Pharmacokinetics of dexmedetomidine in elderly patients undergoing sedation after abdominal aortic surgery

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Introduction:. Dexmedetomidine (DEX) is an α2-agonist which has been increasingly used for analgosedation. The aim of this study was to characterize the population pharmacokinetics (PK) of dexmedetomidine in patients undergoing sedation after abdominal aortic surgery and to investigate the potential benefits of individualization of drug dosing based on patients' characteristics including genetic polymorphism, cardiac index and other cardiovascular parameters.

Methods: Dexmedetomidine (Dexdor, Orion Pharma Poland Sp. z.o.o.) was administered by continuous intravenous infusion without a loading dose. The infusion was started at the rate of 0.7 μg/kg/h and titrated to achieve the desired level of sedation according to the monitored bispectral index (BIS, Philips Medical Systems B.V, Netherlands). BIS values were kept between 60 and 80. Cardiac index (CI), a hemodynamic parameter related to cardiac output was measured and recorded by FloTrac System (Edwards Lifescences, USA). Blood samples for DEX assay were collected daily during the infusion and at the selected time points after its termination. The DEX concentrations in the plasma were measured using LC-MS/MS method. The following covariates were examined to influence DEX PK: patients' age, sex, body weight, systolic and diastolic blood pressure, heart rate, cardiac index, infusion duration as well as CYP2C19, CYP1A2, CYP2A6, UGT1A4 and UGT2B genetic polymorphism. Non-linear mixed-effects modelling in NONMEM (Version 7.3.0, Icon Development Solutions, Ellicott City, MD, USA) was used to analyze the observed data.

Results: Concentration-time profiles of DEX were obtained from 11 patients. Duration of infusion was less than 24 hours in all patients (Table 1). The DEX PK was best described by a two-compartment model. The typical values of PK parameters were estimated as 53.4 L for the volume of the central compartment, 112 L for the volume of the peripheral compartment, 51.1 L/h (for a typical patient) for systemic clearance and 36.7 L/h for the distribution clearance. Those values are consistent with literature findings. We were unable to show any significant relationship between collected covariates and DEX PK.

Parameter, unit	Median [Range or Number]
Age, years	64.5 [61-79]
Weight, kg	74.5 [55-85]
Male/Female	11/1
Infusion Time, h	4.8 [3.7-8.4]
Total dose of dex, mg	0.28 [0.16-0.60]

Table 1. Demographic characterization of patients. Results are expressed as median or range.

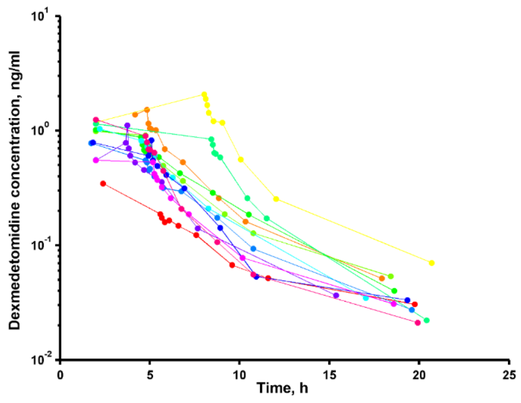
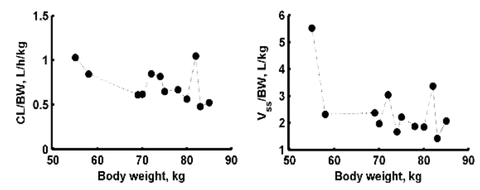


Figure 1. The individual dexmedetomidine concentration-time profiles.



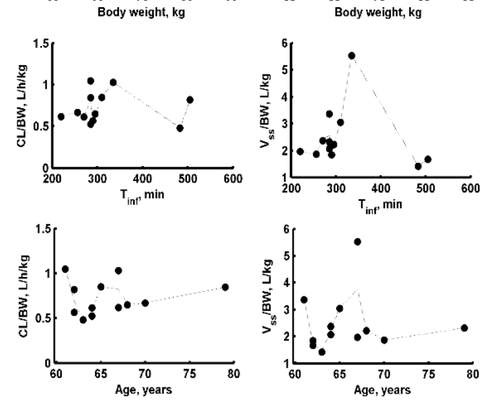


Figure 3. Relationship between body weight normalized clearance and volume of distribution at steady state versus age, body weight, infusion duration and sex for all patients in the study.

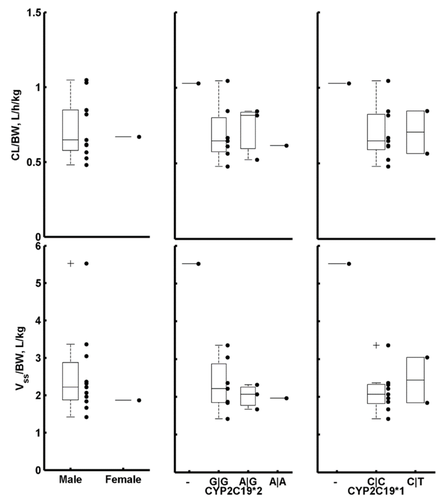


Figure 5. Relationship between body weight normalized clearance and volume of distribution at steady state versus sex, CYP2C19*2 and CYP2C19*1 polymorphism.

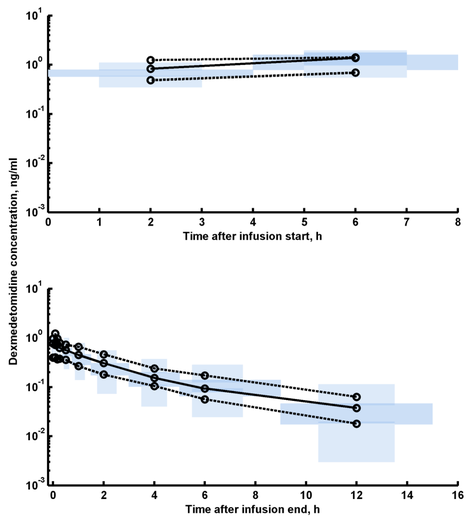


Figure 2. The VPC plots for dexmedetomidine PK. The VPC plots show the simulation-based 90% confidence intervals around the 10th, 50th, and 90th percentiles of the PK data in the form of blue (50th) and gray (10th and 90th) areas. The corresponding percentiles from the prediction corrected observed data are plotted in black color.

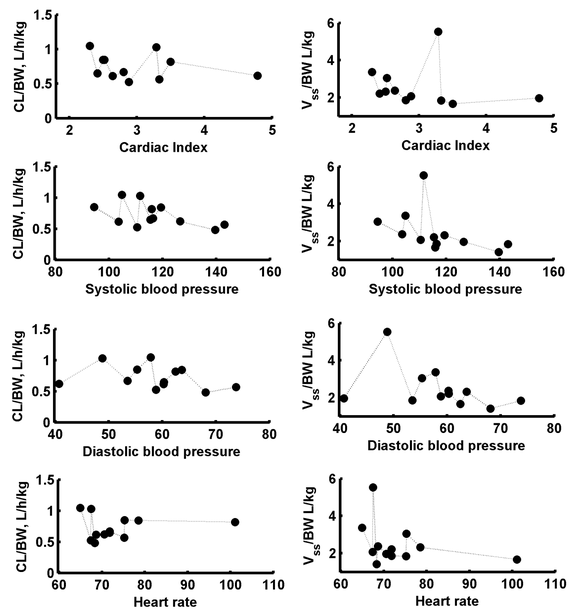


Figure 4. Relationship between body weight normalized clearance and volume of distribution at steady state haemodynamic parameters for all patients in the study.

Parameter [unit]	Description	θ, Estimate (%RSE) [Shrinkage]	Estimate, Bootstrap Median [5th 95th CI]
θ_{VC} [L]	Volume of central compartment	53.4 (19.5)	52.9 [19.5 – 79.9]
θ_{CL} [L/h]	Systemic clearance	51.1 (6.3)	50.3 [45.7 – 56.2]
θ_{VT} [L]	Volume of peripheral compartment	112 (16.4)	115 [88.6 – 152]
θ_{Q} [L/h]	Inter-compartmental clearance	36.7 (29.7)	35.4 [20.6 – 61.5]
Between Subject Variability			
ω^2_{VC} [%CV]	Inter-individual variability of V_C	0 FIX	-
ω^2_{CL} [%CV]	Inter-individual variability of CL	21.3 (29.7) [0.0]	20.0 [9.8 – 28.7]
ω^2_{VT} [%CV]	Inter-individual variability of V_T	44.4 (26.6) [2.5]	37.0 [12.8 – 54]
ω^2_{Q} [%CV]	Inter-individual variability of Q	58.3 (34.3) [10.7]	52.3 [3.0 – 81.7]
Residual Error Model			
σ^2[%CV]	Proportional residual error variability	21.1 (11.6) [11.9]	21.2 [16.9 – 25.5]

Table 2. The parameter estimates of the final PK model of dexmedetomidine. The bootstrap estimates are given for comparison. 25 out of 1000 bootstrap runs terminated early.
RSE denotes relative standard errors whereas CV coefficient of variation.

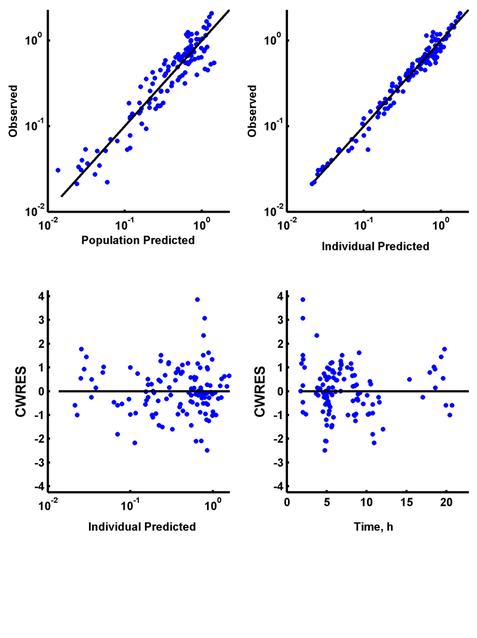


Figure 6. Goodness-of-fit plots for the final dexmedetomidine PK model: the observed versus the population predicted responses, the observed versus the individual predicted responses, C. the conditional weighted residuals (CWRES) versus the individual predicted responses, and the CWRES versus time.

Conclusion: **This study does not provide sufficient evidence to support the individualization of DEX dosing based on age, sex, body weight, Cardiac Index, genetic polymorphysm and infusion duration.**

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