# MODELLING DRUGS' PHARMACODYNAMIC INTERACTION DURING GENERAL ANAESTHESIA: THE CHOICE OF PHARMACOKINETIC MODEL

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Abstract: The effect of drugs' interaction on the brain signal Bispectral Index (BIS) is of great importance for an anaesthesia control drug infusion system. In this study, two renowned pharmacokinetic (PK) models for propofol are compared, in order to evaluate its influence on the performance/predictably of a drug interaction model for BIS, considering data of 45 patients. The model was fitted per patient during anaesthesia induction, and tested for prediction under surgery. The results showed that the choice of PK model had influence on the overall performance. In the prediction phase, only one PK model presented good results with small errors.


Keywords: Pharmacokinetic data, modelling, biomedical systems, prediction

## 1. INTRODUCTION

Anaesthesia can be defined as the lack of response and recall to noxious stimuli, involving the use of three drugs, a muscle relaxant, an anaesthetic (hypnotic) and an analgesic. The analgesic drug is of great importance since it affects the pharmacodynamics of the anaesthetic drug and there is no clear indicator of the degree of pain. The analgesic and anaesthetic drugs are interconnected, since they interact with each other so as to achieve an adequate level of depth of anaesthesia (DOA) and analgesia (Vuyk, 1999). The bispectral index of the EEG (BIS) is a numerical processed, clinically-validated EEG parameter, used as an indicator of the level of DOA, measuring the degree of depression in the central nervous system. The BIS is a number between 0 and 100, where values near 100 represent an "awake" clinical state while 0 denotes the maximal EEG effect possible (i.e., an isoelectric EEG) (Schaarg *et al.*, 1999). Overall, general anaesthesia consists of both loss of consciousness through the action of anaesthetic drugs, and the inhibition of noxious stimuli reaching the brain through the acting of the analgesics. The intravenous anaesthetic drug propofol is used in combination with the analgesic remifentanil.

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Propofol and remifentanil have a synergistic relationship. The effect of the combination of these two drugs is greater than that expected as based on the concentration-effect relationships of the individual agents (Vuyk *et al.*, 1997). A model for anaesthetic drug interactions can prove to be very useful in understanding the full relationship between the concentrations of the two drugs and drug effects. This model should take into consideration the interactions between drugs and variability between patients.

In this study, two well known and commercialised pharmacokinetic (PK) models were used for the plasma and effect concentrations of propofol, Marsh (Marsh *et al.*, 1991) (PK Model 1) and Schnider (Schnider *et al.*, 1998) (PK Model 2). The interaction model (Bruhn *et al.*, 2003)(Minto *et al.*, 2000) was fitted to the data of each patient in the induction phase (first 15 min). The individual patient models were then used to predict BIS during maintenance of anaesthesia (surgery), considering the drugs' concentrations. Since the interaction model is based on the modelled effect concentrations its results could be greatly influenced by the choice of PK model. Therefore, a comparative study will be performed on a wide group of patients to evaluate the influence of PK model on the overall performance of the interaction model and its prediction ability.

The clinical data, the two PK models for propofol (PK Model 1 (Marsh *et al.*, 1991) and PK Model 2 (Schnider *et al.*, 1998)), and the remifentanil PK model are presented in section 2. Section 3 describes the interaction model (Bruhn *et al.*, 2003) for the concentration-effect relationship on BIS, while section 4 presents the results on the data. Sections 5 and 6 present the discussion and the conclusion, respectively.

## 2. CLINICAL DATA

Data collected during 45 neurosurgical interventions were used in this study. All 45 patients were subject to general anaesthesia using propofol and remifentanil. The level of unconsciousness (DOA) was manually controlled by the anaesthetist using as reference the patient's vital signs and BIS. The following data were recorded during the surgery every 5 seconds: BIS, infusion rate of propofol and remifentanil. The infusion rates were used to calculate the plasma and effect concentration of both drugs, as described in the following subsections. The patients studied were 51±16 years, 70±13 kg, 163±9 cm, 28 female. Anaesthesia started with a constant infusion 200 ml/hr of propofol until loss of consciousness (LOC), thereafter propofol was changed according to the BIS value. The remifentanil infusion started at LOC.

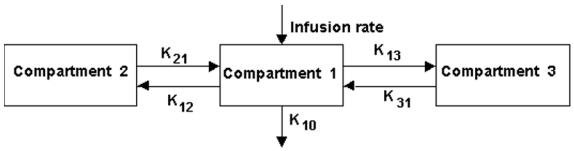


Fig. 1. 3-compartment pharmacokinetic model. The plasma concentration is defined as the concentration in compartment 1.

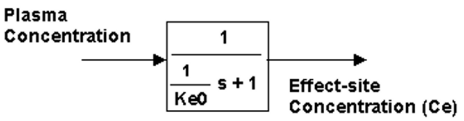


Fig. 2. Effect compartment model

### *2.1 Pharmacokinetic (PK) Models*

The PK models of the two drugs use a 3-compartment model (Figure 1). For propofol, the PK parameters from Marsh (Marsh *et al.*, 1991) (PK Model 1) and from Schnider (Schnider *et al.*, 1998) (PK Model 2) were used, whereas for remifentanil, the parameters from Minto (Minto *et al.*, 1997a) were used. PK Model 2 has its parameters adjusted to age, gender, weight and height of the patients, whereas PK Model 1 only takes into consideration the patient's weight.

### *2.2 Effect Compartment*

The effect compartment is a hypothetical compartment describing the delay between the plasma concentration and the effect concentration. Figure 2 shows the diagram of the effect compartment relationship. The pharmacodynamic parameters $ke0$ used were described by Marsh (Marsh *et al.*, 1991) (PK Model 1) and from Schnider (Schnider *et al.*, 1999) (PK Model 2) for propofol, and for remifentanil by Minto (Minto *et al.*, 1997b).

## 3. INTERACTION MODEL

Figure 3 shows the block diagram of the BIS model. The objective is to describe the relationship between the drugs effect concentrations and its effect.

Bruhn et al. (Bruhn *et al.*, 2003) used an interaction model to relate the electroencephalographic parameter values (including BIS) to the effect concentrations of propofol and remifentanil. This model was developed by Minto et al. in a previous study (Minto *et al.*, 2000).

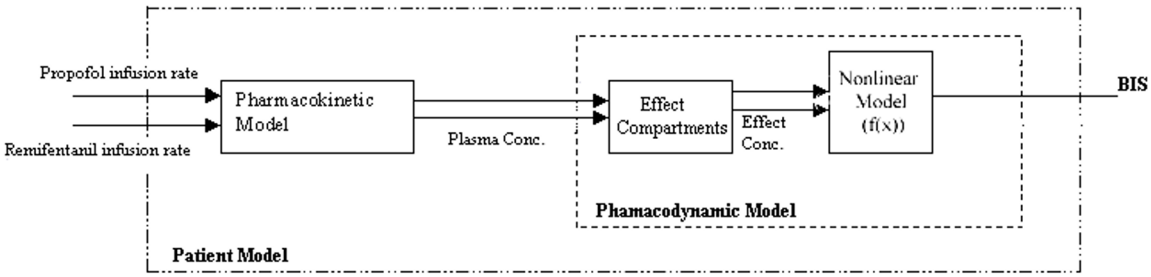


Fig. 3. Block diagram of BIS model.

First, the concentrations were normalised to their respective potencies ($EC_{50p}$ and $EC_{50r}$ for propofol and remifentanil, respectively), i.e. the effect concentration at half the maximal effect:

$$U_{remi} = \frac{Ce_r(t)}{EC_{50r}} \quad U_{prop} = \frac{Ce_p(t)}{EC_{50p}} \tag{1}$$

where $Ce_r$ and $Ce_p$ are the respective effect concentrations of remifentanil and propofol. For an additive interaction, the "effective" concentration is the sum of the individual concentrations normalised, so the effect ($E$, in this case the effect is BIS) can be described as equation 2.

$$E = E_0 \left(1 - \frac{U_{prop} + U_{remi}}{1 + U_{prop} + U_{remi}}\right) \tag{2}$$

where $E_0$ is the effect at zero concentrations (e.g. $BIS_0 = 97.7$ for the case of BIS - monitor restriction). Deviation from a purely additive interaction is modelled by changing the potency of the drug mixture depending on the ratio of the interacting drugs (equation 3).

$$\theta = \frac{U_{prop}}{U_{prop} + U_{remi}} \tag{3}$$

By definition, $\theta$ ranges from 0 (remifentanil only) to 1 (propofol only). Thus, the concentration-response relationship for any ratio of the two drugs regardless of the type of interaction can be described as equation 4.

$$E = E_0 \left(1 - \frac{\left(\left(U_{prop} + U_{remi}\right)/U_{50(\theta)}\right)^{\gamma}}{1 + \left(\left(U_{prop} + U_{remi}\right)/U_{50(\theta)}\right)^{\gamma}}\right) \tag{4}$$

where $\gamma$ is the steepness of the concentration-response relation, and $U_{50(\theta)}$ is the number of units ($U$) associated with 50% of maximum effect at ratio $\theta$. According to (Minto *et al.*, 2000) equation 3 can be simplified to a quadratic polynomial (equation 5).

$$U_{50(\theta)} = 1 - \beta_{2,U50}\theta + \beta_{2,U50}\theta^2 \tag{5}$$

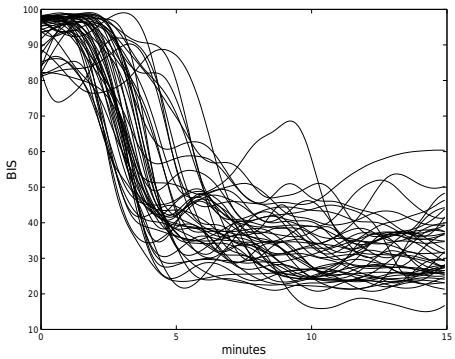


Fig. 4. Recorded BIS values of the 45 patients during the induction phase, i.e. the first 15 min.

## 4. RESULTS

Both models were fitted to the data of the 45 patients in the induction phase of anaesthesia (first 15 min). The interaction model parameters were fitted using nonlinear least squares with the software MATLAB 6.5.1. The BIS signal was prefiltered with a lowpass second order Butterworth filter. For the interaction model, the parameters $EC_{50p}$, $EC_{50r}$, $\gamma$ and $\beta_{2,U50}$ were obtained for each patient. The mean absolute error was calculated for the results of the two models (interaction model using the PK Model 1 and the interaction model using the PK Model 2) and for each patient. Figure 4 shows the BIS trends for the 45 patients during the induction phase. Figure 5 shows the effect concentrations of propofol using PK Model 1 and PK Model 2. Figure 6 shows the remifentanil effect concentrations.

### *4.1 Results with PK Model 1*

Figure 7 shows the results of the interaction model when the PK Model 1 is used for the propofol effect concentrations. The mean absolute errors for the induction of anaesthesia (fitting phase) and for the maintenance phase (from 15 min until the end of surgery - prediction results) are presented in Figure 8. Only in 6 patients, the fitting model errors were statistically different from zero (*t-test*, P<0.05). However, for 2 patients the prediction

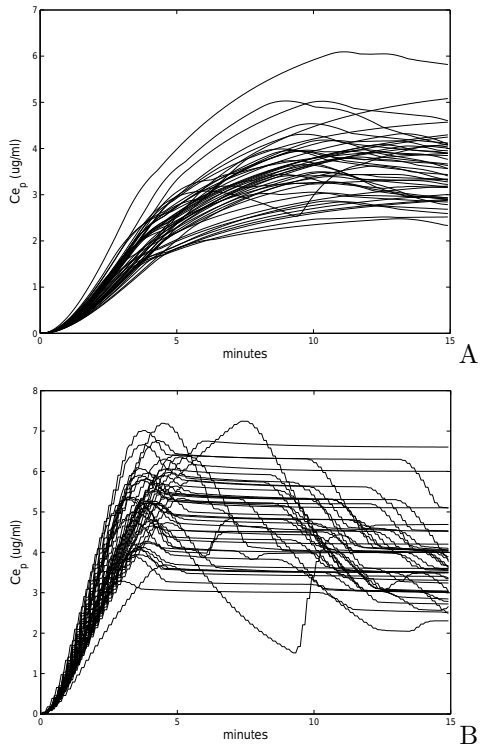


Fig. 5. Propofol effect concentration ($Ce_p$) for the 45 patients during the induction phase (i.e. the first 15 min) using: **A**- PK Model 1; **B**- PK Model 2

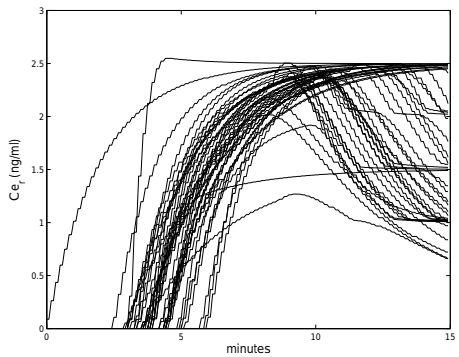


Fig. 6. Remifentanil effect concentration ($Ce_r$) for the 45 patients during the induction phase, i.e. the first 15 min.

errors were not statistically different from zero (*t-test*, P<0.05).

### *4.2 Results with PK Model 2*

Figure 9 shows the results of the interaction model using the PK Model 2 for the propofol effect concentration, for the 45 patients. The model had a good performance in the induction phase (fitting phase) with statistical zero error (*t-test*, P<0.05) in some patients. The mean absolute errors for the fitting and prediction phases are presented in Figure 10. In 13 patients, the fitting model

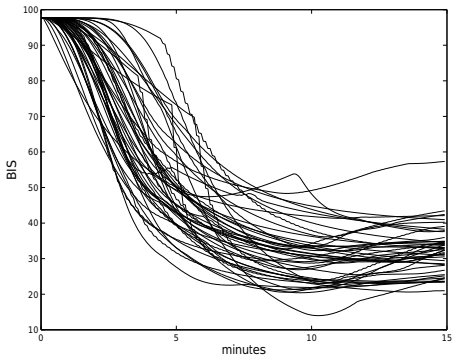


Fig. 7. Modelled BIS values for the interaction model using PK Model 1 for the propofol effect concentration, for the 45 patients during the induction phase, i.e. the first 15 min.

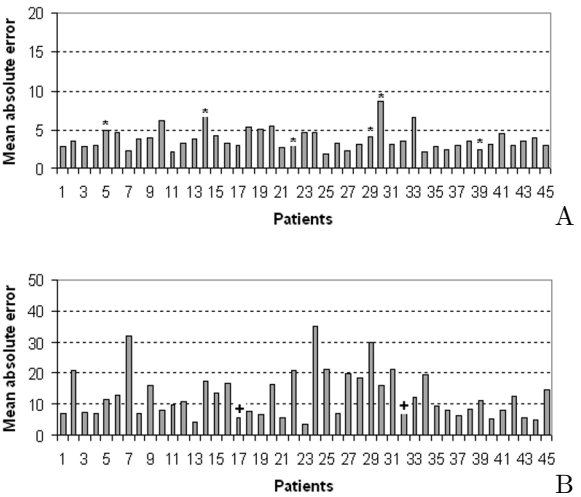


Fig. 8. Mean of absolute errors for the interaction model using PK Model 1 in: **A**- induction phase (fitting phase). * errors are statistically different from zero (*t-test*, P<0.05); **B**- maintenance phase (prediction phase). + errors that are not statistically different from zero (*t-test*, P<0.05).

errors were statistically different from zero (*t-test*, P<0.05). The prediction results were not good.

## 5. DISCUSSION

Comparing the results of the two models at its best and worst case, it is possible to analyse the performance of the two techniques. In the fitting phase, the result of the interaction model using PK Model 1 had smaller errors than when using PK Model 2, but both models follow the BIS trend. However, it is in the maintenance phase (prediction phase - from 15 min until the end of surgery) that the difference is clearer.

The interaction model using PK Model 2 did not capture the BIS trend. Figure 11 shows the pre-

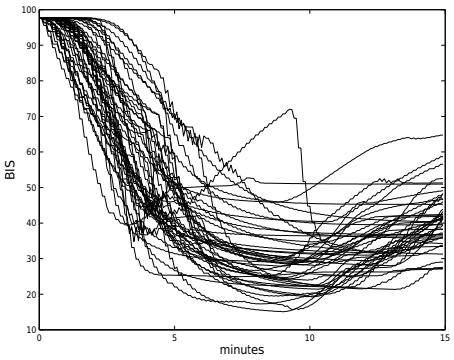


Fig. 9. Modelled BIS values for the interaction model using PK Model 2 for the propofol effect concentration, for the 45 patients during the induction phase, i.e. the first 15 min.

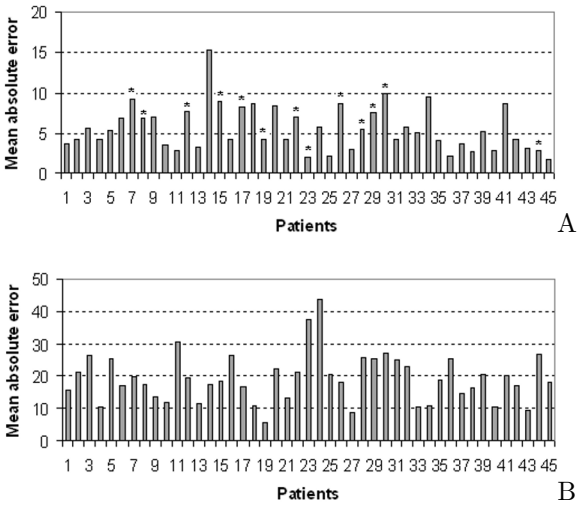


Fig. 10. Mean of absolute errors for the interaction model using PK Model 2 in: **A**- induction phase (fitting phase). * errors are statistically different from zero (*t-test*, P<0.05); **B**- maintenance phase (prediction phase).

diction results with both models for Patient 23, which had the smallest prediction error with PK Model 1. Figure 12 shows the prediction results for the patient with the smallest prediction error with PK Model 2 (Patient 19). The mean absolute error with PK Model 2 is smaller than with PK Model 1 for Patient 19 (5.85 and 6.86, respectively), however the results present a greater oscillation around the BIS value. Figure 13 shows the results of both models for Patient 17, which had prediction errors statistically not different from zero, and a small mean absolute prediction error when using PK Model 1.

The patient with the worst model performance in the prediction phase was Patient 24, which had the biggest mean absolute prediction error using both PK models. Maybe one could be in the presence of an extreme case.

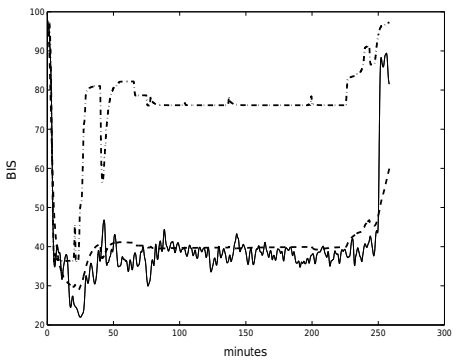


Fig. 11. Recorded BIS (solid line) versus modelled BIS using PK Model 1(dashed line) and PK Model 2 (dashed dot line) in the prediction phase (from 15 min until end of surgery), for Patient 23 which had the smallest mean absolute prediction error with PK Model 1

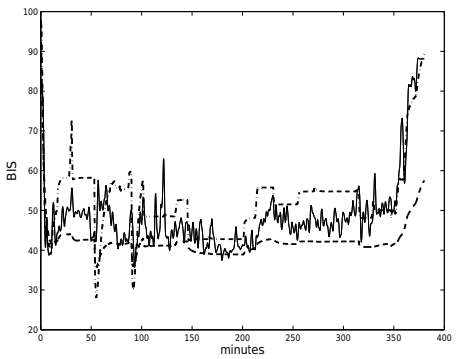


Fig. 12. Recorded BIS (solid line) versus modelled BIS using PK Model 1(dashed line) and PK Model 2 (dashed dot line) in the prediction phase (from 15 min until end of surgery), for Patient 19 which had the smallest mean absolute prediction error with PK Model 2.

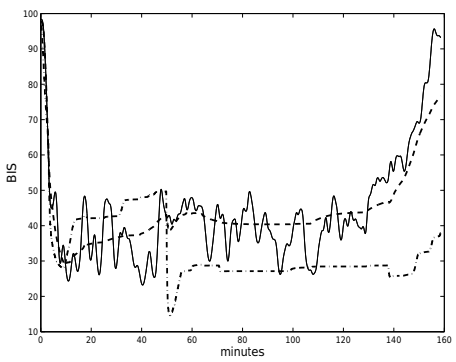


Fig. 13. Recorded BIS (solid line) versus modelled BIS using PK Model 1(dashed line) and PK Model 2 (dashed dot line) in the prediction phase (from 15 min until end of surgery), for Patient 17 which had prediction errors statistically not different from zero, and a small mean absolute prediction error when using PK Model 1.

## 6. CONCLUSIONS

The induction phase of anaesthesia can be used to establish the patient's individual response to the drugs. The degree of resistance of the patient to the drugs has a great influence on the amount of drugs necessary during surgery to maintain an adequate level of unconsciousness and analgesia. Information extracted during induction can be used to adapt the infusion rates of both drugs, improving the patient's safety and comfort, avoiding cases of overdosage or awareness. The control system parameters can be adjusted or adapted to individual patient requirements.

The two models tested in this study are already credited and published models. In addition, both models are currently commercialised in Target Controlled Infusion (TCI) devices for propofol.

The interaction model described by Bruhn et al. (Bruhn *et al.*, 2003) and previously developed by Minto et al. (Minto *et al.*, 2000), uses a drug interaction model based on a Hill equation structure. This model proved to be effective by adequately modelling the induction BIS trend in all 45 patients with both PK models. However, the use of PK Model 1 improves the results of the interaction model for BIS. In addition, when using PK Model 1, the interaction model can capture the BIS trend during the prediction phase in many patients. Therefore, the performance of the interaction model is greatly influenced by the choice of PK models. Bruhn et al. tested the interaction model considering steady state conditions in volunteers, and when Minto et al. first presented it, they used the PK Model 2 for propofol. This study has proved that the model could be used in non-steady state conditions (i.e. induction) and also used to predict. In addition, the results were very different and for the better when using PK Model 1.

In conclusion, the model can capture the individual patient response during induction identifying unique characteristics ($EC_{50p}$, $EC_{50p}$, $\gamma$ and $\beta_{2,U50}$), e.g. patients that respond slower or faster to the same infusion dose (sensitive or resistant), and will need different infusion control profiles to obtain the same level of anaesthesia. This information can be used in the future to develop a control system for the infusion rate of both drugs.

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