Dexmedetomidine pharmacokineticpharmacodynamic modelling in healthy volunteers


Published in:
British Journal of Anaesthesia

DOI:
10.1093/bja/aex085

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Dexmedetomidine pharmacokinetic–pharmacodynamic modelling in healthy volunteers: 1. Influence of arousal on bispectral index and sedation

P. J. Colin1,2,* L. N. Hannivoort1, D. J. Eleveld1, K. M. E. M. Reyntjens1, A. R. Absalom1, H. E. M. Vereecke1 and M. M. R. F. Struys1,3

1Department of Anesthesiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands, 2Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium and 3Department of Anaesthesia and Peri-operative Medicine, Ghent University, Ghent, Belgium

*Corresponding author. E-mail: p.j.colin@umcg.nl

Abstract

Background. Dexmedetomidine, a selective α2-adrenoceptor agonist, has unique characteristics, such as maintained respiratory drive and production of arousable sedation. We describe development of a pharmacokinetic–pharmacodynamic model of the sedative properties of dexmedetomidine, taking into account the effect of stimulation on its sedative properties.

Methods. In a two-period, randomized study in 18 healthy volunteers, dexmedetomidine was delivered in a step-up fashion by means of target-controlled infusion using the Dyck model. Volunteers were randomized to a session without background noise and a session with pre-recorded looped operating room background noise. Exploratory pharmacokinetic–pharmacodynamic modelling and covariate analysis were conducted in NONMEM using bispectral index (BIS) monitoring of processed EEG.

Results. We found that both stimulation at the time of Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) scale scoring and the presence or absence of ambient noise had an effect on the sedative properties of dexmedetomidine. The stimuli associated with MOAA/S scoring increased the BIS of sedated volunteers because of a transient 170% increase in the effect-site concentration necessary to reach half of the maximal effect. In contrast, volunteers deprived of ambient noise were more resistant to dexmedetomidine and required, on average, 32% higher effect-site concentrations for the same effect as subjects who were exposed to background operating room noise.

Conclusions. The new pharmacokinetic–pharmacodynamic models might be used for effect-site rather than plasma concentration target-controlled infusion for dexmedetomidine in clinical practice, thereby allowing tighter control over the desired level of sedation.

Clinical trial registration. NCT01879865.

Key words: dexmedetomidine; healthy volunteers; hypnotics and sedatives; noise; pharmacology
Dexmedetomidine sedation and arousal in volunteers

Editor’s key points

- Most target-controlled infusion (TCI) programmes are based on plasma concentrations rather than effect-site concentrations.
- Using a previously developed pharmacokinetic model, effect-site concentrations were modelled from bispectral index and sedation scale pharmacodynamic data in 18 healthy volunteers.
- The resulting pharmacokinetic–pharmacodynamic model will be useful in developing improved TCI programmes that more tightly control sedation using effect-site concentrations.

Dexmedetomidine use in clinical practice is popular because of its unique characteristics as a selective α2-adrenoceptor agonist. It is currently licensed for sedation in intensive care units in Europe and the USA and for procedural sedation in the USA. Moreover, there is frequent off-label use, for instance for procedural sedation (in Europe), sedation during awake fibreoptic intubation, and awake craniotomies. Patients under dexmedetomidine sedation experience little respiratory depression, are more easily roused, and are better able to communicate compared with propofol or midazolam sedation. Also, dexmedetomidine has been investigated as a possible opioid-reducing technique and might attenuate perioperative inflammatory responses.

For sedation in intensive care units, a slow titration to effect, with or without a loading dose, is acceptable, because a fast onset of effect is often not necessary. However, during procedural sedation or in the operating room, a faster onset of effect is often desired. Fast titration to the desired effect with limited or no overshoot, thereby limiting potential side-effects, can be attained using target-controlled infusion (TCI). For effect-site TCI, an accurate pharmacokinetic–pharmacodynamic (PKPD) model is necessary. Currently, only pharmacokinetic (PK) models are available for dexmedetomidine; no PKPD models.

We recently published an optimized dexmedetomidine PK model. In this twin paper, we describe the pharmacodynamic effects of dexmedetomidine in healthy volunteers, and model these effects into PKPD models. In this article, we describe and model the sedative effects of dexmedetomidine using our previously published PK model, and using bispectral index (BIS) and the Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) as measures of sedative effects. In an accompanying paper, we describe and model the haemodynamic effects of dexmedetomidine.

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). Written informed consent was obtained from all volunteers. The study conduct was described in detail by Hannivoort and colleagues, who reported on the development of a pharmacokinetic model based on measured dexmedetomidine plasma concentrations collected throughout the study.

In brief, 18 healthy volunteers, nine male and nine female, stratified according to age and sex (18–34, 35–54, and 55–72 yr) received dexmedetomidine i.v. on two separate occasions, at least 1 week and at most 3 weeks apart. Both sessions were identical in protocol, except for the use of acoustic noise-cancelling headphones (Bose QuietComfort 15, Framingham, MA, USA), either without background noise or with pre-recorded looped operating room background noise (monitor beeps and alarms, air conditioning noise, talking, equipment noise etc.). In both sessions, the volunteers were instructed to keep their eyes closed throughout the session, and they were stimulated as little as possible apart from at set times for the assessment of depth of sedation. Randomization using sealed envelopes was used to determine the order of the ‘background silence’ and ‘background noise’ sessions.

Standard anaesthesia monitoring was applied, with the inclusion of an arterial line for blood pressure monitoring and blood sampling, as described by Hannivoort and colleagues. An initial short infusion, given at 6 μg kg⁻¹ h⁻¹ for 20 s, was followed by a 10 min recovery period. Thereafter, dexmedetomidine was delivered as a TCI using the Dyck model with step-wise increasing targets of 1, 2, 3, 4, 6, and 8 ng ml⁻¹. Each target was maintained for 30 min. The maximal infusion rate was limited to 6 μg kg⁻¹ h⁻¹ for the first four steps; for the target of 6 and 8 ng ml⁻¹, the maximal infusion rate was increased to 10 μg kg⁻¹ h⁻¹ to facilitate attainment of the target within a reasonable time. Volunteers were monitored until 300 min after cessation of the TCI dexmedetomidine infusion. The syringe pump (Orchestra® Module DPS, Orchestra® Base A; Fresenius Kabi, Bad Homburg, Germany) that was used to deliver the dexmedetomidine infusion was controlled by RUGLOOP II software (Demed, Temse, Belgium) programmed with the Dyck model.

Pharmacodynamic measurements

A BIS Vista monitor (Covidien, Boulder, CO, USA) was used to record BIS continuously to study depth of hypnosis. The MOAA/S scale was used to quantify the level of sedation and rousability of the volunteer at the following time points: immediately before the start of dexmedetomidine infusion, 2 min after the start of the initial short infusion, immediately before the start of the TCI infusion, and at the end of each TCI target step. During the recovery period, MOAA/S scores were recorded every 2 min for the first 30 min, and every 10 min thereafter, until the volunteer reached the maximal score on the MOAA/S scale. All monitored parameters were recorded electronically using RUGLOOP II software.

Data handling

The final data set contained BIS measurements at a sampling rate of 1 Hz, which, for some subjects, resulted in >30 000 observations per session. To reduce the computational burden, we reduced the number of BIS 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 the first out of every 50 consecutive median filtered observations.

The data set used for modelling contained a median of 372 (range 115–556) BIS measurements per subject per session, corresponding to a sampling rate of ~1 min⁻¹. All unfiltered MOAA/S observations were retained in the data set, with a median of 25 (range 8–40) observations per subject per session.

Population pharmacokinetic–pharmacodynamic modelling

The PKPD modelling was based on individual PK parameter estimates from the dexmedetomidine PK model published
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 BIS data. For the categorical MOAA/S data, the Laplacian approximation to the likelihood was used. Inter-individual variability and inter-occasion variability (IOV) were modelled using an exponential model. Residual unexplained variability was described using additive or proportional error models, or both.

During model building, the 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. As a safeguard to over-parameterization, only models with a condition
number of the Fisher information matrix (FIM) < 500 were re-
tained in the model building hierarchy. Finally, models were
validated internally using prediction-corrected visual predictive
checks (pcVPC) according to Bergstrand and colleagues.7
All models were fitted to the data using PeN4 and Pirana5 as
back or front end, or both, to NONMEM.6 The numerical and graph-
ical assessment of the GOF and the construction of the pcVPCs
were conducted in R7 (R Foundation for Statistical Computing,
Vienna, Austria). All simulations were performed in a Microsoft
Excel Macro-Enabled Worksheet (Microsoft Office Professional Plus
2013), which is supplied in the Online Supplementary material.
The worksheet depends on the ‘PKPD tools for Excel’ package de-
developed by T. Schnider and C. Minto, which is available from http://

Statistics analysis
All model parameters are reported as typical values with associ-
ated relative standard errors (RSE) and 95% confidence intervals
(CIs) derived from log-likelihood profiling.10

Results
Data
Figure 1 shows the median filtered BIS signal and the observed
MOAA/S for four representative subjects from our study during
the step-up TCI administration. The dashed lines indicate when
a new TCI target was set. Immediately before changing the TCI

![Median filtered BIS values and MOAA/S observations for the step-up TCI administration for four representative subjects. Dashed vertical lines indicate when a new TCI target was set. Immediately before this, MOAA/S was assessed. BIS, bispectral index; MOAA/S, Modified Observer’s Assessment of Alertness/Sedation; TCI, target-controlled infusion.](image-url)
target, MOAA/S was scored. This figure clearly shows the perturbation in the BIS signal induced by stimulating the subjects at the time of MOAA/S scoring and the subsequent attenuation of the effect of stimulation. The complete time courses of BIS and MOAA/S observations for all subjects used for modelling are shown in Online Supplementary Figs S1 and S2.

**Model development for BIS**

In a first attempt to describe the effect of dexmedetomidine on BIS measurements, a sigmoid model was used. Rousability was accounted for according to equations (1)–(4), and the delay between plasma PK and BIS effects was described using an effect compartment model. Modifications to this base structure were evaluated. Firstly, the Hill coefficient (ε) was fixed to 1, resulting in a decrease in the condition number from 1327 to 13.0%. Secondly, a logit transform, as shown in equations (6) and (7), was used to describe the intersubject variability in BIS at baseline. The inclusion of the logit transformation decreased the MdAPE to 13.5% underpinning the importance of accounting for the rousability component of the model.

The significance of the rousability component of the model was evaluated by exclusion of this component, as described by equations (1), (2) and (4), from the final model. The resulting decrease in GOF (ΔAIC = 50) compared with our final model. Inter-individual variability was estimated to be 69.5 and 81.8% for C50 and ΔC50, respectively. The model illustrates that the effect of stimulation attenuates slowly, with an estimated half-life of 5.3 min. Moreover, the time for the BIS signal to normalize is highly variable within our study population, with 95% of the estimates for the half-life of attenuation between 0.82 and 34.6 min.

**Final model for BIS**

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 Fig. 2. Online Supplementary Fig. S4 shows the pcVPC. Overall, these figures demonstrate that the presented model adequately describes observed changes in BIS during and after dexmedetomidine administration and that all parameters of the model are estimated with acceptable precision.

We found that changes in plasma dexmedetomidine concentrations are reflected in BIS, with a half-life of effect-site equilibration of 5.8 min. In unstimulated subjects, half of the maximal effect (~BIS40) is attained at 2.63 ng ml⁻¹. In the stimulated state, patients achieve a BIS value of 48, on average, where the dexmedetomidine effect-site concentration approaches 7.13 ng ml⁻¹. The post hoc predicted values of C50 and ΔC50 were found to be uncorrelated but highly variable within our study population. Inter-individual variability was estimated to be 69.5 and 81.8% for C50 and ΔC50, respectively. The model illustrates that the effect of stimulation attenuates slowly, with an estimated half-life of 5.3 min. Moreover, the time for the BIS signal to normalize is highly variable within our study population, with 95% of the estimates for the half-life of attenuation between 0.82 and 34.6 min.

**Model development for MOAA/S**

As a starting point, a linear drug effect model was used to describe dexmedetomidine-induced changes in the logit of the cumulative probabilities. Subsequently, the model was refined by introducing the following: (i) an Emax drug effect model (ΔAIC=−173.3); and (ii) inter-individual variability on the baseline logit of observing an MOAA/S score equal to 0 (ΔAIC=−187.6). The assumption of proportional odds was challenged by fitting a differential odds model, as described by Kjellsson and colleagues. The differential odds model had a slightly lower AIC (ΔAIC=−6.7) compared with our final model. However, the condition number of the Fisher information matrix (FIM) was high (1110), and no differences were seen between the pcVPCs of both models. Based on these findings, we decided not to implement the differential odds assumption into our final model.

In line with our approach to model the influence of the rousability on the BIS signal, we evaluated a model with an additional Emax curve to model potential transient changes in MOAA/S scores attributable to subject stimulation inherent in
MOAA/S scoring. This modification led to a marginal improvement in GOF (ΔAIC = −13.9 for two additional parameters). The estimate for the half-life of attenuation was significantly lower than what was found for the BIS model (0.65 vs 5.3 min, respectively), whereas the estimate for the $\Delta C_{50}$ was significantly larger (4.21 vs 1.71). The predictive performance, as evaluated by pCvPC, did not improve, and the model suffered from some numerical difficulties, resulting in a high condition number (1203). Overall, these findings led us to the decision not to include a rousability component, describing the time-varying effect of rousability on the MOAA/S, in our final model.

Covariate screening identified session (background silence vs background noise session) as a significant covariate. Inclusion of session as a covariate on the $C_{50}$ led to a significant increase in GOF (ΔAIC = −10.5). The effect of the covariate was confirmed by graphical analysis of the raw data stratified by session. This graphical analysis confirmed that the distribution of MOAA/S scores as a function of TCI targets was different.
between both sessions (data not shown). Inclusion of the covari-
ate did not increase the condition number of the FIM and was
therefore retained in the final model. Age, weight, height, and
sex were found not to have a significant impact on the OFV.
Furthermore, introduction of inter-occasion variability also
did not improve the GOF of the model.

Final model for MOAA/S
The final model parameters and associated standard errors are
shown in Table 1. Online Supplementary Fig. S3 shows the like-
lihood profiles for the final model. The GOF of the final model,
for three subjects representing the best, median, and worst fit,
respectively, is shown in Fig. 2 (post hoc predicted vs observed
MOAA/S scores as a function of time for all subjects are shown
in Online Supplementary Fig. S2). Simulation-based GOF diag-
nostic plots are favoured here owing to the inability to calculate
individually predicted dexmedetomidine plasma concentra-
tions and conditionally weighted residuals-based diagnostic
plots for ordered categorical models. A visual predictive check
for the final model is shown in Online Supplementary Fig. S8.
Overall, these diagnostics show that our final model is ade-
quately developed and that the predictive performance is suffi-
cient to characterize our observations.

The equilibration between effect-site concentrations and
plasma concentrations for dexmedetomidine is fairly slow, with
an estimated half-life for effect-site equilibration of 14 min.
Subjects who were deprived of normal ambient background
noise from the operating room achieved half of the maximal
MOAA/S effect at an effect-site concentration of 0.43 ng ml⁻¹.
Volunteers who were exposed to background noises were some-
what more sensitive to the sedative effects of dexmedetomidine
and achieved half of the maximal effect at an effect-site concen-
tration that was, on average, 32% lower (i.e. 0.29 ng ml⁻¹).

According to the model, the difference between the logit of
observing an MOAA/S of 0 and an MOAA/S score ≤ 1 is small
(Δ logit = 0.394). Compared with the other estimates for the differ-
ces in logits, this small estimate results in a fairly low pre-
dicted probability of observing an MOAA/S ≤ 1. This is in line with
our observations. Indeed, when we look at the observed propor-
tion of MOAA/S ≤ 1 across time (black line in Online
Supplementary Fig. S5) we see that, as opposed to the other
MOAA/S categories, the profile for observing an MOAA/S ≤ 1 is rel-
atively flat, not exceeding 10%. An overview of the probability of
observing the different MOAA/S scores as a function of effect-
site concentration is given in Fig. 3 and commented on further
in the Discussion.

Discussion
We developed a PKPD model that characterizes the relationship
between dexmedetomidine plasma concentrations and the re-
sulting changes in BIS and MOAA/S. Owing to the specific char-
acteristics of dexmedetomidine, our models were built taking
into account the time-varying rousability that was introduced
by stimulation of the subject during MOAA/S scoring. Fur-
thermore, our study protocol was such that we were able to
determine the confounding effect of another type of stimula-
tion, continuous background auditory stimulation, on the seda-
tive properties of dexmedetomidine. A unique characteristic of
our model is that it incorporates the rousability effect on BIS.
Stimulation of subjects at the time of MOAA/S scoring induced a
transient increase in the BIS signal. The effect of the stimulus
diminishes over time and typically disappears within ~21 min
(4×t½) in the absence of stimulation. However, if the subject is
stimulated more frequently, accumulation occurs and the ‘stimu-
lated’ state persists for prolonged periods of time.

Our model also explains the potential for an apparent para-
doxical response of transiently increasing hypnosis (decreasing
BIS) in the presence of decreasing drug concentrations as the in-
dividual transitions from a stimulated to an unstimulated pharmacodynamic state. This is visible in Fig. 4, where the observed
BIS signals during step-up TCI administration and the subse-
quently observed recovery for three subjects representing examples of the
best, median, and worst fit of our model against the observed data are shown. The good agreement between the observed BIS
signal and the post hoc predicted BIS curves (shown in blue) after
single and repeated stimulation inspires confidence in the va-
C0
lidity of our proposed PKPD model.

The basis for our MOAA/S model is an Emax model, using the
logit of cumulative probabilities of MOAA/S scores rather than
the MOAA/S scores themselves. A time-varying rousability ef-
sert similar to the effect found for BIS was not retained in our fi-
nal PKPD model describing MOAA/S observations. When we
tried to estimate the half-life of attenuation, we found an esti-
mate for k_e of 1.3 min⁻¹, corresponding to a T_1/2 of 0.65 min, indi-
cating that, for the typical patient, the effect of stimulation
diminishes over time and typically disappears within 3.6 min. In the context of our protocol, in
which MOAA/S were scored at least 2 min apart, inclusion of the
time-varying rousability had no significant impact on the pre-
dicted probabilities. However, in other situations, where stimula-
tion occurs more frequently, this might be important, and our
suggested approach could be used to take the confounding ef-
f ect of stimulation into account.

Our analysis showed that the C50 for MOAA/S was signifi-
cantly higher, and thus subjects were more responsive, when
deprived of ambient noise in comparison to exposure to ambient
operating room noise. This could be because auditory impul-
ses, such as the name of the volunteer being spoken, are
more clearly perceived against a silent background. However,
our model indicates that even responsiveness towards a painful
stimulus was significantly different between sessions. This
finding was confirmed by graphical analysis (data not shown)
that showed that, after controlling for the TCI target, the fre-
quency of MOAA/S 0 was significantly different between ses-
sions. These results suggest that other more complex
physiological phenomena might govern the interaction between
the presence of background noise and the sedative properties of
dexmedetomidine.

Surprisingly, we found no influence of age on sensitivity to
the sedative effects of dexmedetomidine. Inclusion of age as a
covariate on θLED and C50 in the MOAA/S and BIS model did not
result in a significant decrease in the OFV. In contrast to this
finding, Schneider and colleagues12 and Minto and colleagues13
found that for propofol and remifentanil the sensitivity to EEG
effects increases with age. By including volunteers into our
study in age- and sex-stratified cohorts, we maximized the a pri-
or possibility of detecting a potential influence of age and sex
on the sedative properties of dexmedetomidine. Nevertheless,
the limited number of subjects in our study could have obscured
an age effect. In contrast, the different receptor pathways in-
volved in dexmedetomidine sedation (α2-receptor agonist) vs
propofol (GABA_A receptor agonist) and remifentanil (opioid) se-
dation might explain the lack of an age effect.

Our PKPD models allow us to define target effect-site con-
centrations that maximize the possibility of attaining a particu-
lar level of sedation and inform us on the BIS values that
Corr et al.

ambient operating room noise, loss of responsiveness to verbal stimulation (i.e. MOAA/S score ≤2) is predicted to occur at an effect-site concentration of 0.91 ng ml\(^{-1}\). At this effect-site concentration, BIS immediately before the MOAA/S stimulation is 72. Volunteers deprived of ambient noise lose responsiveness to verbal stimulation at a \(C_e\) of 1.3 ng ml\(^{-1}\) and BIS value of 64.

Based on a study in healthy volunteers, Kasuya and colleagues\(^{14}\) found that the correlation between BIS and MOAA/S scales is significantly different between dexmedetomidine and propofol. When considering the same level of sedation, BIS values for dexmedetomidine were generally lower than those in the propofol group. Our analysis contradicts these findings. The results in Table 2 are in (very) good agreement with earlier work on propofol. Struys and colleagues\(^{15}\) found that for propofol the BIS values where 50% of the population loses responsiveness (BIS\(_{50}\)) to MOAA/S scales 5, 4, and 3 were 85, 74, and 66, respectively. However, earlier findings by Kearse and colleagues\(^{16}\) and Iselin-Chaves and colleagues\(^{17}\) showed that the BIS\(_{50}\) for loss of responsiveness to verbal stimulation was 65 and 64, respectively. These results are in good agreement with our estimates for dexmedetomidine, indicating that the calibration for BIS is very similar between dexmedetomidine and propofol. Overall, these findings suggest that target BIS values between 60 and 40, which generally indicate adequate general anaesthesia, are appropriate when dexmedetomidine-based deep sedation is required. Between these target BIS values, corresponding to a \(C_e\) of 1.6 and 3.6 ng ml\(^{-1}\), loss of responsiveness to verbal stimulation is predicted to occur in 58 and 81% of patients, respectively, and MOAA/S scores will be ≤2.

Besides the discrepancy with the work of Kasuya and colleagues\(^{14}\), our results are generally in line with earlier reports from experimental studies with dexmedetomidine in healthy volunteers. In a study where healthy volunteers received dexmedetomidine in a step-up TCI titration, Kaskanoro and colleagues\(^{18}\) found that, on average, loss of responsiveness to
verbal stimulation occurred at 1.9 ng ml$^{-1}$. Although it is not entirely clear whether volunteers were exposed to or deprived of ambient noise, this concentration is in agreement with our predictions, considering the variability associated with assessment of loss of responsiveness to verbal stimulation. In a study where healthy volunteers received a 10 min 6 μg kg$^{-1}$ h$^{-1}$ loading dose followed by a 0.2 or 0.6 μg kg$^{-1}$ h$^{-1}$ i.v. infusion, Hall and colleagues$^{19}$ found that BIS decreased by 31 and 36% after 60 min. When we simulated a similar experimental study, we found a 21 and 28% decrease in BIS, which is slightly lower, but still inspires confidence given that we are dealing with an independent data set and that it is not clear whether volunteers in the study by Hall and colleagues$^{19}$ were stimulated, which could explain the higher BIS values.

**Fig 4** Observed (pink lines) and post hoc predicted BIS (blue lines) for the subjects with the best, median, and worst fit. The dashed vertical lines indicate when a new TCI target was set. Immediately before this, MOAA/S was assessed. BIS, bispectral index; MOAA/S, Modified Observer’s Assessment of Alertness/Sedation; TCI, target-controlled infusion.
The approach we present, which models the drug effect in both the unstimulated and the stimulated state, was used previously by Heyse and colleagues\textsuperscript{20} to account for the differences in hypnotic and analgesic effects between stimulated and unstimulated volunteers receiving sevoflurane–remifentanil anaesthesia. However, in contrast to the analysis of Heyse and colleagues\textsuperscript{20} we used this approach to account for the time-varying effect of stimulation. Correcting for the confounding effect of stimulation is pivotal for modelling dexmedetomidine. Not only does it significantly increase the GOF, without the rousability component in the model a significant bias is seen in estimated PKPD parameters. For example, the $C_{50}$ for BIS, which is the parameter of primary interest, increases by 82% after stimulation. Dosing regimens taking into account both the pre- and post-stimulation effects with dexmedetomidine could result in better titration, targeting values with the highest probability for the desired MOAA/S. If deep sedation is required, the target that results in the least increase in BIS without oversedating the patient could be chosen. Whenever BIS is used to target a specific degree of sedation with dexmedetomidine, one should be aware of the confounding effect of stimulation. An applied stimulus is expected to disturb the BIS signal for up to 20 min. Implementing our model into a drug display could correct for this time-varying effect of stimulation and could provide a more robust system to titrate dexmedetomidine-based sedation.

In conclusion, we present a PKPD model that adequately describes the sedative and hypnotic effects of dexmedetomidine in healthy volunteers. This model integrates the well-known rousability associated with dexmedetomidine sedation and accounts for changes in responsiveness between volunteers attributable to repeated auditory stimulation. After validation of our PKPD model in a patient population, our model might be used to transition towards effect-site TCI rather than plasma concentration TCI for dexmedetomidine in clinical practice, thereby allowing tighter control over the desired level of sedation.

### 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.

### Table 2

<table>
<thead>
<tr>
<th>Ambient operating room noise cohort</th>
<th>Silent cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{50}$ (mg ml$^{-1}$) BIS$50$</td>
<td>$C_{50}$ (mg ml$^{-1}$) BIS$50$</td>
</tr>
<tr>
<td>Loss of MOAA/S 5 0.29 87</td>
<td>0.43 83</td>
</tr>
<tr>
<td>Loss of MOAA/S 4 0.54 80</td>
<td>0.79 74</td>
</tr>
<tr>
<td>Loss of MOAA/S 3 0.91 72</td>
<td>1.34 64</td>
</tr>
<tr>
<td>Loss of MOAA/S 2 4.10 38</td>
<td>5.99 29</td>
</tr>
<tr>
<td>Loss of MOAA/S 1 9.88 20</td>
<td>14.4 15</td>
</tr>
</tbody>
</table>

### Supplementary material

Supplementary material is available at British Journal of Anaesthesia online.

### Declaration of interest


K.M.E.M.R.: 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/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/department received grants and funding from The Medicines Company (Parsippany, NJ, USA), Masimo (Irvine, CA, USA), Fresenius (Bad Homburg, Germany), Acada 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 (Temse, Belgium). He is an editorial board member of the British Journal of Anaesthesia and a senior editor of Anesthesia & Analgesia.

### Funding

This study was supported by departmental funding.

### References


Handling editor: Hugh C Hemmings Jr