# A two-compartment effect site model describes the Bispectral Index Score (BIS) after administration of propofol

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## Background and Objectives

Different estimates of the rate constant for the effect-site distribution ($k_{e0}$) of propofol have been reported, depending on the rate and duration of administration [1,2]. This analysis aimed at finding a more general pharmacodynamic model that could be used when the rate of administration is changed during the treatment.

## Methods

Twenty healthy volunteers were randomized to receive a 1-minute infusion of 2 mg/kg of propofol at one occasion (Bolus), and a 1-minute infusion of 2 mg/kg of propofol immediately followed by a 29-minute infusion of 12 mg/kg/h of propofol (Primed Constant Infusion) at another occasion, in a cross-over fashion. Arterial plasma concentrations of propofol were collected up to 4 hours after dosing, and Bispectral Index Score (BIS) was collected before start of infusion and until the subjects were regarded as no longer sedated after the anaesthesia. The population pharmacokinetic/pharmacodynamic (PK/PD) analysis was performed using NONMEM VI. Goodness of fit was assessed using objective function values, standard errors, graphics and visual predictive checks (VPC). Since the dose was different in all patients due to different body weights, PRED-corrected VPC´s were performed [3].

## Results

An empirical model with time-dependent clearance parameters (CL, Q2, Q3, Q4) described the PK well for both regimens, and was used as an input to the BIS model, since the ordinary three-compartment model under-estimated the propofol concentrations during the constant infusion. The $t_{50}$ for the time dependence was 50 and 70 seconds for the bolus and primed constant ifusion, respectively. A two-compartment effect site model was used to describe BIS (Figure 1). The model included a central and a peripheral effect site compartment, and the decrease in BIS was linked to the central effect site compartment concentrations through a sigmoidal $E_{max}$ model. The model described BIS well (Figure 2), in contrast to the ordinary one-compartment effect-site model which could not accurately describe the delay in the effects of propofol for both treatments. The parameter estimates of the BIS model are shown in Table 1.

| Parameter | Estimate | CV% | IIV (%) | CV% |
|---|---|---|---|---|
| $k_{e0}$ ($min^{-1}$) | 0.159 | 5.96 | 15 | 38 |
| Baseline BIS | 92.5 | 0.75 | 3.5 | 35 |
| $EC_{50}$ (ng/mL) | 2550 | 4.78 | 18 | 36 |
| $\gamma$ | 2.93 | 4.98 | - | - |
| $E_{max}$ (% decrease from baseline) | 90.4 | 2.74 | - | - |
| $k_{e12}$ ($min^{-1}$) | 0.114 | 13.16 | - | - |
| $k_{e21}$ ($min^{-1}$) | 0.0214 | 9.44 | - | - |
| Additive residual error | 6.55 | 3.51 | - | - |

***Table 1.*** *Parameter estimates for the BIS-model.*

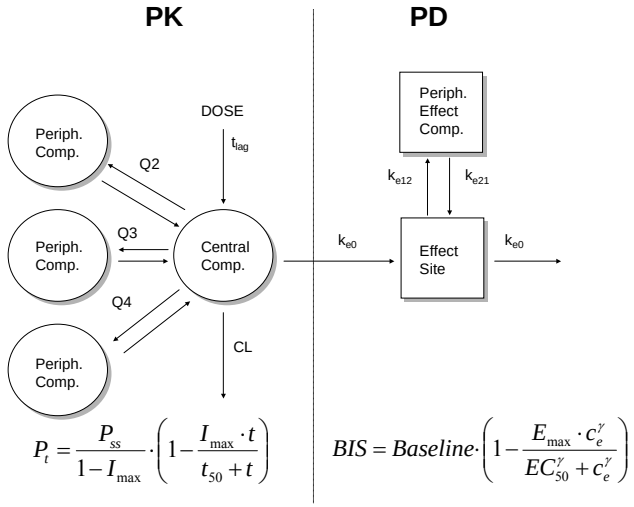


***Figure 1.*** *BIS is related to the concentrations at the effect site by the inhibitory sigmoidal $E_{max}$ model. The effect site of the 2-compartment PD-model (right part) is connected to the central compartment of the PK-model (left part). CL, Q2, Q3, Q4 are time dependent, with a maximum decrease of $I_{max}$ to the steady state value $P_{ss}$.*

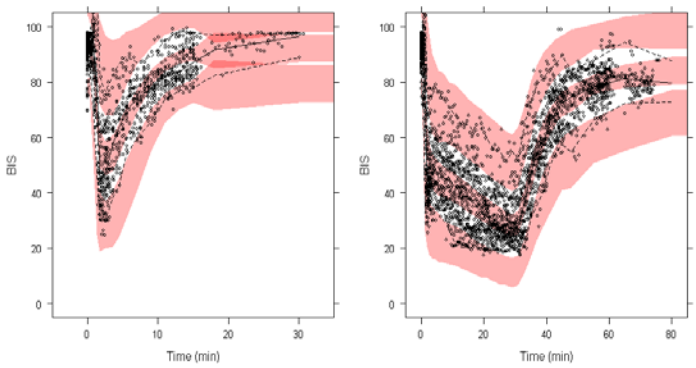


***Figure 2.*** *The 2-compartment effect site model describes BIS for both the Bolus dose (left) and the Primed Constant Infusion (right). Circles represent the PRED-corrected observations, lines represent the median, 2.5th and 97.5th percentile of the PRED-corrected observations, and areas represent the confidence intervals for the PRED-corrected simulated median and prediction interval.*

## Conclusions

The time-courses of BIS after both treatments were well described by a two-compartment effect-site model, possibly representing a distribution within the brain.

## References

[1] Doufas AG et al., Anesthesiology 2004; 101:1112-21
[2] Struys MMRF et al., Anesthesiology 2007; 107:386-96
[3] Karlsson MO and Holford N. PAGE 17 (2008) Abstr 1434 [www.page-meeting.org/?abstract=1434]