A Bayesian approach for population pharmacokinetic modeling of dexmedetomidine during long-term infusion in critically ill pediatric patients

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Objectives

The purpose of this study was to assess the pharmacokinetics of dexmedetomidine in the ICU settings during the long-term infusion and to compare it with the existing literature data using the Bayesian population modeling with literature-based informative priors [1].

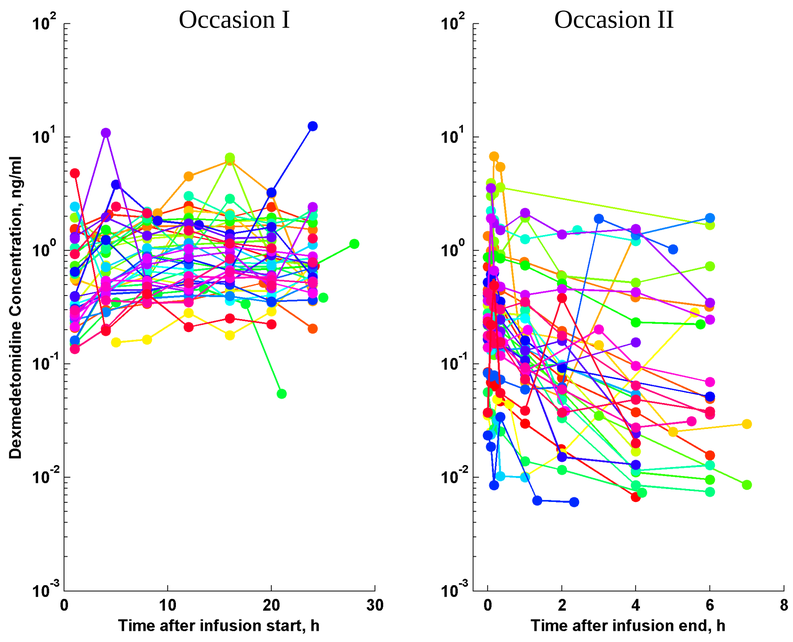
Methods

Thirty eight patients were included in the analysis with concentration measurements obtained at two occasions: first from 0 to 24 hr after infusion initiation and second from 0 to 8 hr after infusion end [1]. Population modeling was performed using WinBUGS 1.4.3. The BUGS language interface was implemented using WBDev and BlackBox 1.5 compiler. Data management, launching WinBUGS, and analysis of the MCMC samples were done in Matlab Software (Version 8.1; The MathWorks, Natick, MA, USA) using the MatBUGS interface.

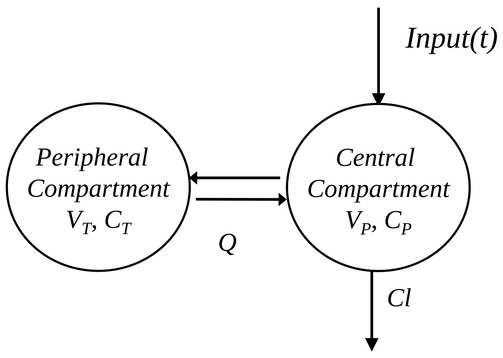
Demographic characteristic of patients:

Parameter, unit	Median [Range] or Number
Age, months	70 [1.4 – 188.6]
Weight, kg	18.5 [4.7 – 60]
Dose, µg	1153.8 [248.8 – 4732.2]
Infusion Duration, h	97.3 [45.0 – 229.2]
Pediatric Risk of Mortality (PRISM)	0.5 [0 – 11]
Male/Female	23/15

The individual dexmedetomidine concentration-time profiles



PK model:



$$V_P \frac{dC_P}{dt} = R_0(t) - CLC_P - QC_P + QC_T \qquad C_P(0) = 0$$

$$V_T \frac{dC_T}{dt} = QC_P - QC_T \qquad C_T(0) = 0$$

$$\ln P_i = \ln \theta_P + \ln f_P + K \ln\left(\frac{BW_i}{70}\right) + \eta_{P,i}$$

$$\ln CL_i = \ln \theta_{CL} + \ln f_P + K \ln\left(\frac{BW_i}{70}\right) + \ln\left(\frac{\mathrm{PMA}_i^{\mathrm{Hill}}}{\mathrm{PMA}_i^{\mathrm{Hill}} + \mathrm{TE}_{50}^{\mathrm{Hill}}}\right) + \eta_{CL,i}$$

$$\eta_{P,i} \sim MVN(0, \Omega^{-1})$$

$$\ln C_{P,ij} = \ln C_P + \varepsilon_{C,ij}$$

$$\varepsilon_{C,ij} \sim t(0, \sigma_C^{-2}, \nu)$$

Prior Elucidation:

The prior information on dexmedetomidine pharmacokinetics was elicited from the literature study pooling results from a relatively large group of children [2].

Table 1
Study characteristics, mean (range)

Study	n	Age (year)	Weight (kg)	Surgery/ procedure	Infusion/ bolus	Dose	Sampling type	Sample collection times
1 (16)	24	5.6 (2.0–12.0)	16.8 (10–42)	Urologic, lower abdominal or plastic surgery	Slow bolus over 10 min	2, 4 or 6 µg·kg^{-1}	Venous	10, 15, 30, 75 min, 2.5, 4, 6, 12, 24 h
2 (17)	10	3.0 (0.3–7.9)	13.1 (4.1–27.5)	Low risk cardiac or craniofacial surgery	Infusion	1 µg·kg^{-1} bolus, 0.2 µg·kg^{-1}·h^{-1} infusion	Venous	10, 30 min, 2, 4, 6, 8, 16 h during infusion, 2, 4, 8 h after infusion
3 (18)	16	2.75 (0.2–10.0)	14.58 (5.3–37.5)	Bronschoscopy or NMRI	Slow bolus over 5 min	1 µg·kg^{-1}	Venous	5, 10, 20 min, 1, 2, 3, 4, 5 h
4 (19)	45	3.38 (0.01–14.4)	15.1 (3.1–58.9)	Cardiac surgery	Slow bolus over 10 min	1–4 µg·kg^{-1}	Arterial	5–30 min, 1–2, 3–4, 6–10 h
Current pooled analysis		3.83 (0.01–14.4)	16.05 (3.1–58.9)					

$\bar{\mu}$ Ω_0 Σ

$$\sigma_C \sim Uniform(0.001, 1000)$$

$$\upsilon \sim 1 + Exponential(0.1)$$

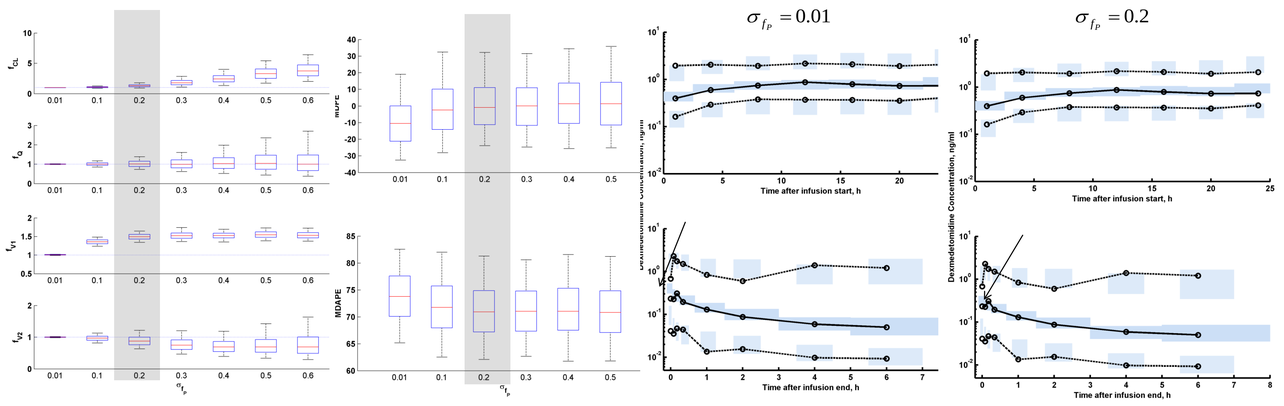
$$\ln \theta \sim MVN(\ln \bar{\mu}, \Sigma^{-1})$$

$$\Omega^{-1} \sim Wishart(\rho\Omega_0, \rho)$$

Parameter	Estimate	%BSV	%SE	95% CI
(a) Pharmacokinetic parameter estimates				
CL_{std} (l·h^{-1}·70 kg)	42.1	30.9	4.4	38.7, 45.8
$V1_{std}$ (l·70 kg)	56.3	61.3	8.7	44.5, 67.4
Q_{std} (l·h^{-1}·70 kg)	78.3	37.0	14.4	50.7, 98.4
$V2_{std}$ (l·70 kg)	69	47.0	8.2	57.5, 80.3
TM_{50} (weeks)	44.5	–	6.9	36.8, 50.3
N	2.56	–	17.6	1.65, 3.78

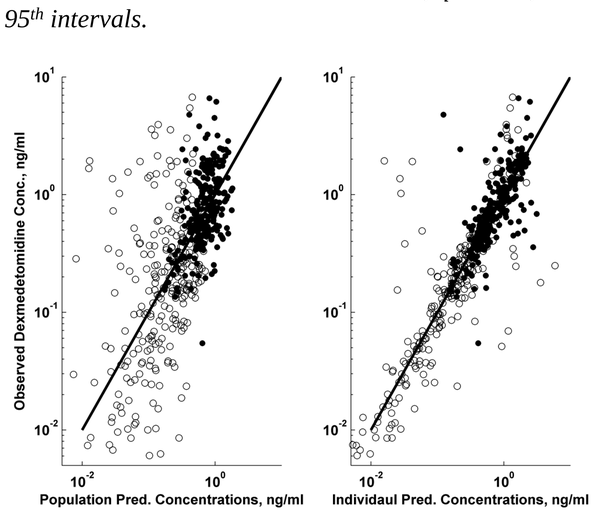
ρ = 30 was assumed. It was determined empirically by simulating from the Wishart distribution in MATLAB (Version 8.1, The MathWorks, Natick, MA) to ensure 25% of variability in Ω_0 parameters. The standard errors for BSV were not reported in the original article.

Results

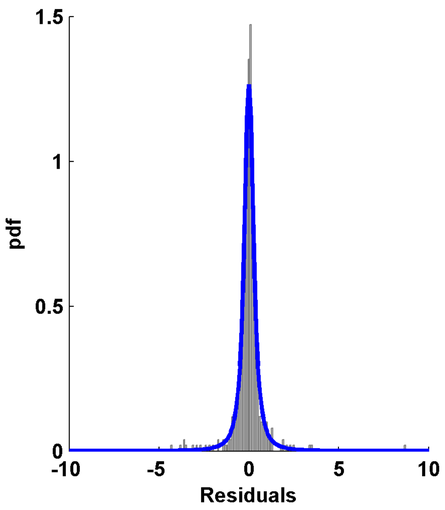


The effect of prior precision (σ_{fP}^{-2}) on the posterior distribution of fraction effects (f_P) corresponding to a particular PK parameter and on the predictive properties of the DEX PK models as reflected by the bias (MDPE) and inaccuracy (MDAPE) of the model. The σ_{fP} = 0.2 is the most conservative choice for the prior uncertainty leading to the highest predictive accuracy. The posterior distributions are summarized as median, quartiles, and 5th-95th intervals.

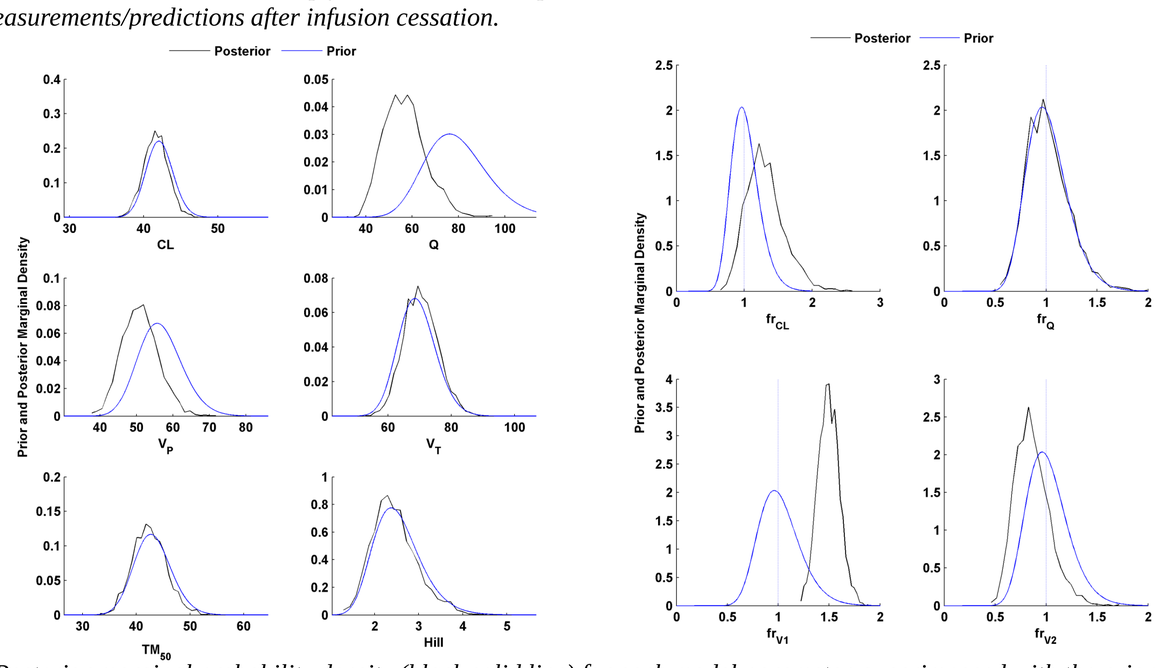
The visual a posteriori predictive plots for the initial and final PK model. The plots show the individual prediction-based 95% confidence intervals around the 10th, 50th, and 90th percentiles of the PK data (blue areas). The corresponding percentiles from the experimental data are plotted in black color.



Goodness of fit plots for the final PK/PD model. The filled circles denote observed/predicted concentrations during the infusion duration, the empty circles corresponds to measurements/predictions after infusion cessation.



The empirical and model predicted probability density of residuals



Posterior marginal probability density (black solid line) for each model parameter, superimposed with the prior probability density (blue solid line).

Conclusions

A two compartment PK model with allometrically scaled parameters, maturation of clearance and t-student residual distribution on a log-scale successfully described the data. The incorporation of time-depended (different between the two occasions) PK parameters improved the model. It turned out that volume of distribution is 1.5-fold higher during the second occasion. There was also an evidence of increased (1.3-fold) clearance for the second occasion with posterior probability of 62%. The application of Bayesian modeling with informative priors allowed elucidation of time-dependent changes in PK parameters during the long-term infusion using poorly informative data.

Literature

1. Wiczling P, Bartkowska-Śniatkowska A, Szerkus O, Siluk D, Rosada-Kurasińska J, Warzybok J, Borsuk A, Kaliszan R, Grześkowiak E, Bienert A, The pharmacokinetics of dexmedetomidine during long-term infusion in critically ill pediatric patients. A Bayesian approach with informative priors. J Pharmacokinet Pharmacodyn. 2016 May 24.

2. Potts AL, Anderson BJ, Warman GR, Lerman J, Diaz SM, Vilo S. Dexmedetomidine pharmacokinetics in pediatric intensive care – a pooled analysis. Paediatr Anaesth. 2009 19:1119-29.

Acknowledgment

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