Dexmedetomidine pharmacodynamics in healthy volunteers: Striking a balance between the hypnotic and sedative properties and the haemodynamic side effects

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Background and Objectives

Dexmedetomidine (DMED) use in clinical practice is popular because of its **unique characteristics** as a selective α2-adrenoreceptor agonist. Patients under DMED sedation experience **little respiratory depression**, are more **easily roused**, and are better **able to communicate** compared with propofol or midazolam sedation. **Effect-site TCI**, which allows a fast titration to the desired effect with limited or no overshoot in the plasma concentrations would be beneficial for **procedural sedation in the operating room**. However, PKPD models necessary to develop these effect-site TCI algorithms are lacking at present.

Using a modelling approach and data from a healthy volunteer study we aimed to:

- ✓ Describe DMED induced changes in BIS, MOAA/S, MAP and HR
- ✓ Study the effects of continuous background auditory and short, sudden verbal/tactile/painful stimulation on the sedative properties of DMED
- ✓ Explore the BIS vs. MOAA/S relationship and compare this against other frequently used hypnotics
- ✓ Establish whether the haemodynamic effects could serve as a surrogate for the sedative properties in case BIS monitoring is not available to guide dosing

Methods

18 age- and gender-stratified healthy volunteers received i.v. DMED using TCI on 2 separate occasions. HVs were randomized to receive DMED while being isolated from background noise or while exposed to looped operating room background noise.

Mean arterial blood pressure (MAP), heart rate (HR) and bispectral index (BIS) were recorded continuously throughout the study. The modified observer's assessment of alertness/sedation (MOAA/S) scale was assessed at regular intervals along with arterial blood sampling.

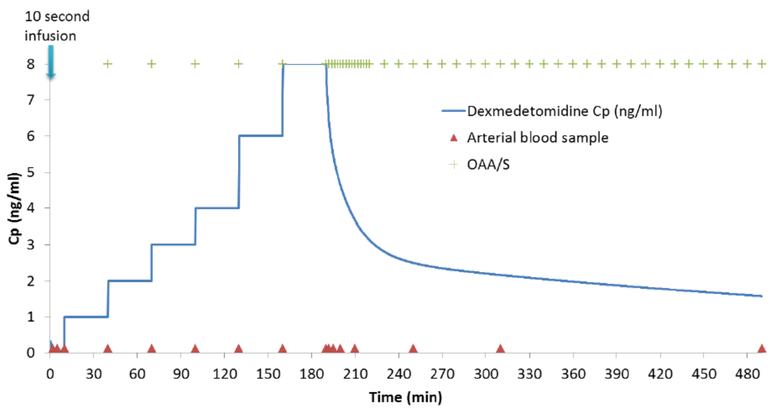


Figure 1 – Study protocol: Dexmedetomidine plasma concentration targets (and predicted dexmedetomidine washout) – blue line; arterial blood sampling times – red triangle; OAA/S score observations – green +.

After median filtering and data reduction, data were fitted with NONMEM® (v7.3).

Final PKPD models

HR and MAP were best described by an Emax model and a double Emax model. No covariate effects were found apart from an age effect on baseline MAP.

$$MAP_{ij} = Base_{MAP,i} \times \left(1 - \frac{C_{e,Hypo}}{EC50_{Hypo}+C_{e,Hypo}} + \frac{(1+E_{max,Hyper})\times C_{e,Hyper}}{(EC50_{Hypo}+\Delta EC50)+C_{e,Hyper}}\right)$$

Effects on BIS and the influence of sudden stimulation on BIS were described using a latent variable based linear interpolation between two Emax curves.

$$\frac{dRELAX}{dt} = k_{in} \times [(1 - A(RELAX))] \quad (1)$$

$$BIS_{i,NSTIM} = \text{Baseline } BIS_i \times \left(1 - \frac{C_e}{C_e + C_{50,i}}\right) \quad (2)$$

$$BIS_{i,STIM} = \text{Baseline } BIS_i \times \left(1 - \frac{C_e}{C_e + [C_{50,i} \times (1 + \Delta C_{50,i})]}\right) \quad (3)$$

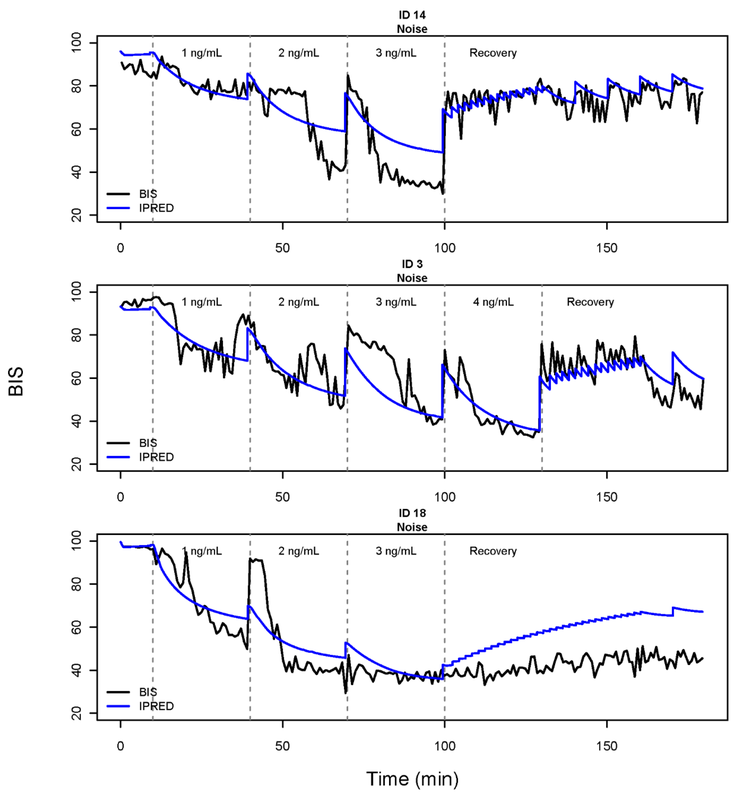
$$BIS_i(t) = BIS_{i,NSTIM} \times A(RELAX) + BIS_{i,STIM} \times (1 - A(RELAX))] \quad (4)$$

Changes in MOAA/S were described using a proportional odds logistic regression model with different C_{50}s for the silent and noisy session (32% decrease in C_{50} for HV exposed to ambient OR noise)

Increasing delay between plasma DMED and HR, BIS, MAP and MOAA/S with half-lives for effect-site equilibration ranging from 1.7 to 14.3 min.

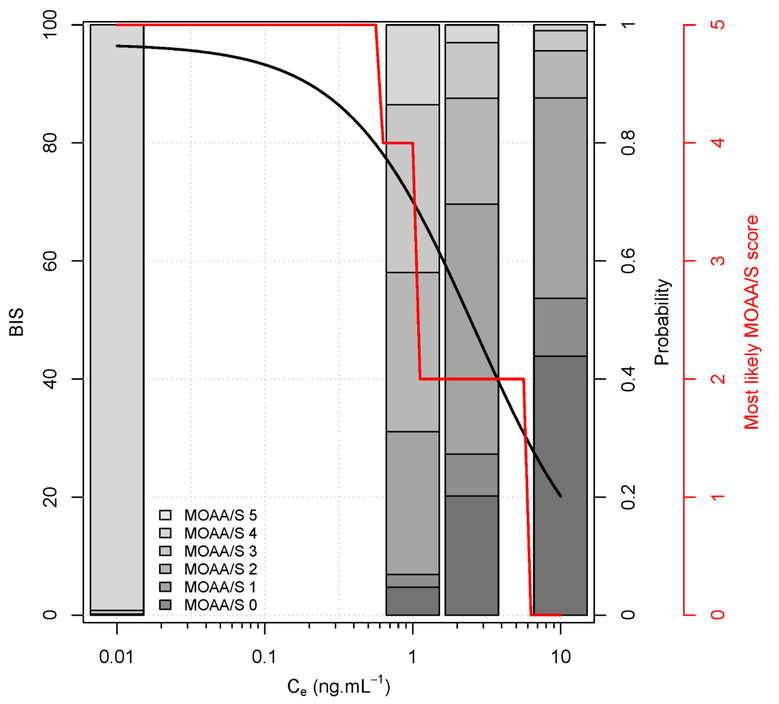
The effect of stimulation

The MOAA/S assessment introduces a transient increase in BIS with a half-live of attenuation of approx. 5.3 min. If stimulation occurs frequently the patient is maintained in an "aroused state".



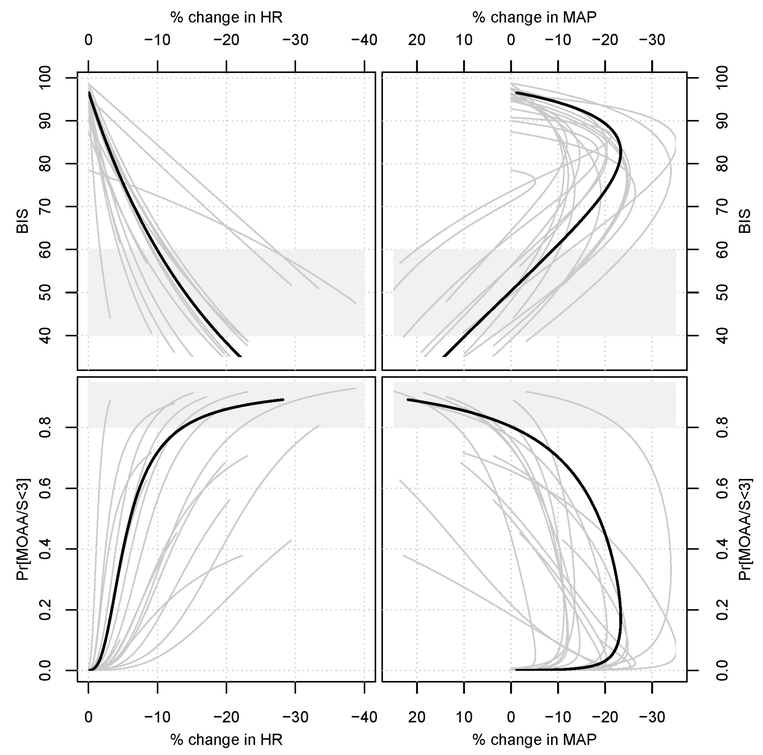
BIS calibration

The calibration for BIS is similar to propofol, indicating that also for DMED target BIS values (in an unstimulated patient) between 40 and 60 are appropriate when deep sedation is required.



HDs as surrogate for BIS

The sedative and haemodynamic effects of DMED are highly correlated, providing potential surrogate haemodynamic markers to guide sedation.



Conclusions

1. Depriving a volunteer of background noise alters the sensitivity towards the sedative properties of DMED.
2. Stimulation due to MOAA/S scoring transiently confounds the BIS signal. Our model-based approach accounts for this effect by describing this time-varying rousability.
3. Once corrected for the effect of stimulation, the relationship between BIS and clinical signs of sedation are similar to other hypnotic drugs (e.g. propofol).
4. The haemodynamic side effects go hand in hand with the sedative properties, making the HDs a potential surrogate to guide DMED dosing in absence of a BIS monitor.

[1] *P.Colin et al. Dexmedetomidine pharmacokinetic-pharmacodynamic modelling in healthy volunteers: 1. Influence of arousal on bispectral index and sedation. British Journal of Anaesthesia; doi: 10.1093/bja/aex085*

[2] *P.Colin et al. Dexmedetomidine pharmacodynamics in healthy volunteers: 2. Haemodynamic profile. British Journal of Anaesthesia; doi: 10.1093/bja/aex086*