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Dexmedetomidine pharmacodynamics in healthy volunteers: 2. Haemodynamic profile

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Abstract

Background. Dexmedetomidine, a selective α2-adrenoreceptor agonist, has unique characteristics, with little respiratory depression and reusability during sedations. We characterized the haemodynamic properties of dexmedetomidine by developing a pharmacokinetic–pharmacodynamic (PKPD) model with a focus on changes in mean arterial blood pressure (MAP) and heart rate.

Methods. Dexmedetomidine was delivered i.v. to 18 healthy volunteers in a step-up fashion by target-controlled infusion using the Dyck model. Exploratory PKPD modelling and covariate analysis were conducted in NONMEM.

Results. Our model adequately describes dexmedetomidine-induced hypotension, hypertension, and bradycardia, with a greater effective concentration for the hypertensive effect. Changes in MAP were best described by a double-sigmoidal Emax model with hysteresis. Covariate analysis revealed no significant covariates apart from age on the baseline MAP in the population pharmacokinetic model used to develop this PKPD model. Simulations revealed good general agreement with published descriptive studies of haemodynamics after dexmedetomedine infusion.

Conclusions. The present integrated PKPD model should allow tighter control over the desired level of sedation, while limiting potential haemodynamic side-effects.

Clinical trial registration. NCT01879865.

Key words: dexmedetomidine; haemodynamics; healthy volunteers; hypnotics and sedatives; pharmacology

Dexmedetomidine, a selective α2-adrenoreceptor agonist, is widely used in clinical practice as a sedative drug. Owing to its high affinity and selectivity for the α2-adrenergic receptors, dexmedetomidine produces a typical biphasic haemodynamic response.1 At low plasma concentrations, the sympatholytic effect predominates, and dexmedetomidine tends to lower mean arterial blood pressure (MAP) and heart rate (HR) through activation of presynaptic α2-adrenergic receptors in the central nervous system and through activation of α2-adrenergic receptors in vascular endothelial cells, which causes vasodilation.2-7 At higher concentrations, peripheral vasoconstrictive effects attributable to activation of α2-adrenergic receptors in vascular smooth muscle become dominant, resulting in an increase in MAP and a further decline in HR.4-5

The haemodynamic effects of dexmedetomidine have been descriptively summarized after short (2, 5, or 10 min) infusions1-8 at doses between 0.25 and 4 μg kg-1 or target-controlled infusion (TCI) systems1-5 at target concentrations ranging between 0.5 and 8 ng ml-1. Although a significant dose–response relationship was
Editor’s key points

- Dexmedetomidine has marked effects on haemodynamic
  - there are only limited pharmacokinetic–
  - A novel integrated pharmacokinetic–pharmacodynamic model described the hypotensive, hypertensive, and
  - The sedative and haemodynamic effects of dexmedetomidine are highly correlated, providing potential surrogate
  - observed, only very limited pharmacokinetic–pharmacodynamic (PKPD) models exist relating the time course of dexmedetomidine plasma concentrations to its effects on MAP and HR. In order to gain a better understanding and predict these haemodynamic alterations, an integrated PKPD model would be useful to characterize these effects.

We previously developed a pharmacokinetic model for dexmedetomidine based on data from an extensive healthy volunteer study. In an accompanying paper, we describe the sedative effects of dexmedetomidine based on data from an extensive healthy volunteer study. In an accompanying paper, we describe the sedative effects of dexmedetomidine, using the EEG-derived bispectral index (BIS).

In this article, we present a PKPD model describing the haemodynamic effects of dexmedetomidine to characterize the relationship between dexmedetomidine plasma concentrations, effect-site concentrations (C_e), and resulting changes in MAP and HR.

Methods

Study design

This study was approved by the local Medical Ethics Review Committee (METC, University Medical Center Groningen, Groningen, the Netherlands; METC number: 2012/400), and was registered in the ClinicalTrials.gov database (NCT01879865). The study conduct has been described in detail, including development of a pharmacokinetic (PK) model based on the study data. In brief, after obtaining written informed consent, 18 healthy volunteers, stratified according to age and sex (18–34, 35–54, and 55–72 yr; three males and three females in each group) received dexmedetomidine i.v. on two separate occasions. Dexmedetomidine was delivered through TCI using the Dyck model, as described in the accompanying paper.

Pharmacodynamic measurements

Continuous arterial blood pressure monitoring was performed via an arterial cannula in the same arm as the i.v. cannula used to deliver the drug. Heart rate was monitored via a continuous ECG wave (lead II) that was recorded throughout the study at a frequency of 500 Hz. Vital signs were monitored using a Philips MP50 monitor (Philips, Eindhoven, The Netherlands). Heart rate was derived from the raw ECG wave, by measuring the R–R interval using a Visual Basic macro in Microsoft Excel (Microsoft, Redmond, WA, USA). All monitored parameters and raw waveforms were recorded electronically using RUGLOOP II software (Demed, Temse, Belgium).

Data handling

The final data set contained MAP and HR measurements at a sampling rate of 1 Hz, which resulted in > 50 000 observations per session for some individuals. In an attempt to reduce the computational burden during model development, we reduced the number of MAP and HR measurements per subject. We also applied a median filter to reduce the influence of artifacts, outlying data, or both during model development. The width (span) of the median filter was 60 s. Data reduction was performed by retaining only the first out of every 50 consecutive median filtered observations in the data set.

The data set used for modelling contained a median of 458 (range 268–672) MAP measurements and 394 (range 234–542) HR measurements per subject per session, corresponding to a reduced sampling rate of ~ 1 min⁻¹.

Population PKPD modelling

For pharmacodynamic (PD) modelling, we used the parameter estimates from the dexmedetomidine PK model published earlier by our group. The individual predicted PK parameters (V₁, V₂, V₃, CL, Q₀, and Q₂) were fixed for each individual and each session (Hannivoot and colleagues reported that V₁ was different between occasions) during further PD modelling.

Different structural models were evaluated to test whether hysteresis exists between the individually predicted dexmedetomidine plasma concentrations (IPRED_plasma) and the PD measures. Direct models relating IPRED_plasma directly to the PD measure were compared against delay drug effect models, such as an effect compartment model or an indirect response model. Drug effects were described using linear, E_max, and sigmoid E_max models. In the event of numerical difficulties with the estimation algorithm, leading to imprecise estimates of E_max and C₀₅₀, an alternative E_max model (shown in equation 1), as described by Schoemaker and colleagues, was evaluated. This equation relies on a parameter (S₀) equal to E_max/C₀₅₀ and could be advantageous for PD model estimation when few data are available near the maximal effect.

\[
E = \frac{S₀ \times E_{\text{max}} \times \text{IPRED}_{\text{Plasma}}}{E_{\text{max}} \times S₀ \times \text{IPRED}_{\text{Plasma}}}
\]

Once the base model structure was established, graphical analysis was conducted to identify potential correlations between post hoc predicted PKPD parameters and patient covariates. The covariates considered were weight, height, BMI, age, sex, and session. Subsequently, these covariates were tested by inclusion in the model, and the resulting change in goodness of fit was evaluated. Here, for the continuous covariates (age, height, and weight) a linear relationship was assumed, whereas for the categorical covariate (sex) an additional parameter was added to the model to differentiate between males and females. Where appropriate, inclusion of model parameters, covariates, or both was tested at the 5% significance level by comparing the decrease in objective function (OFV) against the critical quantile of the corresponding \( \chi^2 \) distribution (e.g. 3.84 for inclusion or exclusion of a single parameter).

Parameter estimation and model evaluation

The first-order conditional estimation algorithm with interaction (FOCE-I) as implemented in NONMEM® (version 7.3, Icon Development Solutions, Hannover, MD, USA) was used to fit the continuous MAP and HR data. Inter-individual variability (IV)
and inter-occasion variability were modelled using exponential models. Residual unexplained variability was described using additive or proportional error models, or both. During model building, the goodness of fit (GOF) of the different models was compared numerically using the Akaike information criterion (AIC) and the median absolute (population) prediction error (MDAPE). At each stage, GOF was graphically evaluated by inspecting plots of the individual or population predicted vs observed responses and plots of the conditionally weighted residuals (CWRES) vs individual predictions and time. To ensure numerical stability, only models with a condition number of the estimated variance–covariance matrix <500 were retained. Finally, models were validated internally using prediction-corrected visual predictive checks (pcVPC) as described by Bergstrand and colleagues.13 Models were fitted to the data using PeN14 and Pirana15 as back- or front-end, or both, to NONMEM. The numerical and graphical assessment of the GOF and the construction of the pcVPCs were conducted in R (R Foundation for Statistical Computing, Vienna, Austria). Simulations were performed in a Microsoft Excel7 Macro-Enabled Worksheet (Microsoft Office Professional Plus 2013), which is supplied in the Online Supplementary material to this paper. The worksheet depends on the ‘PKPD tools for Excel’ package developed by T. Schnider and C. Minto, available from http://www.pkpdtools.com/excel (last accessed April 18, 2017).

Statistical analysis
Model parameters are reported as typical values with associated relative standard errors (RSE) and 95% confidence intervals derived from log-likelihood profiling.16

Results
Data
Figure 1 shows the median filtered HR and MAP signals for four representative subjects from our study during the step-up TCI administration. The dashed lines indicate when a new TCI target was set. This figure clearly shows the monotonic decrease in HR and the biphasic behaviour of the MAP with increasing dexmedetomidine plasma concentrations. Median filtered MAP and HR observations for all subjects throughout the entire study are shown in Online Supplementary Figs S1 and S2.

Mean arterial pressure model development
As a starting point for model building, we used two \(E_{\text{max}}\) models to characterize the dependency between \(IPRED_{\text{plasma}}\) and the MAP. This model was deemed necessary to describe the biphasic effect of dexmedetomidine on MAP adequately. As seen in Fig. 1, at low dexmedetomidine concentrations the hypotensive effect dominates, whereas at higher concentrations this effect is counteracted and then reversed to profound hypertension.

The model was further modified by fixing the \(E_{\text{max}}\) term for the hypotensive effect to increase numeric stability (\(\Delta\text{AIC}\) for fixing \(E_{\text{max}}\) to 1—0.8) and by adding a parameter describing the correlation in IV in baseline MAP (\(Base_{\text{MAP}}\)) and the \(EC_{\text{50}}\) for the hypotensive effect (\(\Delta\text{AIC}=16\)). In addition, an effect compartment model was included to characterize the hysteresis between \(IPRED_{\text{plasma}}\) and MAP. Two effect compartments, with a separate \(k_{\text{off}}\) for the hypotensive (\(k_{\text{hyp}}\)) and hypertensive effect-site concentrations (\(k_{\text{hyp}}\)), gave the highest improvement in

\[
\text{MAP}_{ij} = Base_{\text{MAP}} \times \left(1 + \frac{C_{\text{hyp}}}{EC_{\text{50hyp}} + C_{\text{hyp}}} + \frac{(1 + E_{\text{maxhyp}})}{(EC_{\text{50hyp}} + \Delta EC_{\text{50hyp}}) + C_{\text{hyp}}} \right) \\
\]  

(2)

In the next step, the post hoc predicted parameters for which IIV was included in the model (\(Base_{\text{MAP}}\), \(EC_{\text{50hyp}}\), and \(\Delta EC_{\text{50hyp}}\)) were plotted against the covariates to detect potential covariate relationships. For age, a correlation was observed with \(Base_{\text{MAP}}\). Subsequently, this dependency vs \(Base_{\text{MAP}}\) was formally tested in the model. Inclusion of age on \(Base_{\text{MAP}}\), according to equation (3), resulted in a significant improvement in GOF (\(\Delta\text{AIC}=9.6\)) and a reduction in the population MDAPE from 9.4 to 7.8%.

\[
Base_{\text{MAP}} = Base_{\text{MAP}} \times e^{(\text{Age}/20)} \\
\]  

(3)

Inclusion of age, weight, height, or sex on \(EC_{\text{50hyp}}\) or \(\Delta EC_{\text{50hyp}}\) did not result in a significant decrease in the OFV; therefore, these covariates were not included in the final model.

Final MAP model
The final model parameters are described in Table 1. The likelihood profiles, which were generated to identify potential problems with parameter identification, are shown in Online Supplementary Fig. S3. Goodness-of-fit plots, such as post hoc predictions vs observations and CWRES vs time, are shown in Online Supplementary Figs S4 and S5. Online Supplementary Fig. S5 shows the pcVPC. Overall, these figures demonstrate that the presented model adequately describes the observed changes in MAP during dexmedetomidine administration and that all parameters of the model are estimated with acceptable precision. In the recovery phase, there is increased MAP variability around the model predictions. This is seen in the individual post hoc predicted vs observed MAP plots, shown in Online Supplementary Fig. S1. As subjects were not restrained during the recovery phase of the experiment, (small) movements most probably led to the increased noise in the MAP signal.

The baseline MAP in our study, for a 20-yr-old individual, was estimated to be 80 mm Hg and was found to increase by 5.2% for every 10 yr increase in age. The half-lives for effect-site equilibration for the hypotensive and hypertensive effect-site compartments were estimated to be 13 and 7.7 min, respectively. Furthermore, a significant difference was found between the population typical sensitivity (i.e. \(EC_{\text{50}}\)) for the hypotensive and hypertensive effects, with the latter being 1.20 ng ml \(^{-1}\) higher on average. The difference between both \(\Delta EC_{\text{50hyp}}\) sensitivities was positively correlated to the baseline (\(r=0.755\)). Thus, individuals with a higher baseline MAP tend to show a more profound hypotensive phase compared with individuals having a lower baseline MAP.

A graphical presentation of the change in MAP according to \(C_{\text{p}}\) for a typical 20-yr-old individual, is shown in Fig. 2. The MAP decreases below baseline at low dexmedetomidine \(C_{\text{p}}\), followed by a return to baseline at \(\sim2.4\) ng ml \(^{-1}\). Above this concentration, dexmedetomidine induces hypertension, with a maximal MAP 43% higher than the initial baseline.
Heart rate model development

Initially, HR data were analysed using a model that assumed a linear decrease in HR as a function of IPRED$_{\text{plasma}}$. The model modifications that led to a significant decrease in AIC were as follows: (i) use of a non-linear drug effect model according to Schoemaker and colleagues$^{12}$ (AIC = $-731.1$); (ii) inclusion of an effect compartment model as opposed to a direct model (AIC = $-448.9$); and (iii) use of a model that assumed exponentially decreasing HR variability (HRV), as shown in equation (4) (AIC = $-817.5$).

$$SD_y = \sigma_{\text{RUV, Additive}} \times e^{-c_{\text{max}} \times (\text{BASE}_{\text{HR}} - \text{IPRED}_{\text{HR}})} \quad (4)$$

This error model was evaluated to give more weight to lower HR values which, in light of a potential dexmedetomidine-induced bradycardia, are clinically more important. The residual unexplained variability (RUV) was described by an additive error model with an $s_0$ for subject $i$ at time $j$ ($s_{ij}$) that exponentially decreased, at a rate equal to $h_{\text{min}}$, with the difference between baseline HR ($\text{BASE}_{\text{HR}}$) and the predicted HR at time $j$ ($\text{IPRED}_{\text{HR}}$).

The baseline RUV (i.e. before the start of the dosing) for each subject ($\sigma_{\text{RUV, Additive}}$) was adequately described by a population so with an exponential inter-individual variability term.

The relationship between dexmedetomidine effect-site concentrations and HR was best described by an adaptation of the model described by Schoemaker and colleagues.$^{12}$ In our version of this model, as illustrated in equation (5), the maximal drug effect was dependent on the individual baseline HR and a population parameter describing the minimal attainable HR during dexmedetomidine administration ($HR_{\text{min}}$). Other approaches to model the drug effect, using an $E_{\text{max}}$ or a sigmoid $E_{\text{max}}$ model, failed as a result of numerical instability of the estimation algorithm.
OFV; therefore, no covariates were included in the final model.

The final model adequately describes the time course of HR during/after dexmedetomidine administration (Online Supplementary Fig. S4). This conclusion is further supported by the pcVPC shown in Online Supplementary Fig. S5. The final model parameters and associated standard errors (derived from the log-likelihood profiles in Online Supplementary Fig. S3) are presented in Table 1. Again, post hoc predicted vs observed HR as a function of time for all individuals in the study are shown in Online Supplementary Fig. S2.

In the final model, baseline HR variability was described by a combination of inter-individual and inter-occasion variability, accounting for 13 and 2.2% of baseline variability, respectively. Changes in dexmedetomidine plasma concentrations induced relatively rapid changes in HR, with a half-life for effect-site equilibration of 1.75 min ($t_{1/2}^\text{HR} = 1.75$).

The estimated lower boundary for HR during dexmedetomidine therapy was 22 beats min$^{-1}$ and was significantly different from zero (the OFV increased by 226 when this lower boundary was fixed to zero). The slope parameter ($E_\text{max}$) was estimated to be 4.37 beats min$^{-1}$ ml ng$^{-1}$ and had considerable inter-individual variability (110%). The RUV in HR at baseline was relatively high and variable between subjects. We found a population so for the RUV of 5.6 beats min$^{-1}$ and a inter-individual variability of 48%, respectively. On an individual level, the RUV varied between 2.9 and 12.5 beats min$^{-1}$ at baseline. During dexmedetomidine administration, HR variation correlated with the post hoc predicted HR, with an approximate reduction in RUV of 45% with every 10 beats min$^{-1}$ decrease in HR.

### Effects of infusion duration and dose on MAP and HR

To get a clearer clinical picture of the effects of dexmedetomidine on MAP and HR, several drug infusions with varying infusion durations and doses were simulated. The top and bottom panels of Fig. 3 show the influence of increasing dexmedetomidine doses and infusion duration on the MAP (left panels) and HR (right panels) for doses ranging from 0.25 to 4.0 μg kg$^{-1}$ for a 27-year-old healthy volunteer weighing 77 kg (the Excel workbook used to simulate these dosing regimens is available from the Online Supplementary material of Colin and colleagues).10

For MAP, dexmedetomidine administration up to 1 μg kg$^{-1}$ throughout 5 min causes no hypertension, but with higher doses (2 and 4 μg kg$^{-1}$) profound hypertension occurs, with an

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**Table 1** Final model parameters with associated relative standard errors (expressed as percentages) derived from log-likelihood profiling.

<table>
<thead>
<tr>
<th>Parameter Description</th>
<th>Estimate (RSE)%</th>
<th>BSV* (RSE)%</th>
<th>BOV* (RSE)%</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta_1$ BaseMAP (mm Hg)</td>
<td>80.4 (3.60)</td>
<td>10.9 (16.0)</td>
<td>—</td>
</tr>
<tr>
<td>$\theta_2$ $\theta_{\text{dex MAP}}$ (yr$^{-1}$)</td>
<td>0.00507 (20.2)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$\theta_3$ $k_{\text{dex MAP Hype}}$ (min$^{-1}$)</td>
<td>0.0529 (2.80)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$\theta_4$ $k_{\text{dex MAP Hypo}}$ (min$^{-1}$)</td>
<td>0.0902 (2.80)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$\theta_5$ $EC_{50,\text{Hype}}$ (ng ml$^{-1}$)</td>
<td>0.364 (10.0)</td>
<td>51.1 (16.0); $\text{BaseMAP} = 0.755$ (11.6)</td>
<td>—</td>
</tr>
<tr>
<td>$\theta_6$ $\Delta E_{\text{DC}}$ (ng ml$^{-1}$)</td>
<td>1.20 (12.0)</td>
<td>41.8 (37.7)</td>
<td>—</td>
</tr>
<tr>
<td>$\theta_7$ $E_{\text{max, Hype}}$ (relative)</td>
<td>0.43 (0.70)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$\theta_8$ $\text{BaseH}$ (beats min$^{-1}$)</td>
<td>59.6 (3.30)</td>
<td>13.4 (38.2)</td>
<td>2.24 (42.7)</td>
</tr>
<tr>
<td>$\theta_9$ $HR_{\text{min}}$ (beats min$^{-1}$)</td>
<td>22.5 (3.90)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$\theta_{10}$ $k_{\text{HR min}}$ (min$^{-1}$)</td>
<td>0.396 (7.50)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$\theta_{11}$ $S_0$ (beats min$^{-1}$ ml ng$^{-1}$)</td>
<td>4.37 (22.4)</td>
<td>110 (37.7)</td>
<td>—</td>
</tr>
<tr>
<td>$\theta_{12}$ $\theta_{\text{RUV Additive}}$ (beats min$^{-1}$)</td>
<td>0.0613 (3.10)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$\sigma_{\text{RUV Additive}}$ (mm Hg)$^2$</td>
<td>5.77 (1.10)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$\sigma_{\text{RUV Additive}}$ (beats min$^{-1}$)$^2$</td>
<td>5.58 (11.4)</td>
<td>48.6 (37.6)</td>
<td>—</td>
</tr>
</tbody>
</table>

---

**Fig 2** Change in mean arterial pressure (continuous blue line) and heart rate (dashed black line) for a typical 20-yr-old individual, as a function of the respective effect-site concentrations $C_e$, effect-site concentration; HR, heart rate; MAP, mean arterial pressure.

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**Final HR model**

The final model adequately describes the time course of HR during/after dexmedetomidine administration (Online Supplementary Fig. S4). This conclusion is further supported by the pcVPC shown in Online Supplementary Fig. S5. The final model parameters and associated standard errors (derived from the log-likelihood profiles in Online Supplementary Fig. S3) are presented in Table 1. Again, post hoc predicted vs observed HR as a function of time for all individuals in the study are shown in Online Supplementary Fig. S2.

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For MAP, dexmedetomidine administration up to 1 μg kg$^{-1}$ throughout 5 min causes no hypertension, but with higher doses (2 and 4 μg kg$^{-1}$) profound hypertension occurs, with an...
increase from baseline MAP of 7 and 19%, respectively (Table 2). For all simulated drug regimens, profound postinfusion hypotension is predicted, although the decrease in MAP levels off at around 25–27% below baseline, even at increasing doses. Furthermore, our model predicts that the recovery period (time necessary to return to baseline MAP once the infusion is stopped) increases from 3.7 to 13 h for the 0.25 and 4.0 µg kg\(^{-1}\) dose, respectively.

For HR, there is a clear dose–response relationship between infused dose and infusion duration and decrease in HR (Table 2). For increasing doses from 0.25 to 4.0 µg kg\(^{-1}\) administered throughout 5 min, the decrease in HR increases from 5.5 to 38%.

**Table 2** Influence of dexmedetomidine dose and infusion duration on various pharmacokinetic and pharmacodynamic end points. *Time necessary to return to within 5% from the initial baseline value

<table>
<thead>
<tr>
<th>Dose (µg kg(^{-1}))</th>
<th>Infusion duration (min)</th>
<th>C(_{\text{max}}) (ng ml(^{-1}))</th>
<th>T(_{\text{max}}) (min)</th>
<th>HR(_{\text{min}}) (%)</th>
<th>T(_{\text{HR,min}}) (min)</th>
<th>T(_{\text{HR,base}^*}) (min)</th>
<th>MAP(_{\text{max}}) (%)</th>
<th>T(_{\text{MAP,max}}) (min)</th>
<th>MAP(_{\text{min}}) (%)</th>
<th>T(_{\text{MAP,min}}) (min)</th>
<th>T(_{\text{MAP,base}^*}) (h)</th>
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<tbody>
<tr>
<td>0.25</td>
<td>5</td>
<td>1.1</td>
<td>5.0</td>
<td>-5.5</td>
<td>5.0</td>
<td>6.0</td>
<td>—</td>
<td>—</td>
<td>-19</td>
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<td>10</td>
<td>—</td>
<td>—</td>
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</tr>
<tr>
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<td>5</td>
<td>4.2</td>
<td>5.0</td>
<td>-17</td>
<td>5.0</td>
<td>24</td>
<td>—</td>
<td>—</td>
<td>-27</td>
<td>66</td>
<td>8.1</td>
</tr>
<tr>
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<td>5</td>
<td>8.5</td>
<td>5.0</td>
<td>-27</td>
<td>5.1</td>
<td>63</td>
<td>7</td>
<td>5.7</td>
<td>-27</td>
<td>102</td>
<td>10.4</td>
</tr>
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<td>4.0</td>
<td>5</td>
<td>17.0</td>
<td>5.0</td>
<td>-38</td>
<td>5.1</td>
<td>132</td>
<td>19</td>
<td>5.7</td>
<td>-25</td>
<td>214</td>
<td>12.6</td>
</tr>
<tr>
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<td>0.5</td>
<td>47</td>
<td>0.5</td>
<td>-33</td>
<td>1.2</td>
<td>61</td>
<td>8</td>
<td>1.9</td>
<td>-27</td>
<td>100</td>
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Fig 3 Influence of dexmedetomidine dose (top panels) and infusion duration (lower panels) on mean arterial pressure (left panels) and heart rate (right panels) for short (30 min at most) infusions. Base\(_{\text{HR}}\), baseline heart rate; Base\(_{\text{MAP}}\), baseline mean arterial pressure.
from baseline. Increasing the infusion duration gives a smaller effect on HR decrease, and increases the time until maximal HR reduction is reached.

**Comparison between the haemodynamic and sedative properties of dexmedetomidine**

We used our combined PKPD model to investigate whether the haemodynamic responses after dexmedetomidine administration could be used as a surrogate marker for the sedative effects.10 The individual responses across different end points were predicted from the post hoc PKPD parameters, and plasma concentrations, effect-site concentrations, and the resulting haemodynamic and sedative effects were predicted for all subjects during the time course of the study. In order to increase the interpretability of these results, differences in baseline MAP and HR across subjects had to be accounted for. This was achieved by expressing the changes in haemodynamic end points relative to individually predicted baseline values.

The decrease in BIS and the increase in the probability of achieving an MOAA/S < 3 (i.e. loss of responsiveness) are shown in Fig. 4 as a function of the simultaneous changes in HR and MAP. For HR, a straightforward correlation is seen with the predicted sedative effects. For the typical individual, we expect that BIS values between 60 and 40 are accompanied by a decrease in HR of ~10 and ~20%, respectively. This HR reduction corresponds to a high probability (i.e. ≥80%) for loss of responsiveness.

The relationship between MAP and the sedative effects of dexmedetomidine is less straightforward. Nevertheless, for the typical individual, the point where MAP normalizes (after the hypotensive phase and before the hypertensive phase) appears to indicate sufficient sedation depth. At this point, BIS is predicted to be between 60 and 40, and the probability of loss of responsiveness is high (i.e. ≥80%).

**Discussion**

We present a PKPD model describing dexmedetomidine-induced changes in mean arterial pressure and heart rate in healthy volunteers. Knowledge of these relationships is crucial for optimizing dexmedetomidine drug administration profiles to avoid undesirable haemodynamic side-effects. Dexmedetomidine-induced changes in MAP were best described by a double-sigmoidal E\text{max} model, which characterizes the
biphasic effect of hypotension at low concentrations and hypertension at higher doses. We also found a hysteresis between plasma concentration and both hypertensive and hypotensive effects, and this hysteresis is different for both effects. This results in two effect compartments with two different equilibration constants, \( k_{EO} \). This can be physiologically explained by the hypertensive and hypotensive effects occurring at different receptor sites. The hypertensive effect is thought to originate from \( a_2 \)-receptor activation in the vascular smooth muscle, whereas the hypotensive effect is mediated by \( a_2 \)-receptor activation in the vascular endothelium and in the central nervous system. The concentration at which the hypertensive effect overcame the hypotensive effect was 2.4 ng ml\(^{-1}\), in good agreement with information from other groups. For example, the assessment report of the European Medicines Agency\(^{17}\) on dexmedetomidine and Ebert and colleagues\(^{8}\) report significant hypertension starting at plasma concentrations of 3.2 and 1.9 ng ml\(^{-1}\), respectively. The only covariate found was the effect of age on baseline MAP, where older volunteers had a higher baseline MAP, but no effect was found between age and dexmedetomidine-induced MAP changes.

The effect of dexmedetomidine on HR was best described by a non-linear model, as described by Schoemaker and colleagues.\(^{12}\) This model provides greater numerical stability compared with the \( E_{\text{max}} \) model, when estimating maximal effect from observations made predominantly around \( C_{\text{EO}} \). The increased precision in the estimated maximal drug effect (i.e. the lower HR range) is also clinically the most important range to evaluate, as bradycardia could be one of the limiting factors in dexmedetomidine administration at higher concentrations. This is especially true in patients with pre-existing bradycardia or in patients who perform better with a higher HR, such as patients with dilated cardiac failure. A narrow hysteresis was found between plasma concentration and HR effects, with a high \( k_{EO} \), describing a fast change in HR in response to changes in plasma concentration. No covariates were found to be associated with baseline HR or dexmedetomidine-induced HR changes.

Our MAP model resembles the model presented by Potts and colleagues,\(^{9}\) with a few important differences. While both models include a double-sigmoidal \( E_{\text{max}} \) model, describing both the sympatholytic and the vasoconstrictor effects of dexmedetomidine, our model uses an effect-site compartment for both the hypertensive and hypotensive effects, whereas the Potts model describes an effect-site compartment only for the hypotensive effects. Possible explanations are the usually shorter delays in drug effects in children, and less frequent non-invasive monitoring of blood pressure (every 5 min), obscuring the hysteresis for the vasoconstrictor effects. Also, Potts and colleagues\(^{9}\) included a parameter describing the maximal sympatholytic effect, whereas we chose to omit this parameter from the model because it resulted in numerical difficulties with model estimation. The differences in parameter values between the Potts model and our model are small despite the fact that the Potts model describes paediatric data. In our model, the \( E_{\text{EC50}} \) values for the hypotensive (0.36 ng ml\(^{-1}\)) and hypertensive (1.6 ng ml\(^{-1}\)) effects are only slightly higher than in the Potts model (0.10 and 1.1 ng ml\(^{-1}\), respectively). Furthermore, the maximal decrease and subsequent increase in MAP are similar between populations, where we found a decrease and increase of 27 and 43%, respectively, and Potts and colleagues\(^{9}\) described a decrease and increase of 15 and 62%. The \( k_{EO} \) values for the hypotensive and hypertensive responses were 0.053 min\(^{-1}\) (\( t_{\text{EO}}=12.1 \) min) and 0.090 min\(^{-1}\) (\( t_{\text{EO}}=7.68 \) min), respectively, whereas Potts and colleagues\(^{9}\) estimated a \( k_{EO} \) for the sympatholytic effect of 0.072 min\(^{-1}\) (\( t_{\text{EO}}=9.65 \) min), corresponding to a slightly longer equilibration half-time for our adult volunteer model compared with the paediatric model.

Yoo and colleagues\(^{5}\) used a mechanism-based PKPD model to describe changes in blood pressure and HR after dexmedetomidine administration. Several important differences can be noted here. Firstly, the dexmedetomidine dose resulted only in low plasma concentrations, below 2.4 ng ml\(^{-1}\); therefore, no hypertensive reaction was seen in their study, and also not modelled. Secondly, the predicted lower boundary for the HR was 50.5 beats min\(^{-1}\), which is clearly inconsistent with our data, as several volunteers reached heart rates of \( \sim 40 \) beats min\(^{-1}\).

Our simulations are in good agreement with the observations described by Bloor and colleagues\(^{1} \) and Dyck and colleagues\(^{5} \) on the effects of dexmedetomidine on HR in healthy volunteers. Bloor and colleagues\(^{1} \) found that at 2 min infusions of 1.0 and 2.0 \( \mu \)g kg\(^{-1}\) dexmedetomidine, HR declined from 59 beats min\(^{-1}\) at baseline to 49 and 44 beats min\(^{-1}\) 2–3 min postinfusion. From our simulations, we found a change from baseline of 21% and 31%, respectively. When taking into account a baseline HR of 59 beats min\(^{-1}\), this results in a predicted minimal HR of 47 and 41 beats min\(^{-1}\), which is similar to the results from Bloor and colleagues.\(^{1}\) Dyck and colleagues\(^{5}\) found that after a 5 min infusion of 2 \( \mu \)g kg\(^{-1}\) dexmedetomidine HR decreased to 27% below baseline 4–5 min postinfusion. This is in good agreement with what is predicted by our model (–27% change from baseline at 5.1 min after the start of the infusion).

For the predicted effects of dexmedetomedine on the MAP, especially for the hypertensive phase, our model somewhat underachieves. For the dexmedetomidine infusions of 2 \( \mu \)g kg\(^{-1}\) studied by Bloor and colleagues\(^{1}\) and Dyck and colleagues,\(^{5}\) our model predicts an increase in MAP of 7 and 8%, respectively, which is lower than the 22 and 24% increase observed. In contracts, when we simulate the experimental work described by Snapir and colleagues\(^{10} \) and Ebert and colleagues,\(^{9} \) who used TCI administration to study the haemodynamic effects of dexmedetomidine at steady-state plasma concentrations of 5.1 and 8 ng ml\(^{-1}\), we predict an increase in MAP of 15 and 23%, which is higher than the 10 and 12% increase reported. The fact that the model predictions are not biased when comparing against these independent data sets (i.e. not always over- or underpredicting) inspires confidence. Nevertheless, this aspect has the potential for improvement as more data become available.

Our model adequately describes dexmedetomidine-induced postinfusion hypotension, which is well known from the work of Bloor and colleagues\(^{1}\) and Dyck and colleagues.\(^{5}\) These studies found that MAP was reduced (–17 and –22% for 2 \( \mu \)g kg\(^{-1}\) infusion, respectively) up to 4 and 5.5 h after the start of the infusion. Our predicted decreases in MAP of –16 and –21% are in good agreement with these findings. Based on our model, we expect that it would take 10.4 h for MAP to return to within 5% of its baseline value. As the previously mentioned studies ended 4 and 5.5 h after the start of the dexmedetomidine infusion, this aspect of the model remains to be validated.

Based on our PKPD models, we were able to study the interplay between the sedative and haemodynamic effects of dexmedetomidine. Dexmedetomidine-induced changes in HR and MAP are reflected in the sedative properties and could therefore, at least in theory, be used as surrogate markers for the degree of sedation. For the typical individual, a HR decrease of 10–20% and a normalization of MAP after the initial hypotensive phase could serve as a surrogate marker to target a shallow state of
sedation (i.e. BIS between 60 and 40 and >80% chance of loss of responsiveness). Individual variability in sensitivity to the sedative and haemodynamic responses means that these haemodynamic targets will be associated with some variability in sedation. A larger study should be conducted to refine and validate these targets in a population context. Depending on the precision of the haemodynamic monitoring system used, these targets might be obscured by measurement noise and, as such, might be of limited clinical use in some instances.

Strengths of our study include the use of stratified age groups, a relatively wide range of individual heights and weights, and both male and female volunteers, increasing our chances of detecting relevant covariates. However, apart from an effect of age on baseline MAP, we found no other covariates for baseline values or dexmedetomidine effects on MAP and HR. This is in line with other PKPD analyses \(^6\) \(^7\) which also did not find a significant influence of patient characteristics on estimated PKPD parameters.

Use of healthy volunteers allowed development of a PKPD model that avoids confounding influences of concomitant medications or patient co-morbidity. For example, a study by Talke and colleagues \(^2\) showed that the sympatholytic effect of dexmedetomidine is attenuated under general anaesthesia, while the vasoconstrictive effect remains. It is uncertain whether co-morbidity and concomitant medications might limit or, conversely, increase the haemodynamic effects of dexmedetomidine.

The volunteers in our study mostly did not return to baseline values of HR and MAP. One reason may be the long-lasting effect that dexmedetomidine has on haemodynamics, and our recovery period of 5 h was too short for a full return to baseline, as is also shown in our simulations. Another explanation may be that ‘baseline’ is not the true baseline at rest, and nervousness and stress may cause volunteers to have higher HR and MAP before the start of the study than in the recovery period. Given that our infusion rate was limited to 6 or 10 \(\mu\)g kg \(^{-1}\) h \(^{-1}\), our simulations with higher infusion rates are not validated. One of the characteristics of our model is that even at high infusion rates, there is initial hypotension, followed rapidly by a hypertensive reaction. This phenomenon is not described in the literature. Although this could be explained by the fact that blood pressure monitoring is often too slow to capture this effect, it could also simply be an artifact of the model, and that physiological feedback mechanisms prevent this phenomenon in vivo. Attempts to incorporate such feedback mechanisms in our PKPD model failed because of numerical issues with the estimation algorithm. Further research, focusing on high-resolution haemodynamic monitoring during different infusion rates, is required to validate this effect.

In conclusion, we developed a PKPD model for dexmedetomidine effects on HR and MAP in healthy volunteers. The model accurately describes the reduced HR and the clear biphasic effect on MAP, with two effect-site compartments corresponding to different physiological \(\alpha_2\)-receptor effects. No additional patient covariates beyond those that were already included in the previously developed PK model \(^7\) had an impact on dexmedetomidine-induced changes in the haemodynamics. The sedative and haemodynamic effects of dexmedetomidine are highly correlated, so our model provides surrogate haemodynamic markers to guide dexmedetomidine sedation. Further prospective clinical validation should be conducted to assess the performance of our model and the proposed surrogate haemodynamic markers.

**Authors’ contributions**


Patient recruitment: L.N.H., H.E.M.V., K.M.E.M.R.

Data collection: L.N.H., H.E.M.V., K.M.E.M.R.


First draft of the paper: P.C.


**Supplementary material**

Supplementary material is available at British Journal of Anaesthesia online.

**Declaration of interest**


K.M.E.M.R.: he is a member of the KOL group on patient warming and received funding for travel and lectures of the 37° company (Amersfoort, The Netherlands).

A.R.A: his research group or department received grants and funding from The Medicines Company (Parsippany, NJ, USA), Drager (Lubeck, Germany), Carefusion (San Diego, CA, USA), Orion, and BBraun (Melsungen, Germany). He is a paid consultant to Janssen Pharma (Belgium), Carefusion (San Diego, CA, USA), and The Medicines Company (Parsippany, NJ, USA). He is an editor of the British Journal of Anaesthesia.

M.M.R.F.S.: his research group or department received grants and funding from The Medicines Company (Parsippany, NJ, USA), Masimo (Irvine, CA, USA), Fresenius (Bad Homburg, Germany), Acacia Design (Maastricht, The Netherlands), and Medtronic (Dublin, Ireland), and honoraria from The Medicines Company (Parsippany, NJ, USA), Masimo (Irvine, CA, USA), Fresenius (Bad Homburg, Germany), Baxter (Deerfield, IL, USA), Medtronic (Dublin, Ireland), and Demed Medical (Tense, Belgium). He is an editorial board member of the British Journal of Anaesthesia and a senior editor of Anesthesia & Analgesia.

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**References**


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