$AUC_{nef0\rightarrow\infty}$	1 μg l^{-1} h	28.742	0.079	0.328	0.550	0.021	1.002‡	1.000	1.003	82.4%	0.726	0.056	3280 μg l^{-1} h	
	C_{maxnef}	1 μg l^{-1}	23.335	0.008	0.501	0.829	0.012	1.014‡	1.003	1.026	85.3%	0.774	0.021	437.44 μg l^{-1}	Appropriate
		50 μg l^{-1}					0.012	2.053‡	1.169	3.605					Appropriate
	RC_{maxnef}	1 μg l^{-1} h^{-1}	23.482	0.009	0.497	0.882	0.012	1.007‡	1.002	1.012	85.3%	0.744	0.21	859 μg l^{-1} h^{-1}	Appropriate
		50 μg l^{-1} h^{-1}					0.012	1.416‡	1.078	1.859					Appropriate
Morphine requirement	$AUC_{nef0\rightarrow\infty}$	1 μg l^{-1} h	41.468	0.006	0.253	0.350	0.023	0.988	0.987	1.000	68%	0.745	0.013	947 μg l^{-1} h	Appropriate
	C_{maxnef}	1 μg l^{-1}	41.797	0.007	0.243	0.349	0.048	0.988	0.977	1.000	68%	0.724	0.024	79 μg l^{-1}	Appropriate
	RC_{maxnef}	1 μg l^{-1} h^{-1}	41.567	0.006	0.250	0.353	0.047	0.994	0.988	1.000	68%	0.730	0.020	154 μg l^{-1} h^{-1}	Appropriate

Abbreviations are as follows: $AUC_{nef0\rightarrow\infty}$, Area Under Curve of time course of nefopam plasma concentration; C_{maxnef}, nefopam plasma maximum concentration; CI, confidence interval; OR, odds ratio; OTMC, omnibus test of model coefficients; PONV, postoperative nausea and vomiting; RC_{max}, rate of increase of plasma concentration. *The cut value corresponds to the predicted probability of the model higher than 0.60 for tachycardia, 0.80 for PONV and 0.50 for morphine requirement. †Null hypothesis/true area = 0.5. ‡Adjusted for confounding covariates (see the results of the pharmacodynamics assessment); $AUC_{nef0\rightarrow\infty}$, C_{maxnef} and RC_{maxnef} were ranged, respectively, within 382.5–3620 μg l^{-1} h, 19.2–512.8 μg l^{-1} and 37.7–1037 μg l^{-1} h^{-1}.

levobupivacaine at a dose >125 mg or bupivacaine at a dose >125 mg was administered; score 0, when the same drugs were not administered). However, the final logistic regression model for morphine requirement did not include any covariates.

The odds of developing tachycardia were increased by 58% for every extra 50 μg l^{-1} of C_{maxnef} and by 26.1% for every extra 50 μg l^{-1} h of RC_{maxnef} (Table 3). Odds of developing PONV were increased by 205.3% for every extra 50 μg l^{-1} of C_{maxnef} and by 141.6% for every extra 50 μg l^{-1} h of RC_{maxnef} (Table 3). There was a decrease of 1.2% in odds of morphine requirement score for every 1 μg l^{-1} h of $AUC_{nef0\rightarrow\infty}$ (Table 3). A C_{maxnef} higher than 389 μg l^{-1} and a RC_{maxnef} higher than 764 μg l^{-1} h^{-1} suggested a probability of developing tachycardia higher than 0.6 (60%). A C_{maxnef} higher than 437.44 μg l^{-1} and a RC_{maxnef} higher than 859 μg l^{-1} h^{-1} suggested a probability of developing PONV higher than 0.8 (80%). An $AUC_{nef0\rightarrow\infty}$ of at least 947 μg l^{-1} h suggested a probability of morphine sulfate requirement lower than 0.5 (50%).

Simulations of dosage regimens

A dosage regimen was derived from the simulated C_{maxnef}, RC_{maxnef} and $AUC_{nef0\rightarrow\infty}$. The individual values of C_{maxnef}, RC_{maxnef} and $AUC_{nef0\rightarrow\infty}$ following different durations of infusion with the same single dose of nefopam (20 mg) were studied by 1000 Monte Carlo simulations using the final population pharmacokinetic model and performed by Monolix (version 4.1) software. As the effect of nefopam on morphine requirement seemed to be linked to $AUC_{nef0\rightarrow\infty}$ and therefore to dose, we maintained the same dose of nefopam (20 mg) in order to obtain an equivalent morphine-sparing effect. Tachycardia and PONV were associated with C_{maxnef} and RC_{maxnef} (Table 3). Therefore, we decided to optimize infusion time in order to reduce the level of C_{maxnef} and RC_{maxnef} below the determined cut values (Table 3). The worst regimen was a 15 min infusion of 20 mg of nefopam, resulting in a higher probability (>0.2) of simulated C_{maxnef} and RC_{maxnef} higher than their cut values and a probability equal to 0.28 of simulated $AUC_{nef0\rightarrow\infty}$ below its cut value (Table 3 and Figure 5). Infusions of 20 mg of nefopam over a period of 60, 45 and 30 min were associated with a probability of simulated C_{maxnef} and RC_{maxnef} below their cut values equal to 0.999, 0.94 and 0.88, respectively, and a probability of simulated $AUC_{nef0\rightarrow\infty}$ below its cut value equal to 0.28, 0.30 and 0.28, respectively (Table 3 and Figure 5).

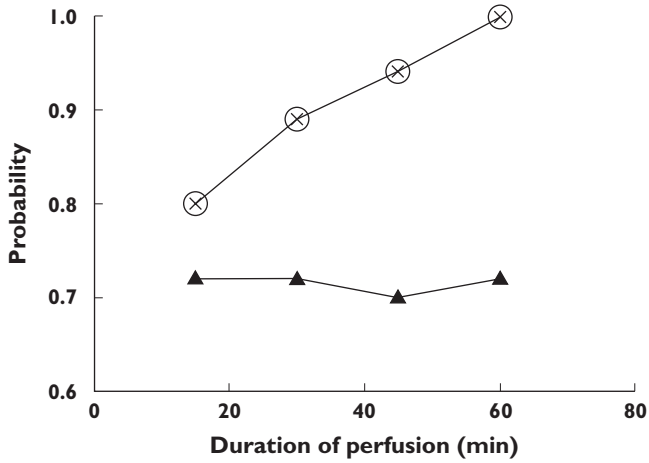

Figure 5

Monte Carlo simulations of different durations in nefopam infusion. The figure shows the probabilities, as a function of duration of infusion, to observe nefopam plasma maximum concentration (C_{maxnef}) and rate of increase of nefopam plasma concentration (RC_{maxnef}) lower than values linked to develop tachycardia or postoperative nausea and vomiting as determined by logistic regression (Table 3) and the probabilities as a function of duration of infusion to observe Area Under Curve of time course of nefopam plasma concentration ($AUC_{nef0\rightarrow\infty}$) above 950 μg h l^{-1}. The probabilities to observe C_{maxnef} and RC_{maxnef} were the same for all durations of infusion. ⊖, C_{maxnef} <389 μg l^{-1}; ⊷, RC_{maxnef} <764 μg l^{-1}; ▲, $AUC_{nef0\rightarrow\infty}$ >950 μg h l^{-1}

Discussion

We report the first study to evaluate the pharmacokinetics of nefopam and its link to treatment response in aged patients with or without renal impairment. First, models able to describe nefopam and desmethyl-nefopam concentrations in the aged patient with or without renal impairment were determined. Then, using a logistic regression approach, the association between pharmacokinetic parameters and morphine requirement, score of tachycardia and score of PONV was assessed. We report that morphine requirement seems to be related to $AUC_{0\rightarrow\infty}$ of nefopam and that nefopam side-effects seem mainly linked to the speed of administration.

Physiological and homeostatic impairments in the elderly may affect the response to drugs [4, 5]. A decrease in hepatic extraction [5] as a result of reduced hepatic flow and reduced liver mass [32, 33], as well as reduced renal function, with a decrease of 10% per decade in the adult years [34], have been reported. These age-related reductions in renal and hepatic function might partly explain the three times lower total clearance of nefopam reported in our study in comparison to previous studies [18, 35, 36]. A decrease in lean body mass associated with an increase in adipose tissue might explain the differences in intercompartmental clearance of nefopam in our series compared with previous studies performed in younger subjects [18, 36]. The central volume of distribution for nefopam was two times lower compared with previously reported values [18]. For the same infusion duration of 20 mg of nefopam, the decrease in total clearance of nefopam associated with the decrease in central volume of distribution might explain the three times higher values of C_{maxnef} in older patients (150 ±

128 μg l^{-1}, range 19.21–512.8 μg l^{-1}) compared with younger subjects [18, 35]. This higher value of C_{maxnef} could also be due to an age-related decrease in cardiac output, as previously described [5]. The mean $AUC_{0\to\infty}$ of nefopam (1411 ± 724 μg l^{-1} h, range 382.5–3620 μg l^{-1} h) in our older population was 1.5 times higher than the value reported for younger subjects [35].

A relationship between $AUC_{0\to\infty}$, C_{max} and RC_{max} of nefopam and morphine requirement was reported (Table 3). Moreover, both C_{maxnef} and RC_{maxnef} were linked to tachycardia and PONV, but the association between $AUC_{nef0\to\infty}$ and PONV and tachycardia was significant (Table 3). Tachycardia and, to a lesser extent, PONV are probably related to the antimuscarinic and sympathomimetic activity of nefopam [17], to inappropriate physiological responses of aged patients and to a rapid rate of administration of nefopam.

Renal impairment had an impact on $AUC_{0\to\infty}$ but not on C_{max} and RC_{max} of nefopam (Table 2). This is explained by the fact that dose and clearance directly influence the AUC, and that the dose and speed of administration, but not clearance, act significantly on C_{max} and RC_{max} of nefopam. The impact of severe renal impairment (GFR <30 ml min^{-1}) on pharmacokinetic parameters of nefopam has been previously reported [18]. In our series, we confirmed the impact of severe renal impairment (Table 2), while moderate renal impairment did not reduce total clearance in aged patients, probably because this effect is confounded by the effect of age on the GFR. Furthermore, renal impairment was not associated with development of tachycardia and PONV, as confirmed by the logistic regression analysis (covariate analysis). The values of $AUC_{nef0\to\infty}$ of patients with severe renal impairment (Table 2) were above the cut value for morphine requirement (950 μg l^{-1} h); consequently, patients with severe renal impairment did not require morphine supplementation.

As shown by Monte Carlo simulations for aged patients (with or without renal impairment), a better-tolerated infusion duration for 20 mg of nefopam would be between 45 and 60 min, with an equal morphine requirement compared with the standard protocol (infusion over 30 min of 20 mg nefopam). By choosing a 45 min infusion, the probability of C_{max} and RC_{max} of nefopam being higher than their cut value is about 5%, whereas it is only 0.1% when the duration of infusion is 60 min.

This study has several limitations. As we studied the pharmacokinetics of a single dose of nefopam in aged patients, we could not extrapolate the impact of renal impairment on outcomes after multiple administrations of nefopam and, in particular, on accumulation of nefopam. The analgesic effect of nefopam in the elderly was not evaluated in our study. Nevertheless, the association between various predictors and morphine requirement was assessed. Further studies are therefore required to clarify these limitations.

In conclusion, we validated the first pharmacokinetic model able to describe nefopam and desmethyl-nefopam concentrations in aged patients. By using clearance of iohexol to evaluate renal function, we found that renal impairment is associated with a decrease in the nefopam clearance of aged patients when GFRio is <30 ml min^{-1}, but not associated with development of adverse effects. Using a logistic regression analysis, pharmacokinetic predictors of morphine requirement and side-effects, such as tachycardia and PONV, were identified. In order to maintain morphine sparing and decrease the side-effects of nefopam, Monte Carlo simulations suggest, for a single dose of nefopam (20 mg), an administration period >45 min in elderly patients (>65 years) with or without renal impairment.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: this study was funded by the Regional Clinical Research Program of Reims University Hospital, in 2004 (PHRC 2004-R11-07); no financial relationships with any organizations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Two compartment models for nefopam population pharmacokinetic
Demethylnefopam population pharmacokinetic