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Clinical Practice

Dexmedetomidine pharmacodynamics in healthy volunteers: 2. Haemodynamic profile

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Abstract

Background. Dexmedetomidine, a selective α_2-adrenoreceptor agonist, has unique characteristics, with little respiratory depression and rousability 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 E_{max} 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 α_2-adrenoceptor agonist, is widely used in clinical practice as a sedative drug. Owing to its high affinity and selectivity for the α_2-adrenoceptors, 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 α_2-adrenoceptors in the central nervous system and through activation of α_2-adrenoceptors in vascular endothelial cells, which causes vasodilation.[2 3] At higher concentrations, peripheral vasoconstrictive effects attributable to activation of α_2-adrenoceptors 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) infusions[1 6–8] at doses between 0.25 and 4 μg kg^{-1} or target-controlled infusion (TCI) systems[4 5] at target concentrations ranging between 0.5 and 8 ng ml^{-1}. Although a significant dose–response relationship was

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Editor's key points

- Dexmedetomidine has marked effects on haemodynamics, but there are only limited pharmacokinetic–pharmacodynamic models for these effects.
- A novel integrated pharmacokinetic–pharmacodynamic model described the hypotensive, hypertensive, and bradycardic effects in healthy subjects.
- The sedative and haemodynamic effects of dexmedetomidine are highly correlated, providing potential surrogate haemodynamic markers to guide sedation.

observed, only very limited pharmacokinetic–pharmacodynamic (PKPD) models exist relating the time course of dexmedetomidine plasma concentrations to its effects on MAP and HR.[6 8] In order to gain a better understanding and predict these haemodynamic alterations, an integrated PKPD model would be useful to characterize these relationships.

We previously developed a pharmacokinetic model for dexmedetomidine[9] 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®; Medtronic, Dublin, Ireland) and Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S).[10] 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,[9] 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,[11] as described in the accompanying paper.[10]

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 $\sim 1\,\text{min}^{-1}$.

Population PKPD modelling

For pharmacodynamic (PD) modelling, we used the parameter estimates from the dexmedetomidine PK model published earlier by our group.[9] The individual predicted PK parameters (V_1, V_2, V_3, CL, Q_2, and Q_3) were fixed for each individual and each session (Hannivoort and colleagues[9] reported that V_1 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 ($\text{IPRED}_{\text{plasma}}$) and the PD measures. Direct models relating $\text{IPRED}_{\text{plasma}}$ 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 C_{50}, an alternative E_{max} model (shown in equation 1), as described by Schoemaker and colleagues,[12] was evaluated. This equation relies on a parameter (S_0) equal to E_{max}/C_{50} and could be advantageous for PD model estimation when few data are available near the maximal effect.

$$E = \frac{s_0 \times E_{\text{max}} \times \text{IPRED}_{\text{Plasma}}}{E_{\text{max}} \times s_0 \times \text{IPRED}_{\text{Plasma}}} \quad (1)$$

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. Hereto, 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 χ^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 (IIV)