Dexmedetomidine (DMED) use in clinical practice is popular because of its unique characteristics as a selective α2-adrenoceptor 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.

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

**The effect of stimulation**

The MOAA/S assessment introduces a transient increase in BIS with a half-life 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.

**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.

**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.

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

Changes in MOAA/S were described using a proportional odds logistic regression model with different C50 for the silent and noisy session (32% decrease in C50 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.