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Compartmental pharmacokinetics of nefopam during mild hypothermia

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Editor's key points

- This study determines compartmental pharmacokinetic parameters for nefopam during hypothermia.
- The plasma concentration time course best fitted a two-compartment model using a population approach with inter-occasional variability.
- No statistically significant covariates were found.
- This model can be used to optimize nefopam administration by target-controlled infusion.

Background. Nefopam is a non-opioid, non-steroidal, centrally acting analgesic which has an opioid-sparing effect. It also reduces the threshold (triggering core temperature) for shivering without causing sedation or respiratory depression. The drug is therefore useful as both an analgesic and to facilitate induction of therapeutic hypothermia. However, compartmental pharmacokinetics during hypothermia are lacking for nefopam.

Methods. We conducted a prospective, randomized, blinded study in eight volunteers. On two different occasions, one of two nefopam concentrations was administered and more than 30 arterial blood samples were gathered during 12 h. Plasma concentrations were determined using gas chromatography/mass spectrometry to investigate the pharmacokinetics of nefopam with non-linear mixed-effect modelling.

Results. A two-compartment mammillary model with moderate inter-individual variability and inter-occasional variability independent of covariates was found to best describe the data [mean (SE): V_1=24.13 (2.8) litre; V_2=183.34 (13.5) litre; Cl_{el}=0.54 (0.07) litre min^{-1}; Cl_{dist}=2.84 (0.42) litre min^{-1}].

Conclusions. The compartmental data set describing a two-compartment model was determined and could be implemented to drive automated pumps. Thus, work load could be distributed to a pump establishing and maintaining any desired plasma concentration deemed necessary for a treatment with therapeutical hypothermia.

Keywords: anaesthesia; hypothermia; nefopam; pharmacokinetics; shivering; thermoregulation

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Mild hypothermia in animals provides substantial protection against cerebral[1 2] and myocardial ischaemia[3] and in humans, mild hypothermia (33–34°C) improves long-term neurological and functional outcome after cardiac arrest.[4 5] Therapeutic hypothermia also improves outcome from neonatal asphyxia.[6 7] A difficulty with therapeutic hypothermia, though, is that even small reductions in core temperature trigger aggressive thermoregulatory defences,[8 9] especially arterio-venous shunt vasoconstriction[10] and shivering.[11] This has led to a search for drugs that impair vasoconstriction and shivering without causing excessive sedation or respiratory toxicity.[12]

Among the potential pharmacological approaches to inducing hypothermic tolerance is nefopam. Nefopam is a non-opioid, non-steroidal analgesic with spinal and supraspinal sites of action that selectively reduces the shivering threshold (triggering core temperature) without impairing respiration or conciousness.[13–19] It is a benzoxazocine compound, structurally related to orphenadrine and diphenhydramine, that inhibits the reuptake of serotonin, norepinephrine, and dopamine[20] in an amphetamine-like fashion.[18] Nefopam reduces the shivering threshold and can thus facilitate the induction of therapeutic hypothermia.[21]

Although limited pharmacological data are available,[22] full compartmental models for nefopam during hypothermia were not readily available. Thus, the goal of this study was to determine compartmental pharmacokinetic (PK) parameters for nefopam during hypothermia.

Methods

Data presented in this report were obtained during a previous study that evaluated the thermoregulatory effects of nefopam.[23] Briefly, with approval of the local Institutional Ethics Committee and informed patient consent, we

evaluated eight young, healthy volunteers who took no medications and denied alcohol or drug abuse. After nefopam administration, lactated Ringer's solution at 4°C was infused to provoke shivering which was the primary outcome of the primary thermoregulatory protocol. The maximum reduction in core temperature was >1.5°C. Throughout the study, volunteers rested supine.

A 14 G catheter was inserted into one antecubital vein for fluid administration and a 16 G catheter into the other for drug administration. Blood samples were drawn from a 20 G catheter inserted into a radial artery on the upper extremity. On two different occasions, with a washout time of more than 48 h, nefopam (Acupan, Laboratoires Biocodex, Montrouge, France; IUPAC name: 5-methyl-1-phenyl-1,3,4,6-tetrahydro-2,5-benzoxazocine) was administered as a continuous i.v. infusion at two randomly assigned concentrations (0.5 mg ml^{-1} or 1.0 mg ml^{-1}) according to one of the schemes displayed in the Appendix (volunteers 1–4, scheme A; volunteers 5–8, scheme B).

Arterial blood was sampled for PK analysis according to the following scheme: a blank sample; during nefopam administration at minutes 2, 4, 6, 8, 10, 12, 15, 20, 30, 45, and 60, and immediately before stopping the nefopam infusion; if applicable, depending on the pharmacodynamic study part, additionally at minutes 120, 150, and 180. The number of samples during nefopam administration depended on the duration of the thermoregulatory study. After stopping the nefopam infusion, samples were gathered at minutes 2, 4, 6, 10, 15, 20, 30, 45, 60, 90, 120, 180, 275, 360, 450, 540, and 630.

Plasma was extracted in a refrigerated centrifuge and stored at −20°C until assayed. Before extraction, plasma samples for nefopam analysis were allowed to thaw at room temperature and vortexed, then centrifuged at 2000 rpm for 5 min. To 0.5 ml of plasma, 0.5 ml of deionized water, internal standard (IS, imipramine hydrochloride, ICN Biomedicals Inc., OH, USA), and 30 μl of orthophosphoric acid were added and vortexed. The samples were loaded (about 0.5 ml min^{-1}) on 96-well solid phase extraction plates with 2 ml capacity and 30 mg extraction bed (OASIS, MCX, Waters Corporation, Milford, PA, USA). The cartridges were rinsed with 2 ml of 0.1 M hydrochloric acid, 2 ml of methanol, and then dried under vacuum for at least 5 min.

The extracts were then eluted from the cartridge with 2.5 ml of freshly prepared methanol–ammonium hydroxide 25% (95:5; vol:vol), by gravity flow. The eluate was evaporated to dryness under a nitrogen stream in a water bath at about 40°C. The residues were redissolved in 30 μl methanol–butylacetate (4:1; vol:vol), briefly vortexed, and loaded into auto-sampler vials with inserts. Samples were analysed by GC–MSD (Agilent Technologies, USA, Model 6890 with a 5972A mass selective detector and automatic injector). Aliquots of 1 μl were injected in a splitless mode onto a Varian FactorFour VF-Xms, 12 m, 0.2 mm ID capillary column with a 0.33 μm film. The helium flow rate was 0.8 ml min^{-1}. Operating temperatures of the GC were: injector 250°C, MSD transfer line 280°C, oven 140°C for 0.2 min rising (25°C min^{-1}) to 280°C, hold 1 min. The MSD was operated in the electron impact mode (70 eV) with selected ion monitoring (SIM) with a dwell time of 100 ms each. SIM ions for quantitation were *m/z* 225 and 235 for nefopam and IS, respectively. The data were processed with proprietary mass spectrometer control software (HP G1701AA).

All calibration curves had correlation coefficients ≥0.99. The coefficient of variation (CV) of intraday reproducibility (n=10) for nefopam at 301, 103, and 10.3 ng ml^{-1} blood content was 2.0%, 2.2%, and 3.7%, respectively. CV of interday reproducibility at the same concentrations (n=6) was 4.5%, 5.3%, and 7.4%, respectively. The mean recovery of nefopam (n=15) at concentrations 10–300 ng ml^{-1} was 92.5% (range 87–104%). The limit of quantification at a signal-to-noise ratio of 10:1 was 4.4 ng ml^{-1}. The limit of detection at a signal-to-noise ratio of 3:1 was 1.3 ng ml^{-1}.

One-, two-, and three-compartment mammillary models were fitted to the nefopam plasma concentration data and compared using the Akaike information criterion.[24] The models were parameterized in terms of volumes of distribution, elimination, and distributional clearance (Cl_{el}, Cl_{dist}).

Pooled data were initially used, which means that each data set was handled as if it was a single subject. In a second step, we specified that the same subject participated on two different occasions. Investigations were done with a non-population and a population approach. In a third step, intra-occasional variability (IOV) was taken into consideration.

Inter-individual variability (IIV) was characterized by an exponential model: $\theta_{(n,i)}=\theta_{(n,m)}\times e^{\eta(n,i)}$, where $\theta_{(n,i)}$ refers to the individual value of the respective PK parameter, $\theta_{(n,m)}$ the population mean of the parameter, and $\eta(n,i)$ denotes the ln-difference between $\theta_{(n,i)}$ and $\theta_{(n,m)}$. IIV is the square root of the variances of the ETAs and is expressed as percentage value. The IOV, the variability within one individual between study occasions, had the same exponential structure: $\theta_{(n,iq)}=\theta_{(n,m)}\times e^{\eta(n,i)+\kappa(n,iq)}$, where q denotes the occasion and $\kappa(n,iq)$ the additional random effect differing from the typical individual value. $\eta(n,i)$ and $\kappa(n,iq)$ are assumed to vary randomly between individuals with a mean of zero and a diagonal variance–covariance matrix ω^2 and π^2, respectively.

Residual variability denotes the discrepancy between the observed and the model-predicted concentrations already containing the IIV and IOV. A multiplicative error model was chosen: $c_{obs}=c_{exp}(1+\epsilon)$, where c_{obs} refers to the observed concentration and c_{exp} to the concentration predicted based on dose, time, and the individual PK parameters. ϵ was assumed to be normally distributed with a mean of zero and variance σ^2.

Covariates were age, weight, height, BMI, lean body mass (LBM), and body surface area (BSA). The parameters were plotted against these covariates for visual inspection. Covariates were added one by one and kept in the model if they improved the goodness of fit (forward inclusion, backward deletion), judged by the likelihood ratio criterion ($P\leq0.01$).

We tested for model misspecification by plotting the ratio of the measured and the predicted nefopam plasma

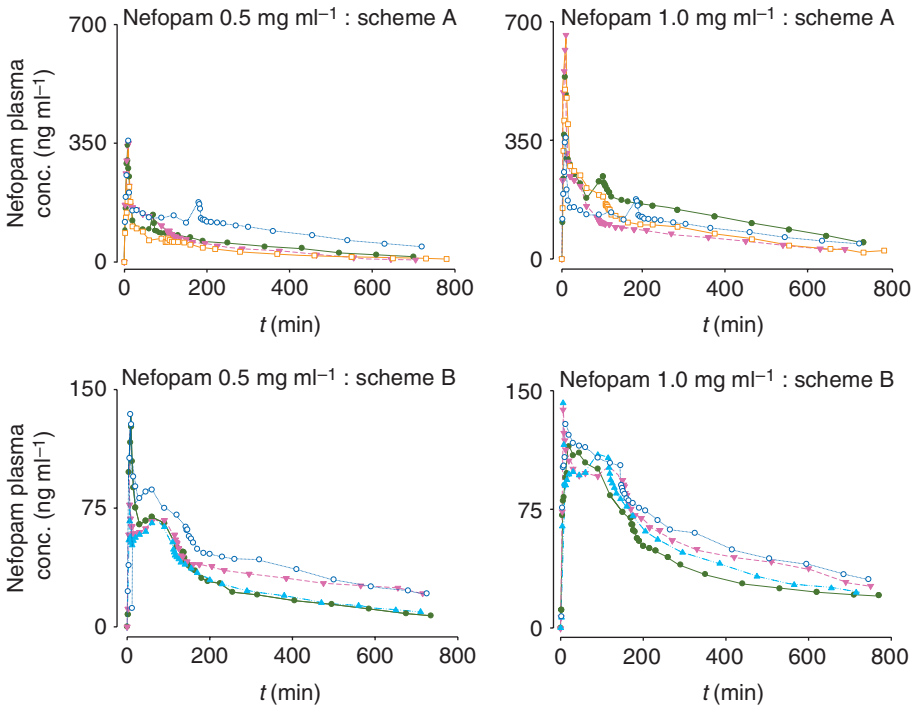

Fig 1 The curves show the concentration–time relationship of i.v. administered nefopam according to scheme A (upper panels) and scheme B (lower panels). Details of the infusion schemes are given in the Appendix. This is a raw data presentation of individualized treatment schemes only. Thermal manipulations finished at different times due to pharmacodynamic defined points in the study (maximum intensity of shivering during cooling with cold infusions). Therefore, the appearance of time and concentration once the concentration decrease begins varies.

concentrations against observation time. Additionally, the predictive performance of the final model was determined applying prediction error (PE) analysis.[25]

$$PE = \frac{100(\text{measured concentration} - \text{predicted concentration})}{\text{predicted concentration}}$$

The median PE (MDPE) indicates the bias of the predicted concentration to the measured one and the absolute value of PE called the median absolute PE (MDAPE) characterizing the precision of the prediction. The model is most accurate the closer the value of MDPE and MDAPE is to 0. Typical accepted values during target-controlled infusion (TCI) are ranging between −20% and 20% for the MDPE and <30% for the MDAPE.[26] For all calculations, NONMEM version VII with the first-order conditional estimation for all model fits and empirical Bayesian estimation of the individual parameters was used.[27] The bootstrap was performed using Perl speaks NONMEM (Version 3.2.12; http://psn.sourceforge.net), with a total of 2000 bootstrap samples being generated by repeated random sampling from the original data set preserving the two occasions per individual. Boundaries for the elimination clearance were 0 and 100 litre min^{-1}. Context-sensitive decrement times for the plasma concentration were calculated using RECOV.C targeting times to 80%, 50%, and 20% decrements.

Results

If not otherwise indicated, the values are presented as mean (SD) (min–max): age 28 (7) (21–39) yr, weight 78 (9) (63–92) kg, and height 179 (4.7) (170–185) cm. Two of the eight volunteers were female. Five hundred blood samples (249 from scheme A and 251 from scheme B) were available for PK calculations, including the blank samples obtained before drug administration. A total of 3.04 (0.78) litre lactated Ringer's solution at 4°C were administered on the low-concentration day (0.5 mg ml^{-1} nefopam) and a total of 3.43 (1.01) litre were used on the high-concentration day (1.0 mg ml^{-1} nefopam).

Raw plots of the measured nefopam plasma concentration were constructed for infusion schemes A and B, and showed a typical initial peak followed by a decrease in the nefopam plasma concentration reaching a plateau until maintenance application was terminated. Subsequently, plasma concentrations decreased (Fig. 1).

The plasma concentration time course best fitted a two-compartment model using a population approach with inter-occasional variability (Table 1). No statistically significant correlation between model parameters and age, weight, height, BMI, LBM, and BSA was found. The influence of sex was not evaluated.

A goodness-of-fit plot for the two-compartment model shows that the Bayesian prediction for each volunteer

Table 1 Objective function values. The model building process is shown by displaying the numbers of the minimum objective function value (OFV) for each model (I, II, III, one-, two-, or three-compartment model) and the approach (NPD, naïve pooled data; POP, population approach). Models (B) and (C) specify that data sets from two different occasions in the same subject were used (individual=non-pooled data) whereas model (A) does not distinguish between occasions (pooled data) and treats every data set as independent. IOV, inter-occasional variability. The lower the number and less complex the model, the better

	I	II	III
(A) Pooled data			
NPD	4481	3352	3344
POP	4396	2858	2830
(B) Individual data			
POP	4412	3045	3017
(C)=(B) with IOV			
POP	4399	2858	Unstable

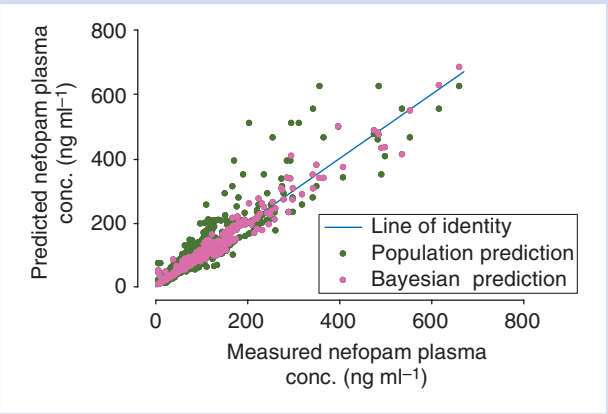

Fig 2 Goodness-of-fit plot. Circles lying on the line of identity correspond to optimal predictions (residual equals zero). Both the population predictions and the Bayesian predictions are calculated with the parameters from Table 2.

matched the observations (measured plasma concentrations) well over the entire concentration range (Fig. 2). The PK parameters of nefopam are shown in Table 2. The central compartment V_1 was 24.3 litre and clearly larger than the blood volume undergoing a quick distribution ($t_{1/2\alpha}$=4.5 min) into an even larger compartment V_2 with 183.3 litre being eliminated from plasma with a terminal plasma elimination half-life of 5 h. IIV ranged from 15.7 (V_2) to 39.1 (V_1) %CV as given in Table 2. The IOV was estimated to be between 7%CV (Cl_{el}) and 16%CV (V_1).

Plotting the relative residuals of the population and Bayesian prediction against time and concentrations, respectively, showed that the model misspecifications were well controlled, the Bayesian approach delivering more accurate predictions (Fig. 3). The MDPE (10th; 90th percentile) for the final model was −6.15 (−25; +16)% and the MDAPE was 16.63 (10; 29)%.

Table 2 Pharmacokinetic parameters for nefopam. (A) NONMEM parameterization implemented for calculations; (B) derived parameters, therefore SE not applicable. IIV, inter-individual variability (square roots of the variances of the ETAs, expressed as percentage value); IOV, inter-occasional variability; CV, coefficient of variation; Cl_{el}, plasma clearance; Cl_{dist}, distributional clearance (Q); V_1, V_2, Vd_{ss}, volumes of distribution in the central or peripheral compartment, or at steady-state, respectively; $t_{1/2\alpha}$, intra-compartmental half-life time; $t_{1/2\beta}$, plasma elimination half-life time; k_{10}, k_{12}, k_{21}, micro rate constants

	Variable	Unit	Typical value (SE)	IIV (CV %)	IOV (CV %)
A	V_1	Litre	24.1 (2.8)	39	16
	V_2	Litre	183.3 (13.5)	15	9
	Cl_{el}	Litre min^{-1}	0.54 (0.07)	23	7
	Cl_{dist}	Litre min^{-1}	2.84 (0.42)	31	12
B	Vd_{ss}	Litre	207.5		
	$t_{1/2\alpha}$	Min	4.5		
	$t_{1/2\beta}$	Min	306.5		
	k_{10}	Min^{-1}	0.022		
	k_{12}	Min^{-1}	0.1177		
	k_{21}	Min^{-1}	0.0155		

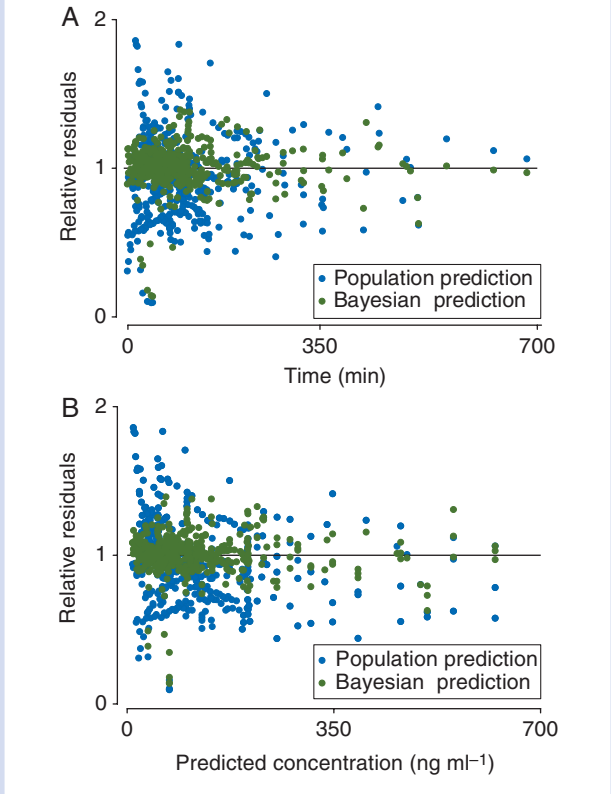

Fig 3 Relative residuals are the ratios $C_{measured}/C_{predicted}$. In (A), the relative residuals are plotted over time, and (B) displays the relative residuals over the predicted concentrations.

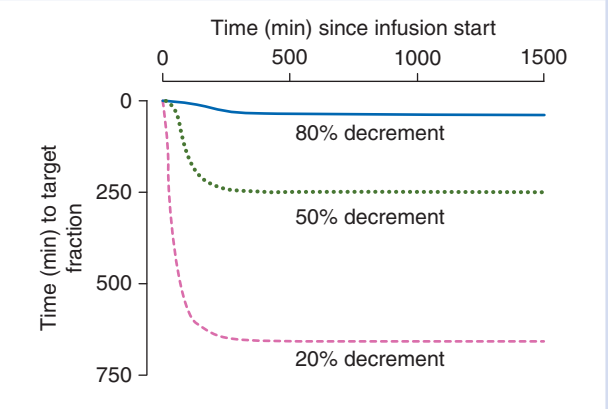

Fig 4 The context-sensitive decrement times in plasma. After a certain infusion time (*x*-axis), stopping the infusion would take the time indicated on the *y*-axis to reach one of the decrement portions. Once steady state is reached, the times for the 80%, 50%, and 20% decrements are 38, 248, and 660 min.

The covariance step of the final model was passed successfully. Sixty-nine runs with minimization terminated and 525 runs with estimates near a boundary (of the elimination clearance) were skipped when calculating the bootstrap results, leaving 1406 runs available for calculation of the SE quantiles during the bootstrap. The values for each variable were as follows {variable (unit), mean [(2.5 and 97.5% standard error) (2.5 and 97.5% confidence interval)]}: V_1 (litre), 24.0 [(18.86, 29.3) (19.4, 29.5)]; V_2 (litre), 184.8 [(155.9, 210.1) (159.0, 213.0)]; Cl_{el} (litre min^{-1}), 0.54 [(0.42, 0.67) (0.43, 0.67)]; and Cl_{dist} (litre min^{-1}), 2.79 [(2.08, 3.6) (2.11, 3.6)].

The 80%, 50%, and 20% context-sensitive decrement times for the plasma concentration were 38, 248, and 660 min after steady-state concentrations were established. Context-sensitive decrement times are displayed in Figure 4.

Discussion

This study determined a complete compartmental PK data set of i.v. administered nefopam during mild hypothermia and checked its reliable predictive value by bootstrap analysis. Therefore, a mathematical model to describe plasma concentrations of nefopam at a specific time point is available, in this case, a two-compartment model. This model could be used to establish and maintain a desired plasma concentration manually or automated with the limitation of the unavoidable variability underlying a TCI system.

With the area under the curve method, Aymard and colleagues[28] calculated (log2)/β (β, elimination rate constant of the terminal log-linear phase) and distinguished a terminal plasma elimination half-life time of i.v. administered nefopam of 5.1 h, which is in good agreement with our result based on compartmental PK. Mather and colleagues[29] calculated a value of 3.8 and 4.1 h, respectively. In our study, an average of 31 arterial blood samples were drawn per volunteer on each study day over the course of 10–13 h. Mather and colleagues reported a period of 24 h and 19 samples. It remains unclear why the terminal plasma elimination half-life time Mather and colleagues found differ from Aymard and colleagues' result, and from ours.

Table 3 Kinetic parameters during hypo- and normothermia. Cl_{el}, plasma clearance; Cl_{dist}, distributional clearance (Q); V_1, Vd_{ss}, volume of distribution in the central compartment or at steady state; N/A, not applicable, derived parameter

Variable	Unit	Typical value (SE %)	
		Hypothermia	Normothermia[31]
V_1	Litre	24.1 (12%)	264 (8%)
Vd_{ss}	Litre	207.5 (N/A)	529 (8%)
Cl_{el}	Litre h^{-1}	32.4 (13%)	52.9 (6%)
Cl_{dist}	Litre h^{-1}	170.4 (15%)	35.2 (13%)

Altered clearance of various medications, especially paralytics, propofol, fentanyl, phenytoin, and verapamil, have been described during hypothermia and decreased the clearance.[30] The elimination clearance [Cl_{el} (SE %)] was 52.9 (6%) litre h^{-1} for healthy volunteers, 37.0 (21%) litre h^{-1} for patients with end-stage renal disease (ESRD) not yet haemodialysed, 27.3 (13%) litre h^{-1} for ESRD patients on chronic haemodialysis,[31] and 32.4 (13%) litre h^{-1} in our hypothermia study, resembling the reduced value of the elimination clearance of patients with ESRD compared with healthy volunteers. Our value fits the picture of decreased elimination clearances during hypothermia for other drugs. The volume of the central compartment and the volume of distribution during steady state present with less volume during hypothermia compared with normothermia (Table 3). This could be explained with vasoconstriction, since the central compartment largely reflects intravascular volume. Nefopam needs to be distributed out of the central compartment quickly, being denoted by a large distributional clearance Cl_{dist}=2.84 (0.42) litre min^{-1}.

Nefopam will be used for the purpose of inducing tolerance to mild hypothermia. The main methods of inducing and maintaining mild hypothermia are i.v. application of cold fluids, applying ice or chemical packs, wrapping in mattresses or other special cooling gants, cold forced air, and endovascular cooling. Often a combination is applied, prioritizing cold fluid application initially. One study used 30 ml kg^{-1} lactated Ringer's solution at 4°C infused over 30 min via a peripheral i.v. access.[32] The median temperature decreased after the bolus was 1.6°C. Another study used ice-cold saline solution, cold packs, and mattresses.[33] Core cooling in our study resulted from infusion of an average of 3.0–3.5 litre cold lactated Ringer's solution. The amount of volume administered in our study is slightly greater than the one based on the recommendation by the above-mentioned studies [2.3 (0.3) litre calculated for our study population] for induction of therapeutic hypothermia but reflects a whole study cycle (induction+maintenance) and

deals with non-anaesthetized volunteers compared with anaesthetized patients. Therefore, the gathered data and derived kinetics mirror clinical handling of the targeted field of nefopam use to a great extent. This is a potential benefit because data obtained in normothermic patients would need to be extrapolated to hypothermic conditions that we already incorporated in the study.

On top of the thermal influence on the kinetic parameters, slight differences in the mode of administration, sampling, and calculating parameters need to be taken into account. In the normothermic study, people received a single dose of 20 mg only, administered over 30 min,[31] whereas the hypothermic study administered up to 64 mg continuously over a period up to 3 h, covering loading and maintenance as well. The normothermic study lacks a maintenance infusion and did not reach a steady state. Therefore, values of the normothermic study are more prone to calculation errors, since kinetic parameters needed to be extrapolated by the software rather than being based on measured concentrations during a real maintenance period.

Both thermal manipulations and volume application in our study reflect current practice in clinical use of mild hypothermia, one field of nefopam assignment. In detail: during the period of mild hypothermia and shivering, the measured nefopam plasma showed a peak in the concentration curves (Fig. 1). It is unclear if this effect could be attributed to periods of increased shivering activity. Before thermal manipulations took place, a stable nefopam plasma concentration was established; after terminating cooling and stopping the nefopam maintenance infusion, a regular decrease in the nefopam plasma concentration was observed (Fig. 1). The determined value for the terminal plasma elimination half-life time of nefopam found in our investigation is in accordance with the one Aymard and colleagues[28] found with a different method and without thermal manipulations. Nevertheless, the model we determined describes the values during all phases, including thermal manipulations.

We used serial samples in each volunteer, administering nefopam with two different concentrations (one concentration per occasion) on two different occasions. The minimum objective function values of the model building process are shown in Table 1. As expected, treating two different infusion regimes in one volunteer as two independent individuals delivers slightly better results. Nevertheless, the correct declaration of two different dosing regimes in the same subject on different occasions was used for the presented data and also distinguishing between a population and a non-population approach. Furthermore, introducing IOV in the model further lowered the minimum value of the objective function from 3045 to 2858 and proved essential to avoid biased population parameter estimates.[34]

During bootstrapping, 525 runs, equalling 26%, were skipped with estimates near a boundary. In all cases, they were estimates of the elimination clearance. From a statistical point of view, the skipped runs could bias the result. The mean of the remaining runs is close to 0, but the SD is only about 0.6. This could lead to an underestimation of the CIs. The value for the elimination clearance derived during model building is in accordance with values of other publications determining it with different methods. Furthermore, the standard errors in modelling during the covariance step show comparable results with bootstrapping (values not displayed). Since we found similar results to other groups for the elimination clearance and results in modelling and bootstrapping are comparable, we hold the compartment model established for a valid tool. It is no secret that there has been a big controversial discussion in the community for years, if parameters reaching a boundary should be discarded from the bootstrap distribution; not only we believe it is the best way to do so. Values beyond the used range could cause numerical problems leading to estimated values outside a reasonable physiological range.

The initial peaks seen in Figure 1 resulted from partial overdosing, since the necessary amount of drug to be infused was derived by estimation from available data. Now, with the determined compartmental data set, such overdosing could be avoided. With the compartmental data set, the initial loading could be calculated to saturate the central compartment without causing an overshoot (and possible side-effects), replenishing the amount of drug being distributed to peripheral compartments, or being eliminated. By implementing this compartmental PK data set (Table 2) into infusion pumps, the process could be automated. After choosing a desired nefopam plasma concentration, the infusion pump will establish and maintain this concentration relieving work load on medical personnel.

In Figure 2, we plotted measured *vs* predicted plasma concentrations [predictions based on individual doses and typical parameter values (=population predictions), individual doses and individual parameter values (=Bayesian predictions)]. The Bayesian predictions match the observations well over the entire concentration range. The fact that several measured concentrations >200 ng ml^{-1} deviate profoundly from the population predictions and that these data points were observed during the initial infusion time becomes obvious when cross-checking Figure 2 with Figure 1. It is well known that compartment models (assuming instantaneous mixing) are not adequate for this initial phase. A second option to explain such a bias for higher concentrations would be non-linearity in such a way that the clearance is not constant over the complete concentration range but limited, for example, by enzyme capacity. Only during the initial phase, loading concentrations >200 ng ml^{-1} were measured. Furthermore, assessing the inter-individual variability of parameters determining the drug concentrations in this phase before steady state (Table 2), both the central volume of distribution and the distribution clearance display the largest IIV (CV 39% and 31%, respectively). After termination of the infusion, the decrease in plasma concentrations is predominantly related to the Cl_{el}, which displays only modest IIV (CV 23%). This fact is supported by the MDPE of -6.15% showing a slight overestimation of the model compared

with the measured values. Thus, we attribute the deviations of the population predictions from the measured values at concentrations >200 ng ml^{-1} to the known effect that compartment models are not completely adequate for the initial phase.

Another limitation of the study is the small age range (21–39 yr) of people participating in the study. Furthermore, the effects (if any) of gender could not be analysed, only two women participated. Thus, nefopam kinetics for children, the elderly, and women remain to be investigated. Because the spread of biometric parameters (age, weight, height, sex) in the study population was insufficient, we cannot conclude that nefopam dosing is independent of weight, although this is the current situation in clinical use.

To achieve and maintain a nefopam plasma concentration of 100 ng ml^{-1}, scheme B with a nefopam concentration of 1 mg ml^{-1} could be used. That scheme incorporates a ramping to minimize the risk of side-effects such as nausea and vomiting or dizziness. Nevertheless, adjusting the infusion rate every few minutes is uncomfortable and time-consuming. Therefore, the use of a target-controlled automated pump using the determined kinetic data set is recommended. Furthermore, it allows us to establish various plasma concentrations, as desired (with the variability underlying a TCI system).

In conclusion, this is the first compartmental pharmokinetics of nefopam during hypothermia. A two-compartment model with IOV reliably characterizes nefopam kinetics and enables predictions of nefopam plasma concentrations at any time point and could be used to establish and maintain nefopam plasma concentrations, even automated by infusion pumps.

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Declaration of interest

None declared.

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Appendix

Each scheme was completed by a total of four volunteers. In a randomized order, one cycle with a concentration of 0.5 mg ml^{-1} nefopam and the other cycle with a concentration of 1.0 mg ml^{-1} nefopam were administered.

Scheme A

Time (min)	Infusion rate (ml h^{-1})
0	164
5	163
10	20.4
15	21.7
20	20.6
25	19.6
30	18.7
35	17.9
40	17.1
45	16.4
50	15.8
55	15.2
60	14.6
65	14.1
70	13.6
75	13.1
80	12.7
85	12.3
90	11.9
95	11.6
100	11.3
105	11.0
110	10.7
115	10.5
120	10.3
125	10.1
130	9.9
135	9.7
140	9.5
145	9.4
150	9.2
155	9.1
160	8.9
165	8.8
170	8.7
175	8.6
180	0.0

Scheme B

Time (min)	Infusion rate (ml h^{-1})
0	60
5	19
20	17
30	14
40	11.5
55	9.5
75	8
100	6.5
135	5.5
180	0

References

1 Popovic R, Liniger R, Bickler PE. Anesthetics and mild hypothermia similarly prevent hippocampal neuron death in an in vitro model of cerebral ischemia. *Anesthesiology* 2000; **92**: 1343–9

2 Sakai F, Amaha K. The effects of hypothermia on a cloned human brain glutamate transporter (hGLT-1) expressed in Chinese hamster ovary cells: −[^{3}H]L-glutamate uptake study. *Anesth Analg* 1999; **89**: 1546–50

3 Dae MW, Gao DW, Sessler DI, Chair K, Stillson CA. Effect of endovascular cooling on myocardial temperature, infarct size, and cardiac output in human-sized pigs. *Am J Physiol Heart Circ Physiol* 2002; **282**: H1584–91

4 Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002; **346**: 549–56

5 Bernard SA, Gray TW, Buist MD, *et al.* Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; **346**: 557–63

6 Shankaran S, Laptook AR, Ehrenkranz RA, *et al.* Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 2005; **353**: 1574–84

7 Azzopardi DV, Strohm B, Edwards AD, *et al.* Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med* 2009; **361**: 1349–58

8 Lopez M, Sessler DI, Walter K, Emerick T, Ozaki M. Rate and gender dependence of the sweating, vasoconstriction, and shivering thresholds in humans. *Anesthesiology* 1994; **80**: 780–8

9 Zweifler RM, Sessler DI. Thermoregulatory vasococonstriction and shivering impede therapeutic hypothermia in acute ischemic stroke patients. *J Stroke Cerebrovasc Dis* 1996; **6**: 100–3

10 Hales JR, Fawcett AA, Bennett JW, Needham AD. Thermal control of blood flow through capillaries and arteriovenous anastomoses in skin of sheep. *Pflugers Arch* 1978; **378**: 55–63

11 De Witte J, Sessler DI. Perioperative shivering: physiology and pharmacology. *Anesthesiology* 2002; **96**: 467–84

12 Sessler DI. Defeating normal thermoregulatory defenses: induction of therapeutic hypothermia. *Stroke* 2009; **40**: e614–21

13 Buritova J, Besson JM. Effects of nefopam on the spinal nociceptive processes: a c-Fos protein study in the rat. *Eur J Pharmacol* 2002; **441**: 67–74

14 Dordoni PL, Della Ventura M, Stefanelli A, *et al.* Effect of ketorolac, ketoprofen and nefopam on platelet function. *Anaesthesia* 1994; **49**: 1046–9

15 Fuller RW, Snoddy HD. Evaluation of nefopam as a monoamine uptake inhibitor in vivo in mice. *Neuropharmacology* 1993; **32**: 995–9

16 Gray AM, Nevinson MJ, Sewell RD. The involvement of opioidergic and noradrenergic mechanisms in nefopam antinociception. *Eur J Pharmacol* 1999; **365**: 149–57

17 Guirimand F, Dupont X, Bouhassira D, Brasseur L, Chauvin M. Nefopam strongly depresses the nociceptive flexion (R(III)) reflex in humans. *Pain* 1999; **80**: 399–404

18 Heel RC, Brogden RN, Pakes GE, Speight TM, Avery GS. Nefopam: a review of its pharmacological properties and therapeutic efficacy. *Drugs* 1980; **19**: 249–67

19 Ohkubo Y, Nomura K, Yamaguchi I. Involvement of dopamine in the mechanism of action of FR64822, a novel non-opioid antinociceptive compound. *Eur J Pharmacol* 1991; **204**: 121–5

20 Rosland JH, Hole K. The effect of nefopam and its enantiomers on the uptake of 5-hydroxytryptamine, noradrenaline and dopamine in crude rat brain synaptosomal preparations. *J Pharm Pharmacol* 1990; **42**: 437–8

21 Bilotta F, Pietropaoli P, La Rosa I, Spinelli F, Rosa G. Effects of shivering prevention on haemodynamic and metabolic demands in hypothermic postoperative neurosurgical patients. *Anaesthesia* 2001; **56**: 514–9

22 Alfonsi P, Passard A, Gaude-Joindreau V, Guignard B, Sessler DI, Chauvin M. Nefopam and alfentanil additively reduce the shivering threshold in humans whereas nefopam and clonidine do not. *Anesthesiology* 2009; **111**: 102–9

23 Taniguchi Y, Ali SZ, Kimberger O, *et al.* The effects of nefopam on the gain and maximum intensity of shivering in healthy volunteers. *Anesth Analg* 2010; **111**: 409–14

24 Yamaoka K, Nakagawa T, Uno T. Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. *J Pharmacokinet Biopharm* 1978; **6**: 165–75.

25 Varvel JR, Donoho DL, Shafer SL. Measuring the predictive performance of computer-controlled infusion pumps. *J Pharmacokinet Biopharm* 1992; **20**: 63–94

26 Glass PS, Shafer S, Reves JG. Intravenous drug delivery systems. In: Miller RD, ed. *Miller's Anesthesia*. Philadelphia: Elsevier (Churchill Livingstone), 2005; 439–80

27 Beal SL, Sheiner LB. *NONMEM User's Guide. NONMEM Project Group*. San Francisco: University of California, 1992

28 Aymard G, Warot D, Demolis P, *et al.* Comparative pharmacokinetics and pharmacodynamics of intravenous and oral nefopam in healthy volunteers. *Pharmacol Toxicol* 2003; **92**: 279–86

29 Mather GG, Labroo R, Le Guern ME, Lepage F, Gillardin JM, Levy RH. Nefopam enantiomers: preclinical pharmacology/toxicology and pharmacokinetic characteristics in healthy subjects after intravenous administration. *Chirality* 2000; **12**: 153–9

30 van den Broek MP, Groenendaal F, Egberts AC, Rademaker CM. Effects of hypothermia on pharmacokinetics and pharmacodynamics: a systematic review of preclinical and clinical studies. *Clin Pharmacokinet* 2010; **49**: 277–94

31 Mimoz O, Chauvet S, Gregoire N, *et al.* Nefopam pharmacokinetics in patients with end-stage renal disease. *Anesth Analg* 2010; **111**: 1146–53

32 Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. *Resuscitation* 2003; **56**: 9–13

33 Wolfrum S, Pierau C, Radke PW, Schunkert H, Kurowski V. Mild therapeutic hypothermia in patients after out-of-hospital cardiac arrest due to acute ST-segment elevation myocardial infarction undergoing immediate percutaneous coronary intervention. *Crit Care Med* 2008; **36**: 1780–6

34 Karlsson MO, Sheiner LB. The importance of modeling interoccasion variability in population pharmacokinetic analyses. *J Pharmacokinet Biopharm* 1993; **21**: 735–50