Pharmacodynamic response modelling of arterial blood pressure in adult volunteers during propofol anaesthesia

Christian Jeleazcov, Marc Lavielle, Jürgen Schüttler, Harald Ihmsen

Title

Pharmacodynamic response modelling of arterial blood pressure in adult volunteers during propofol anaesthesia

Short title

Modeling of the propofol effect on blood pressure

Brief summary statement

For modeling the propofol effect on blood pressure, two effect sites were needed. This may reflect different pathways of blood pressure response to propofol.

Authors

Christian Jeleazcov, M.D.

Associate Professor

Department of Anesthesiology, University Hospital Erlangen, Germany

Marc Lavielle, Ph.D.

Professor

Inria Saclay, France

Jürgen Schüttler, M.D.

Professor

Department of Anesthesiology, University Hospital Erlangen, Germany

Harald Ihmsen, Ph.D.

Research Scientist

Department of Anesthesiology, University Hospital Erlangen, Germany

Department and institution to which the work should be attributed

Department of Anesthesiology, Friedrich-Alexander University Erlangen-Nuremberg,

Erlangen, Germany

Corresponding author

Dr. Christian Jeleazcov

Department of Anesthesiology

University Hospital Erlangen

Krankenhausstrasse 12

91054 Erlangen

Germany

Phone: ++49 (9131) 8539157

Fax: ++49 (9131) 8539161

e-mail: christian.jeleazcov@kfa.imed.uni-erlangen.de

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Abstract

Background: Concentration effect relationships are commonly described with a direct response model as for example the sigmoid E_{max} model with an effect compartment as site of action. In this study we investigated whether models with more than one effect site or indirect response models may be more appropriate for modeling the propofol effect on arterial blood pressure. As comparator, the Bispectral index BIS was also analyzed.

Methods: Nine young healthy volunteers received propofol as target controlled infusion with predefined increasing and decreasing plasma target concentrations. Propofol concentrations were determined from arterial blood samples. BIS and invasively measured arterial blood pressure were recorded continuously. Pharmacokinetic/-pharmacodynamic modeling was performed by population analysis with MONOLIX, testing different direct and indirect response models .

Results: Propofol plasma concentrations were well described by a three-compartment model. The propofol effect on BIS was well described by a direct sigmoid E_{max} model with one effect compartment. The propofol effect on arterial blood pressure was best described by a direct sigmoid E_{max} model with two effect site compartments.

Conclusions: Whereas BIS was modeled well with the standard sigmoid E_{max} model linked to one effect compartment, two effect sites were needed to describe the propofol effect on arterial blood pressure. This may reflect different pathways of arterial blood pressureresponse to propofol.

Introduction

The hemodynamic effect of commonly used anesthetics is reversible, drug specific, and occurs within seconds to minutes. Direct pharmacodynamic effect is induced by drugs that act immediately on the measured variable and is usually modeled by linear or E_{max} models. Because blood plasma is not the effect site of action (called biophase) for most of the drugs, a hypothetical effect-compartment has been introduced to account for the equilibration delay between plasma-compartment and biophase.[1] However, the drug effect may be further delayed even after the drug reaches the biophase. In such cases, the drug inhibits or stimulates the production or dissipation of factors modulating the measured effect, which is called indirect pharmacodynamic response.[2]

Previous studies regarding propofol induced changes in arterial blood pressure expressed the relationship between effect site concentration and drug effect by a sigmoid E_{max} model. The equilibration half-times of propofol concentration between blood plasma and biophase were found to be slower for systolic blood pressure as for processed EEG pharmacodynamic indices like BIS [3]. It also has been shown that propofol reduces cardiac output and systemic vascular resistance, and therefore reduces arterial blood pressure.[4] These findings indicate a potential indirect pharmacodynamic response for propofol rather than a direct response at the biophase. Therefore, this work deals with the application of direct, indirect and counter-regulatory response models with one or more sites of action for studying the concentration-effect relationship of propofol induced changes in arterial blood pressure. Nonlinear mixed-effect modeling is nowadays considered as state of the art in population-based PKPD modeling and is used to optimize dosing of anesthetic agents.[5] It provides estimates for inter- and intraindividual variability and limits the influence of outlying samples and individuals.[6]

The population-based analysis presented here was performed on invasive arterial blood pressure data recorded at radial artery site during experimental propofol anesthesia in volunteers.

Methods

We reanalyzed arterial blood pressure data recorded at radial artery site before, during and after target controlled infusion (TCI) of propofol in 9 healthy volunteers (5 female and 4 male aged 25 ± 4 yr, weight 70 ± 10 kg, height 179 ± 9 cm, (mean ± SD)). The data were part of a neurophysiologic and hemodynamic investigation performed in June 2006 after approval of the local Ethics Committee and written informed consent from participants, and was presented in part at the World Congress on Medical Physics and Biomedical Engineering 2009.[7] Therefore, the information regarding study design and propofol determination in plasma is repeated here.

Study Design

No premedication was given prior to the experiments. After overnight fasting, the volunteers came to the investigation room and a cannula (BD Angiocath™ 20G, Becton Dickinson, Heidelberg, Germany) was inserted into an antecubital vein for the infusion of propofol and for fluid replacement (Ringer's lactate solution of 2 ml kg^{-1} h^{-1}). After local anesthesia, an intra-arterial catheter (Leader Cath 20G, Vygon, Aachen, Germany) was inserted into the left arteria radialis for measuring blood pressure. Invasive arterial blood pressure measurements were performed with a xtrans pressure transducer (CODAN pvb Critical Care GmbH, Forstinning, Germany). Invasive arterial blood pressure, heart rate, pulse oximetry, and ECG were monitored continuously throughout the study with a Siemens SC9000 monitor (Siemens, Erlangen, Germany). The volunteers remained breathing spontaneoulsy throughout the trial. In case of a depressed spontaneous breathing or a decrease of the SaO_2 below 93%, the volunteers received 4 l/min oxygen via a face mask.

Blood pressure data were read from the analogue interface of the Siemens SC9000 monitor and digitized with 100 samples per second. After skin preparation, EEG silver/silver chloride gelfilled electrodes were placed to the left and right frontal regions and referenced to a central vertex electrode. Impedance was maintained at less than 3 kΩ, and the EEG was recorded and analyzed continuously throughout the study using an A1000 EEG monitor (software version 3.12, Aspect Medical Systems, Natick, MA). The digitized BIS® data were obtained from the serial port of the A1000 with a sampling rate of one value per second. Before administration of propofol, the volunteers were asked to lie quietly in supine position and 15 min of baseline recording was performed. Blood pressure and EEG measurements were stopped 10 min after the volunteer had regained consciousness. The study trial was ended after the last blood sample had been taken.

Propofol infusion

Propofol was administered as TCI using the pharmacokinetic model of Marsh et al.[8] to achieve predetermined increasing plasma concentrations of 0.5, 1, 1.5, 2, 2.5, 3 and 4.5 μg/ml. Each target was maintained for 15 minutes. In order to rapidly achieve steady state effect site concentrations, we started each step with higher plasma target concentrations of 1, 1.5, 2, 3, 3.5, 4 and 5.5 μg/ml, respectively. This higher initial target was maintained for 1 min, subsequently the target was reduced to the intended plasma concentration. Following the last step of 4.5 μg/ml the propofol plasma target was further linearly increased by 0.5 μg ml^{-1} min^{-1}, until one of the following endpoints was reached: EEG burst suppression patterns longer than 2 s, flattening of spontaneous breathing, or drop of the mean blood pressure by more than 45% from baseline values. As soon as one of these endpoints was reached, the

achieved target concentration was reduced by 1 µg/ml and maintained for further 5 min. Subsequently the plasma target concentration was reduced to 3, 2.5, 2 and 1.5 µg/ml, maintaining each target for 15 minutes. In order to rapidly achieve steady state effect site concentrations, the plasma target concentrations were initially lowered to 2.5, 2, 1.5 and 1 µg/ml, respectively. As soon as this concentration was reached, the target was increased to the intended plasma concentration. Following the last step of 1.5 µg/ml, the propofol infusion was stopped.

Blood sampling and propofol assay

During the first part of each session with increasing concentrations, one blood sample was collected at the end of each target step. In the second part with decreasing concentrations, four samples were taken 2, 5, 10 and 15 min after the end of the step with the highest target. Subsequently, one sample was again taken at the end of each of the following target steps. After end of the last step with a target of 1.5 µg/ml, further samples were taken 15, 30, 90, and 150 min after stop of infusion.

To determine the arterial propofol concentration, 2.5 ml blood were taken per sample (S-Monovette® Kalium EDTA, Sarstedt, Nürnbrecht, Germany), after 1 ml blood had been taken previously and discarded. After each sample collection, the intra-arterial catheter was flushed with 2 ml of heparinized NaCl-solution. Blood samples were separated immediately and stored at 4°C on ice until extraction and assay. Within 12 h after sampling, plasma concentrations of propofol were determined using high-performance liquid chromatography (HPLC) with electrochemical detection as described previously.[9] The extraction recovery was

more than 90%. The inter- and intra-assay coefficients of variation were 1.7% and 7.7%, respectively. The detection limit was 1 ng.

Pharmacokinetic/-dynamic modeling

As we had a rich but unbalanced data situation with many data both for pharmacokinetics and pharmacodynamics on the one hand, but much more pharmacodynamic than pharmacokinetic data, we performed not a simultaneously pharmacokinetic/-dynamic analysis but a two step analysis where the pharmacokinetics were analyzed first. The individual pharmacokinetic parameters obtained in this step were then used in the pharmacodynamic analysis.

Pharmacokinetic modeling

In a first step, we used the infusion rates obtained from the TCI device as input to the pharmacokinetic (PK) model to describe the time course of propofol concentration in blood plasma. Linear mammillary models with one, two or three compartments and elimination from the central compartment were fitted to the data. Models were parameterized using volumes of distribution and clearances (elimination and intercompartmental). The interindividual variability of the PK parameters was estimated using log-normal distributions with mean zero and variance ω^2. A combined proportional and additive model with means of zero and variances σ_1^2 and σ_2^2 was used to assess the intraindividual residual error. Population as well as individual pharmacokinetic parameters were obtained by population analysis using the software MONOLIX (see below).

Pharmacodynamic modeling

In a second step, the effect of propofol on systolic (SBP), diastolic (DBP) and mean blood pressure (MBP), and on BIS was analyzed. For this purpose, the blood pressure data as well as the BIS values were down-sampled to obtain one value per minute by selecting the effect value closest to the required to the time value. The BIS was modeled by a sigmoid E_{max} model with an effect compartment linked to the central compartment:

$$E = E_0 - E_{max} \cdot \frac{C_E^{\gamma}}{C_E^{\gamma} + EC_{50}^{\gamma}} \qquad \frac{dC_E}{dt} = k_{e0} \cdot (C_P - C_E)$$

where E_0 is the baseline value of BIS, E_{max} is the maximum reduction of BIS, EC_{50} is the concentration for half-maximum effect, γ is the Hill exponent describing the steepness of the concentration effect curve and k_{e0} is the rate transfer constant between central and effect compartment. The plasma concentration C_P was calculated using the individual parameters of the best pharmacokinetic model.

For modeling the effect of propofol on blood pressure we did not only test the simple direct response E_{max} model but also a direct response model with two effect sites. In addition, we also tested several indirect response models and also several counter-regulatory models. In an indirect response model, the rate of change in the effect variable E over time when no drug is present was expressed as following:[2]

$$\frac{\mathbf{dE}}{\mathbf{dt}} = \mathbf{k_{in}} - \mathbf{k_{out}} \cdot \mathbf{E}$$

Where k_{in} and k_{out} are parameters describing generation and loss of blood pressure response.

At baseline, the system is assumed to be stationary with $\frac{\mathbf{dE}}{\mathbf{dt}} = 0$

and the baseline value of the effect variable is given as $E_0=k_{in}/k_{out}$. We assumed that the response of blood pressure on propofol was caused by inhibition of factors modulating the generation of blood pressure (e.g. the reduction in cardiac output and peripheral resistance), and therefore modulating k_{in} :

$$\frac{\mathbf{dE}}{\mathbf{dt}} = \mathbf{k_{in}} \cdot \mathbf{I(t)} - \mathbf{k_{out}} \cdot \mathbf{E}$$

As inhibition function I(t) we tested functions of increasing complexity, taking into consideration that the delay of the response can occur even after the drug reaches the site of action, i.e. the heart and the peripheral arterial system.

Counter-regulatory models assume that the net pharmacodynamic effect results from the direct primary effect (e.g. blood pressure decrease) which is counteracted by some regulatory reaction of the system. This approach has been tested previously for modeling the effect of ketamine on cardiac output[10] and for the hemodynamic effect of nitroglycerin.[11]

In detail, the tested models for blood pressure response were as following:

model 1: a sigmoid E_{max} model with one effect compartment as for the BIS

model 2: a sigmoid E_{max} model with two effect site compartments:

$$E = E_0 - \frac{E_{max,1}\left(\frac{C_{E,1}}{EC_{50,1}}\right)^{\gamma_1} + E_{max,2}\left(\frac{C_{E,2}}{EC_{50,2}}\right)^{\gamma_2}}{1+\left(\frac{C_{E,1}}{EC_{50,1}}\right)^{\gamma_1} + \left(\frac{C_{E,2}}{EC_{50,2}}\right)^{\gamma_2}}$$

$$\frac{dC_{E,1}}{dt} = k_{e0,1} \cdot (C_P - C_{E,1}) \qquad \frac{dC_{E,2}}{dt} = k_{e0,2} \cdot (C_P - C_{E,2})$$

model 3: an indirect response model linked to propofol plasma concentration:

$$I(t) = 1 - \frac{I_{max} \cdot C_p}{IC_{50} + C_p}$$

model 4: a sigmoid indirect response model linked to propofol plasma concentration:

$$I(t) = 1 - \frac{I_{max} \cdot C_p^{\gamma}}{IC_{50}^{\gamma} + C_p^{\gamma}}$$

model 5: a sigmoid indirect response model linked to an effect-site concentration:

$$I(t) = 1 - \frac{I_{max} \cdot C_E^{\gamma}}{IC_{50}^{\gamma} + C_E^{\gamma}}$$

model 6: a sigmoid indirect response model with two effect sites:

$$I(t) = 1 - \frac{I_{max,1}\left(\frac{C_{E,1}}{IC_{50,1}}\right)^{\gamma_1} + I_{max,2}\left(\frac{C_{E,2}}{IC_{50,2}}\right)^{\gamma_2}}{1 + \left(\frac{C_{E,1}}{IC_{50,1}}\right)^{\gamma_1} + \left(\frac{C_{E,2}}{IC_{50,2}}\right)^{\gamma_2}}$$

model 7: a counter-regulatory model with two counteracting effects E_A and E_H which are connected by the time constant k_{off}:

$$E = E_0 - E_{max,1} \cdot E_A + E_{max,2} \cdot E_H$$

$$E_A = \frac{C_E^{\gamma}}{C_E^{\gamma} + EC_{50}^{\gamma}} \qquad \frac{dC_E}{dt} = k_{e0} \cdot (C_P - C_E) \qquad \frac{dE_H}{dt} = k_{off} \cdot (E_A - E_H)$$

model 8: a counter-regulatory model with two counteracting effects E_A and E_H which are connected by the time constants k_1 and k_{off}

$$E = E_0 - E_{max,1} \cdot E_A + E_{max,2} \cdot E_H$$

$$E_A = \frac{C_E^{\gamma}}{C_E^{\gamma} + EC_{50}^{\gamma}} \qquad \frac{dC_E}{dt} = k_{e0} \cdot (C_P - C_E) \qquad \frac{dE_H}{dt} = k_1 \cdot E_A - k_{off} \cdot E_H$$

I_{max} is the maximum fractional ability of propofol to affect blood pressure, IC_{50} is the drug concentration that induces 50% of inhibition in blood pressure, C_p and C_e are the propofol concentrations in plasma and at effect-site, respectively, and are determined by the pharmacokinetics of the drug and the equilibration rate constant k_{e0} between plasma and effect site.

The interindividual variability of the PD parameters was estimated using log-normal distributions with mean zero and variance ω^2. An additive model with mean of zero and variance σ^2 was used to model the residual error.

Simulations

In order to illustrate the findings, we performed simulations with the final pharmacokinetic and pharmacodynamic models, predicting the time courses of BIS and SBP, DBP and MBP for a propofol infusion scheme as suggested by Roberts et al.,[12] consisting of a bolus dose of 1.5 mg/kg, followed immediately by 10 mg kg^{-1} h^{-1} for 10 min, 8 mg kg^{-1} h^{-1} for the next 10 min, and 6 mg kg^{-1} h^{-1} for the remaining 60 min.

Model implementation and evaluation

Population analysis was performed by nonlinear mixed-effect modeling with the software MONOLIX (Version 4.1.2, Lixoft S.A.S, Orsay, France). This software uses a stochastic approximation expectation maximization (SAEM) algorithm to obtain estimates of the

population parameters. Previous studies showed that this approach may give more reliable results than the traditional first (FO) order or first order conditional estimates (FOCE) approach, which are commonly used for population analysis.[13-15] All PD models were expressed in the form of differential equations and implemented in MLXTRAN. The observed likelihood was computed using importance sampling. Then, the likelihood ratio test was used to compare nested models using the difference in the -2 x log-likelihood (-2LL) at a significance level of $p<0.05$. For non-nested models, the model selection was based on the Bayesian information criterion $BIC=-2LL+Ln(N_I)*N_P$, where N_I is the number of subjects and N_P is the number of parameters. The best model was selected as the one with the smallest value of BIC.

Statistics

Goodness of fit was evaluated by visual inspection of the diagnostic plots produced by MONOLIX and descriptive statistics. Diagnostic plots were measured vs. population and individual predictions as well as weighted residuals (WRES) vs. PRED and WRES vs. time. For both population and individual predictions of the pharmacokinetic models as well as for the predictions by the TCI model, the median prediction error and the median absolute prediction error were calculated as as $MDPE=median((C_{meas}-C_{PRED})/C_{PRED})$ and $MDAPE= median(|(C_{meas}-C_{PRED}|/C_{PRED})$. For BIS and SBP, the MDPE was defined as $MDPE=median(SBP_{meas}-SBP_{PRED})$ and $median(BIS_{meas}-BIS_{PRED})$, and the MDAPE was defined as $MDAPE=median(|SBP_{meas}-SBP_{PRED}|)$ and $median(|BIS_{meas}-BIS_{PRED}|)$, respectively. Statistical analysis was performed with R 2.12.2 (The R Foundation for Statistical

Computing), smoothing for diagnostic plots was performed with the loess smoother (span=0.75). All data are reported as mean ± standard deviation if not stated else.

Results

All nine volunteers successfully completed the study in accordance with the study protocol. The total dose of propofol was 1118 ± 193 mg within 159 ± 22 min. The propofol infusion design is illustrated for one typical volunteer in fig. 1. The target peak concentration was 7.2 ± 1.1 µg/ml and the maximum targeted plateau concentration was 5.9 ± 0.6 µg/ml. The measured propofol plasma concentration increased up to 5.8 ± 1.9 µg/ml (fig. 2). The TCI model overpredicted the measured propofol concentrations with MDPE = -12.3% and MDAPE = 23.0%.

Pharmacokinetic modeling

The propofol concentration time courses were best described with a three-compartment model, which was significantly better than a two-compartment model (difference in -2LL=39.2, $p<0.001$). A good quality of fit was seen between the observed and the population as well as the individual predicted plasma propofol concentrations (fig. 3). The MDPE was 0.6% for the individual and 1.8% for the population predictions, the MDAPE was 7.5% for the individual and 15.8% for the population predictions. Table 1 summarizes the results of the pharmacokinetic modeling. The interindividual variances of CL_2 and V_3 showed very small estimates with large standard errors and were therefore fixed to zero.

Pharmacodynamic modeling of BIS

The BIS decreased from a baseline value of 95.0 ± 4.3 to a minimum value of 28.0 ± 4.7 (fig. 4). The sigmoid E_{max} model with one effect site compartment time adequately described the BIS data (fig. 5). The MDPE was 0.0047 for the individual and 0.82 for the population

predictions, the MDAPE was 3.65 for the individual and 6.15 for the population predictions. Table 2 summarizes the results of the pharmacodynamic modeling.

Pharmacodynamic modeling of blood pressure

The systolic, diastolic and mean blood pressure dropped from baseline values of 140 ± 25, 58 ± 11 and 82 ± 14 mmHg, respectively to minimum values of 77 ± 10, 32 ± 8 and 49 ± 9 mmHg, respectively. The individual time courses of MBP are shown in fig. 6. The comparison of the goodness of fit for the various tested direct and indirect response models is given in table 3. Within the direct response models, model 2 with two effect sites was significantly better than model 1 with only one effect site. For the indirect response models we found that a sigmoid inhibitory function with $\gamma>1$ (model 4) was better than a simple inhibitory function with $\gamma=1$ (model 3). Linking the inhibitory function to an effect site concentration (model 5) further improved the fit. Within the indirect response models, the best fit was obtained for an indirect sigmoid response model with two effect sites (model 6). However, this model was worse than the direct sigmoid response model with two effect sites (model 2), and model 2 was therefore chosen as the best pharmacodynamic model for SBP, DBP and MBP. For the two investigated counter-regulatory models, the goodness-of-fit was less than for the direct response model with two effect compartments. The parameter estimates for the final pharmacodynamic model (model 2) are summarized in table 4 and the diagnostic plots for this model are shown in fig. 7. The residual analysis for this model revealed normally distributed, uncorrelated and nearly time-invariant residuals for individual and population predictions. However, the deviation from identity line between population predictions and measured values delineated by the smoother line in fig. 7B was partly caused

by differences in the level of arterial blood pressure between subjects. Although scaling PD-parameters by age lead to a significant improvement of the pharmacodynamic fit and a relevant reduction in the prediction error ($MDPE_{pop}$ -1.78 vs. -0.33 and $MDAPE_{pop}$ 9.48 vs. 8.65 mmHg for the population predictions before vs. after age scaling, respectively), the uncertainty of some parameter estimates increased by more than 100%SE, so that the age scaled model could not be selected as the best model. Best, worse and typical individual cases for individual and population predictions as selected by MDPE for population predictions are shown in fig. 8.

Simulations

Figure 9 shows the simulated time courses of BIS and SBP, DBP and MBP after 80 min propofol infusion according to the Roberts scheme. Compared to the propofol effect on BIS, the blood pressure decreases and recovers with a distinct delay.

Discussion

It was the aim of this study to characterize the effects of propofol on the EEG and on the blood pressure by means of pharmacokinetic/-dynamic modeling. Concentration effect relationships are commonly described with a direct response model as for example the sigmoid E_{max} model with an effect compartment as site of action. This model, which was first proposed on an empirical basis by Hill in order to describe the association of oxygen with hemoglobin,[16] can be derived from drug-receptor kinetics.[17] Whereas this concept seems reasonable for the hypnotic effect of propofol, which is assumed to be mediated by interaction with the GABA receptor,[18] it may not be as reasonable to describe the propofol effect on arterial blood pressure, if one considers that this effect results as an interaction of different actions of propofol, such as reduction of cardiac output and systemic vascular resistance.[4] Therefore, models with more than one effect site may be more plausible for the effect on blood pressure. It may be further reasonable to assume an indirect response mechanism, where the inhibition is modulated by the propofol concentration. Indirect response models typically assume that the inhibition function is linked to the plasma concentration by a simple E_{max} model with a Hill exponent $\gamma=1$. In this study we tested also inhibition functions with a sigmoid E_{max} model ($\gamma>1$), and we also expanded the inhibition function assuming one or two effect sites. On the other hand, counter-regulatory models may reflect physiologic interactions between heart and vascular system for immediate regulation of the arterial blood pressure. Therefore, we additionally tested counter-regulatory models of increasing complexity. Pharmacokinetic/-dynamic modeling was carried out in a sequential procedure, where pharmacokinetics were determined in the first step and pharmacodynamics in the second step using the individual estimates of the pharmacokinetic parameters. Compared to simultaneous

fitting of both pharmacokinetics and pharmacodynamics this approach has not only the advantage that it is less CPU time consuming, but also allows for improved model stability during estimation without bias of the pharmacodynamic parameter estimates.[19,20] In the sequential analysis one assumes that the individual pharmacokinetic parameters have no error, which is clearly not true. However, simultaneous analysis may result in poor estimates of the pharmacokinetic parameters if there is any misspecification in the pharmacodynamic model.[21] In addition, if there are much more pharmacodynamic than pharmacokinetic data (as it was the case in the present study with about 15 concentration measurements and about 150 BIS or SBP measurements per individual) the pharmacodynamic data have more weight with respect to the likelihood function that is to be optimized. This can result in a good pharmacodynamic fit at the cost of less quality of the pharmacokinetic fit. We therefore decided to use the sequential method

Pharmacokinetics

Propofol plasma concentrations were well described by a three-compartment model. The pharmacokinetic parameter estimates for clearances and volumes found in the present study were similar to those reported previously.[8,22] In the model by Marsh et al.[8] which was also used for infusion control, the pharmacokinetic parameters for a typical male individual of our study population (25 yrs, 70 kg, 179 cm) were CL_1=1.83 L/min, V_1=15.4 L, CL_2=1.72 L/min, V_2=31.4 L, CL_3=0.65 L/min and V_3=196 L. In the propofol model published by Schnider et al.[22] the corresponding parameters were 1.74 L/min, 4.3 L, 1.96 L/min, 29.8 L, 0.84 L/min and 238 L. The Schnider model and the Marsh model differ mainly with regard to the central volume of distribution and the present estimate of V_1=7.24 L is nearer to the Schnider model,

but one has to consider that V_1 is the parameter which is presumably most sensitive to the study design, particularly to sampling. The fact that V_3 was estimated with a large standard error may be mainly explained by the relative short post infusion sampling in our study.

Pharmacodynamics: BIS

The propofol effect on BIS could be well described with the classical sigmoid E_{max} model with an effect compartment as site of action. The reported values of k_{e0} in the literature vary considerably. Whereas Struys et al.[23] found a very fast equilibration between central and effect site compartment with a k_{e0} of 1.21 1/min, Doufas et al.[24] and Billard et al.[25] reported a much slower equilibration with a k_{e0} of 0.17 and 0.20 1/min, respectively. One has, however, to consider that the estimates of the pharmacodynamic parameters strongly depend on the pharmacokinetic model which was used in the analysis. In a further study by Struys et al. it became evident that the discrepancies with respect to k_{e0} may have been mainly caused by misspecifications of the pharmacokinetic model, particularly when propofol was administered as bolus.[26] Struys et al. concluded that a value of 0.32 1/min may be appropriate if the maximum infusion rate is between 50 and 150 mg/min. As this was the case in our study, the present finding of 0.25 1/min seems reasonable. A similar value of 0.30 1/min was also found in the study by Kazama et al. when the temporarily initial EEG activation with an increase of BIS was excluded form the analysis.[3] The estimates for EC_{50} and the Hill exponent γ in the present study are also similar to the results by Doufas et al.[24] who found an EC_{50} of 2.4 µg/ml and γ=3.1, and by Billard et al.[25] who reported an EC_{50} of 3.4 µg/ml. Kazama et al. found a higher EC_{50} of 5.6 µg/ml,[3] but it seemed that they assumed in their model $E_{max}=E_0$, so that the BIS approximated zero for very high propofol concentrations, whereas in our model E_{max} was

smaller than E_0 with a minimum BIS value of about 13, so that one cannot directly compare the EC_{50} values.

Pharmacodynamics: SBP, DBP and MBP

Whereas the classical direct response model with one effect compartment was adequate for the BIS, the time of course of SBP, DBP and MBP was best fitted by models with two effect sites with the direct response model being superior to the other response models. In the literature on indirect response models, the inhibitory function is typically linked to the plasma concentration using a simple E_{max} model (as in model 3 in our study).[2] This model was the least adequate compared to all other tested models (tab. 3). Although the use of a sigmoid inhibitory function improved the fit, it was necessary to link the inhibitory function not to the plasma but to a effect site concentration.

Interestingly, the parameters of direct response model with two effect compartments indicate no contradictory, but infraadditive interaction between the effect compartments. This may be a possible explanation for the finding that the counter-regulatory models did not perform better than the best direct response model.

The finding that two effect site compartments were necessary both in the direct response model (model 2) and also in the indirect response model (model 6) indicate that the propofol effect on arterial blood pressure is mediated by two pathways, which differ in the equilibration time between central and effect compartment. If one considers that the change of arterial blood pressure under propofol administration is a result of changes in cardiac output and also changes in the systemic vascular resistance,[4] the need of two effect sites seems to be

reasonable. When compared with the k_{e0} of the BIS model, the much smaller values of $k_{e0,1}$ and $k_{e0,2}$ indicate that the arterial blood pressure reacts much slower than the BIS. This can be seen clearly from the simulations (fig. 9). The different speed of the response between BIS and SBP was also seen in the study by Kazama et al. who found a k_{e0} of 0.12 1/min for SBP and 0.30 1/min for BIS in young patients.[3] As they used a direct sigmoid E_{max} model with one effect compartment, the estimates of k_{e0} for SBP can not be directly compared to our results. Figure 9 demonstrates that in case of a continuous propofol infusion, the effect on blood pressure occurs with a clear delay and remains much longer than the hypnotic effect.

There are some limitations of the present study. Regarding pharmacokinetics, a longer sampling after end of infusion would have presumably allowed to estimate V_3 with more precision, and with a more frequent sampling it may have been possible to estimate also the interindividual variability of the intercompartmental clearance CL_2. However, characterization of the pharmacokinetics was not the primary aim of this study. The pharmacokinetic model was used to estimate the plasma concentration at that time points when BIS and arterial blood pressure were measured. As these measurements lasted only about 240 min, the late elimination phase of the pharmacokinetics was not so important. For pharmacodynamic modeling we used the pharmacokinetic predictions based on the individual pharmacokinetic parameters, and these predictions showed a sufficient precision (fig. 3A). The down sampling of the BIS and arterial blood pressure measurements to one value per minute may introduce some kind of upper limit for the estimation of k_{e0} as very fast changes may be not detectable. However, although BIS values are provided by the Aspect monitor with one value per second, one has to keep in mind that the BIS is determined from signals with a length of at least 60 seconds.[27] For the slower reacting arterial blood pressure, the time

resolution of one value per minute should be even more sufficient. A further limitation of this explorative study was the relatively small and homogeneous population of 9 volunteers aged between 18 and 40 yrs. Particularly in elderly, the parameters of the pharmacodynamic model for arterial blood pressure may be altered, as it was already reported for SBP by Kazama et al.,[3] who found an increased sensitivity (expressed as smaller IC_{50}) and a delayed response (expressed as shorter k_{e0}) in elderly compared to young patients. It would therefore be worthwhile to analyze the propofol effect on arterial blood pressure with the presented models in a larger patient population including elderly.

In addition, any pharmacodymic model developed from infusion data may have some limitations when used for bolus administration. However, we did not use a slow continuous infusion but TCI which started with a bolus-like fast infusion, particularly as each step began with a “peak” in the plasma target concentration in order to rapidly achieve steady state effect site concentration (see fig. 1). Therefore, we think that the data obtained with our infusion regimen allow to build up a valid model.

In conclusion, we have investigated the effect of propofol on BIS and arterial blood pressure comparing different direct, indirect and counter-regulatory response models. We found that BIS was well modeled with the well-known sigmoid E_{max} model linked directly to an effect compartment, whereas the change SBP, DBP and MBP was best described by a sigmoid E_{max} model with two effect sites. This may reflect different pathways of blood pressure response to propofol. As the hemodynamic side effects of propofol are crucial in daily clinical practice, a pharmacodynamic model for these effects may be helpful for the design of drug delivery systems with multiple inputs and multiple outputs.[28,29]

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Tab. 1: Results of the pharmacokinetic modeling

Parameter	Estimate (%SE)	ω^2 (%SE)
CL_1 (L/min)	1.97 (14%)	0.039 (49%)
V_1 (L)	7.24 (17%)	0.18 (67%)
CL_2 (L/min)	1.67 (9%)	0 (*fixed)*
V_2 (L)	35.2 (15%)	0.065 (89%)
CL_3 (L/min)	0.85 (24%)	0.083 (65%)
V_3 (L)	264 (73%)	0 (*fixed)*
σ_1^2	0.013 (22%)	
σ_2^2	0.0009 (84%)	

CL_1=elimination clearance; CL_2, CL_3=intercompartmental clearances; V_1= volume of central compartment; V_2, V_3= volumes of peripheral compartments; ω^2=interindividual variance; σ_1^2=variance of the proportional residual error; σ_2^2=variance of the constant residual error.

Tab. 2: Results of the pharmacodynamic modeling of BIS

Parameter	Estimate (%SE)	ω^2 (%SE)
E_0	91.3 (2%)	0.002 (56%)
E_{max}	78.5 (8%)	0.033 (65%)
EC_{50} (µg/ml)	2.99 (11%)	0.091 (54%)
γ	2.35 (8%)	0.036 (67%)
k_{e0} (1/min)	0.25 (14%)	0.21 (54%)
σ^2	41.9 (4%)	

E_0=baseline value; E_{max}=maximum effect; EC_{50}= propofol effect site concentration for half-maximum effect; γ= Hill exponent; k_{e0}=transfer rate constant between central compartment and effect site compartment; ω^2=interindividual variance; σ^2=variance of the residual intraindividual error.

Tab. 3: Comparison of the goodness of fit for the different pharmacodynamic models of arterial blood pressure

		SBP		MBP		DBP	
Model	N_p	-2LL	BIC	-2LL	BIC	-2LL	BIC
Model 1	5+5+1	8974	8998	7850	7878	7542	7571
Model 2	9+9+1	8573	8615	7053	7099	7402	7448
Model 3	4+4+1	9114	9134	7949	7973	7727	7749
Model 4	5+5+1	9002	9026	7895	7924	7631	7660
Model 5	6+6+1	8968	8996	7630	7676	7478	7511
Model 6	10+10+1	8730	8776	7513	7564	7409	7459
Model 7	7 +7 +1	8640	8677	7705	7742	7418	7456
Model 8	8 +8 +1	8655	8697	7685	7727	7429	7471

SBP=systolic blood pressure; MBP=mean blood pressure; DBP=diastolic blood pressure; -2LL= -2*log likelihood; BIC= Bayes information criterion; N_p= total number of parameters, given as the number of model parameters+ the number of interindividual variances + the number of intraindividual variances.

Tab. 4: Results of the pharmacodynamic modeling of arterial blood pressure.

	SBP		MBP		DBP	
Parameter	Estimate (%SE)	ω^2	Estimate (%SE)	ω^2	Estimate (%SE)	ω^2
E_0 (mmHg)	139 (4%)	0.017	84.5 (4%)	0.016	58.8 (4%)	0.017
$E_{max,1}$ (mmHg)	39.1 (33%)	0.84	21.6 (32%)	0.66	19.5 (16%)	0.20
$EC_{50,1}$ (µg/ml)	1.81 (17%)	0.19	1.88 (18%)	0.18	2.2 (11%)	0.07
γ_1	8.07 (58%)	2.63	3.85 (64%)	2.82	14.8 (59%)	2.28
$k_{e0,1}$ (1/min)	0.033 (45%)	1.60	0.035 (47%)	1.49	0.047 (33%)	0.78
$E_{max,2}$ (mmHg)	44.3 (29%)	0.55	29.8 (22%)	0.34	9.4 (29%)	0.60
$EC_{50,2}$ (µg/ml)	1.66 (22%)	0.38	1.74 (20%)	0.29	0.79 (38%)	0.35
γ_2	3.33 (36%)	0.94	3.23 (39%)	1.21	2.02 (30%)	0.40
$k_{e0,2}$ (1/min)	0.052 (37%)	0.90	0.044 (33%)	0.72	0.019 (48%)	0.62
σ^2	44.6 (4%)	-	22.7 (4%)	-	19.0 (4%)	-
$MDPE_{ind}$ (mmHg)	-0.07		-0.32		-0.25	
$MDAPE_{ind}$ (mmHg)	3.50		2.65		2.45	
$MDPE_{pop}$ (mmHg)	-4.53		-1.78		1.20	
$MDAPE_{pop}$ (mmHg)	15.1		9.48		8.51	

Parameter estimates for the direct sigmoid response model with two effect sites (*model 2*). SBP=systolic blood pressure; MBP=mean blood pressure; DBP=diastolic blood pressure; E_0=baseline value; E_{max}=maximum effect; EC_{50}= propofol effect site concentration for half-maximum effect; γ= Hill exponent; k_{e0}=transfer rate constant between central compartment and effect site compartment; ω^2=interindividual variance; σ^2=variance of the residual

intraindividual error; $MDPE_{ind}$ = median prediction error of the individual estimates; $MDAPE_{ind}$ = median absolute prediction error of the individual estimates; $MDPE_{pop}$ = median prediction error of the population estimates; $MDAPE_{pop}$ = median absolute prediction error of the population estimates

Legends to figures

Fig. 1: Time courses of the targeted and measured propofol plasma concentrations in one volunteer.

Fig. 2: Time courses of the measured propofol plasma concentrations. Each line depicts the data of one volunteer.

Fig. 3: Measured propofol concentrations vs. the individual predictions (A) and the population predictions (B), as obtained with the final pharmacokinetic model. The solid line is the line of identity (measured = predicted).

Fig. 4: Time courses of the measured BIS values. Each line depicts the data of one volunteer.

Fig. 5: Measured BIS values vs. the individual predictions (A) and the population predictions (B), as obtained with the final pharmacodynamic model. The black line is the line of identity (measured = predicted). The blue line is a smoothing line through the data.

Fig. 6: Time courses of the measured mean arterial blood pressure (MBP). Each line depicts the data of one volunteer.

Fig. 7: Measured mean arterial blood pressure (MBP) vs. the individual predictions (A) and the population predictions (B), as obtained with the final pharmacodynamic model (i.e. a

sigmoid E_{max} model with two effect sites). The black line is the line of identity (measured = predicted). The blue line is a smoothing line through the data.

Fig. 8: Measured (grey points) and individual (blue line) and population predictions (red line) of mean arterial blood pressure (MBP) in three individual cases with best (A), typical (B) and worst (C) goodness of fit. MDPE = median prediction error.

Fig. 9: Simulated time course of arterial blood pressure (A) and BIS (B) for a propofol infusion consisting of a bolus dose of 1.5 mg/kg, followed immediately by 10 mg kg^{-1} h^{-1} for 10 min, 8 mg kg^{-1} h^{-1} for the next 10 min, and 6 mg kg^{-1} h^{-1} for the remaining 60 min. The simulations were based on the final pharmacokinetic/-dynamic models for the study population.

Fig.1

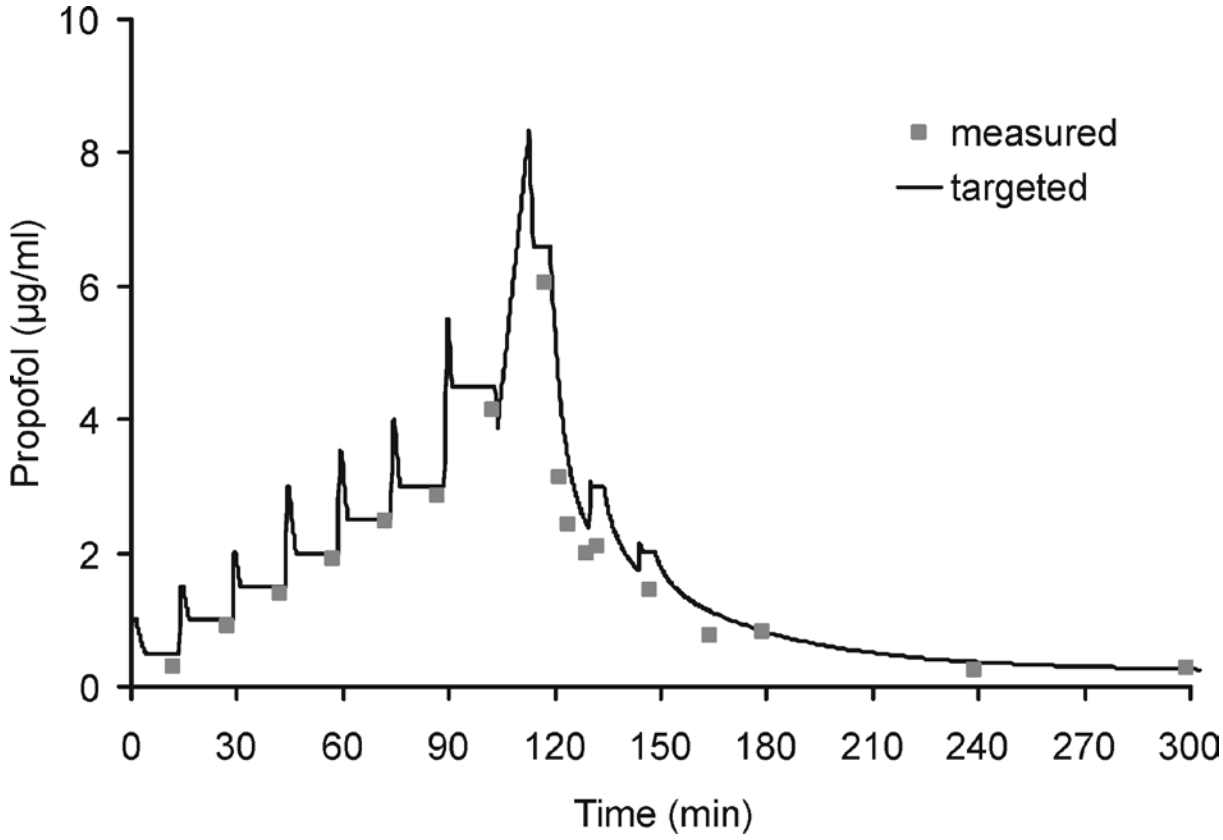

10
8
6
4
2
0
Propofol (µg/ml)
measured
targeted
0
30
60
90
120
150
180
210
240
270
300
Time (min)

Fig. 2

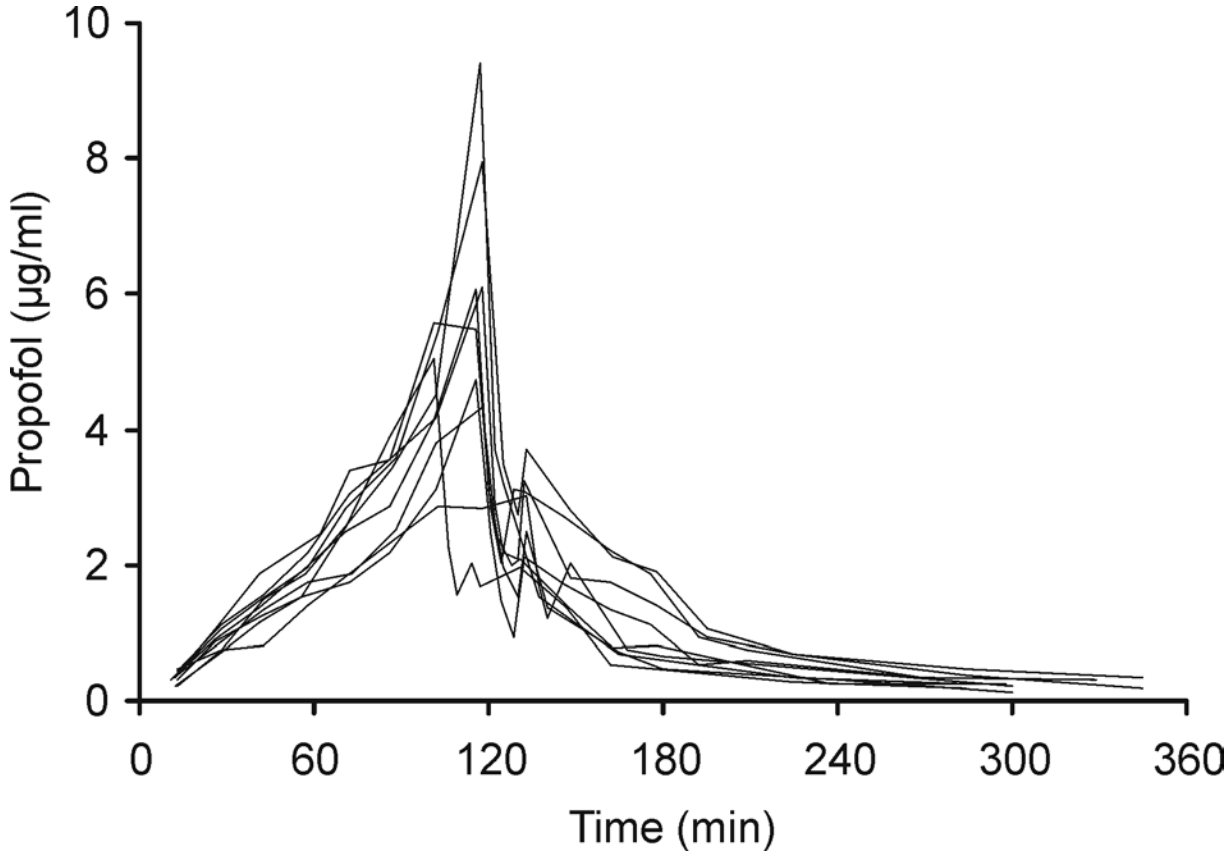


Fig. 3

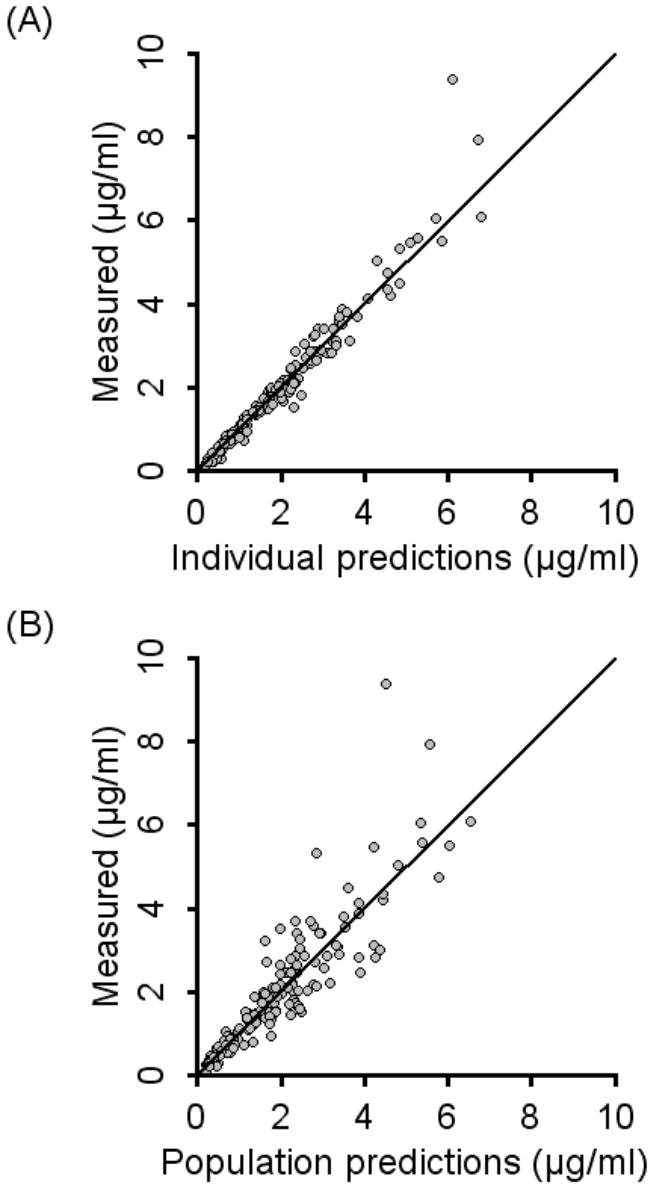

(A)
Measured (µg/ml)
0
2
4
6
8
10
Individual predictions (µg/ml)
(B)
Measured (µg/ml)
Population predictions (µg/ml)

Fig. 4

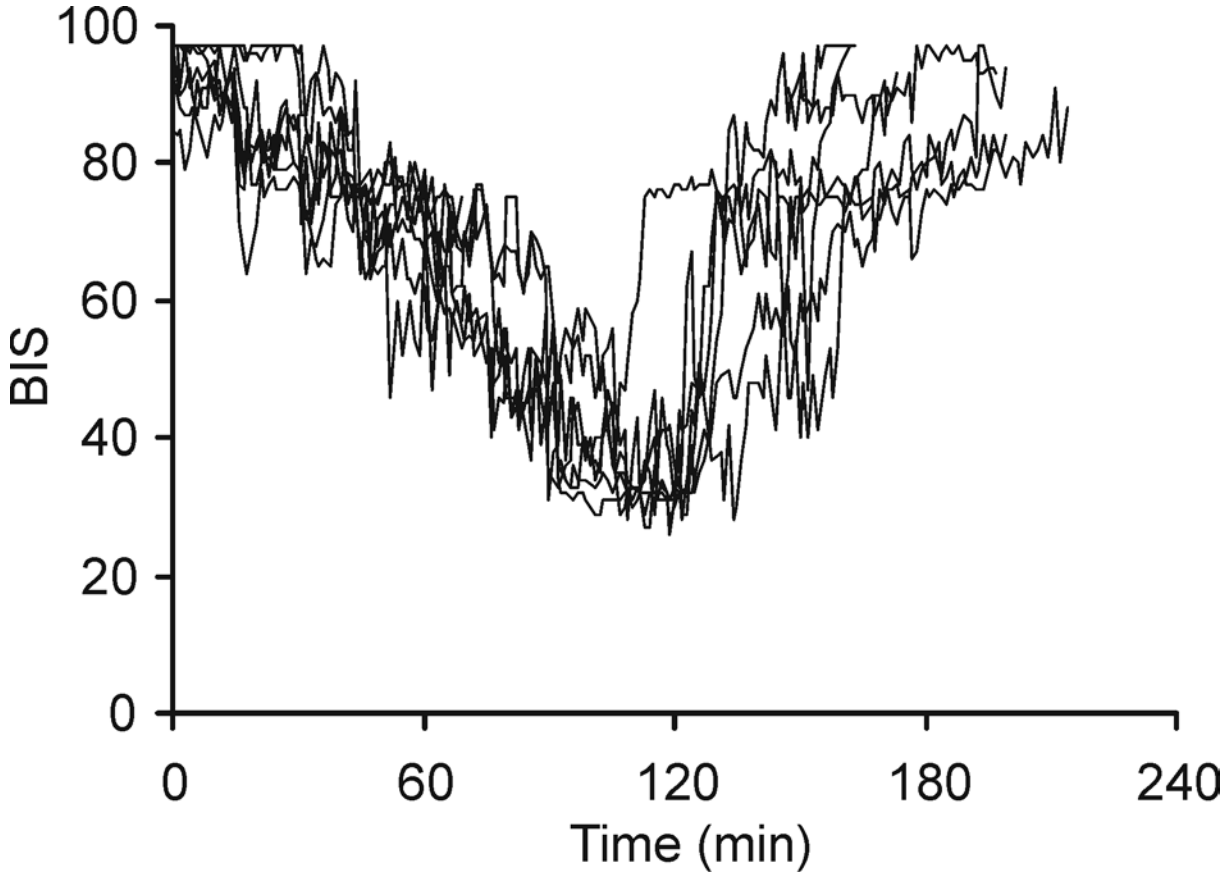


Fig. 5

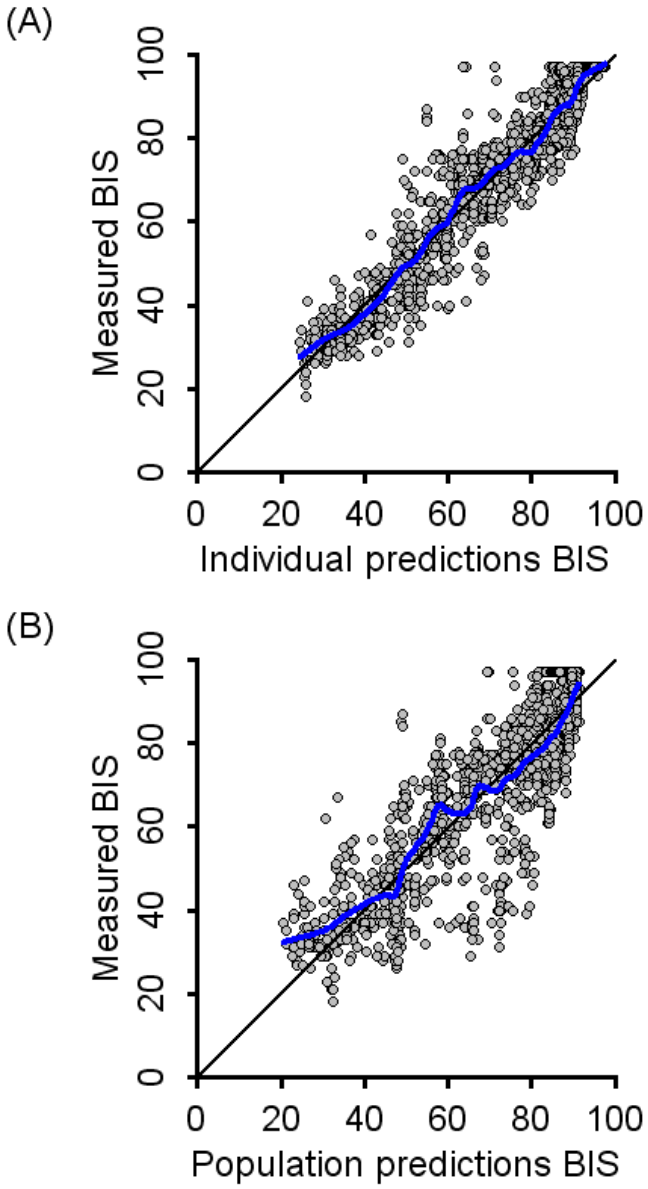

(A)
Measured BIS
0
20
40
60
80
100
Individual predictions BIS
(B)
Measured BIS
0
20
40
60
80
100
Population predictions BIS

Fig. 6

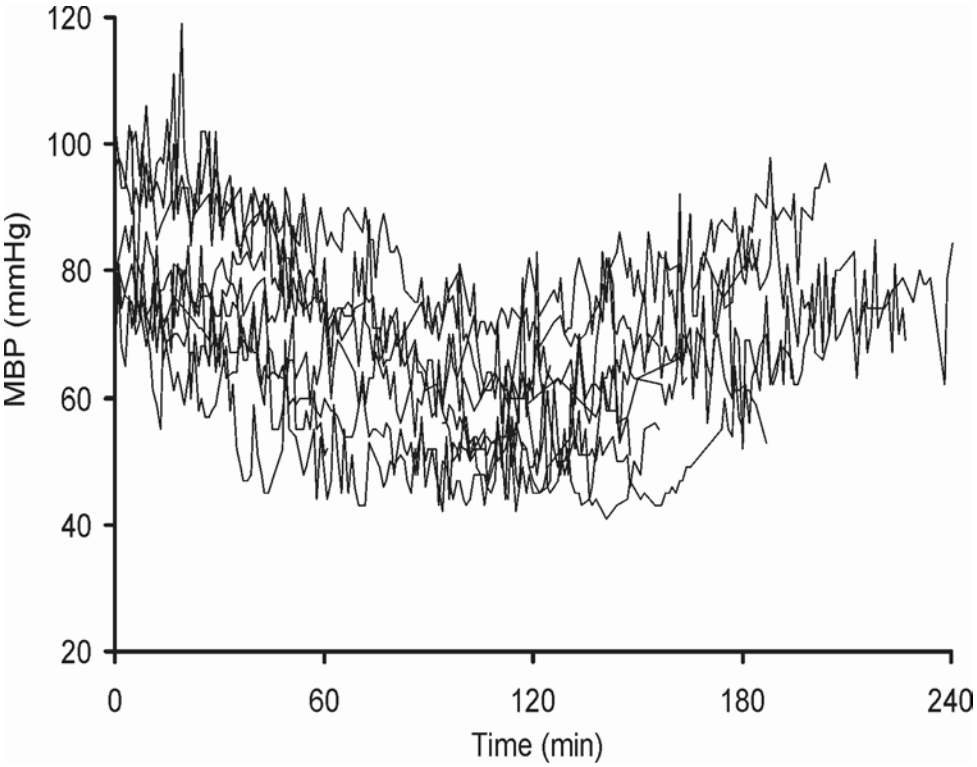


Fig. 7

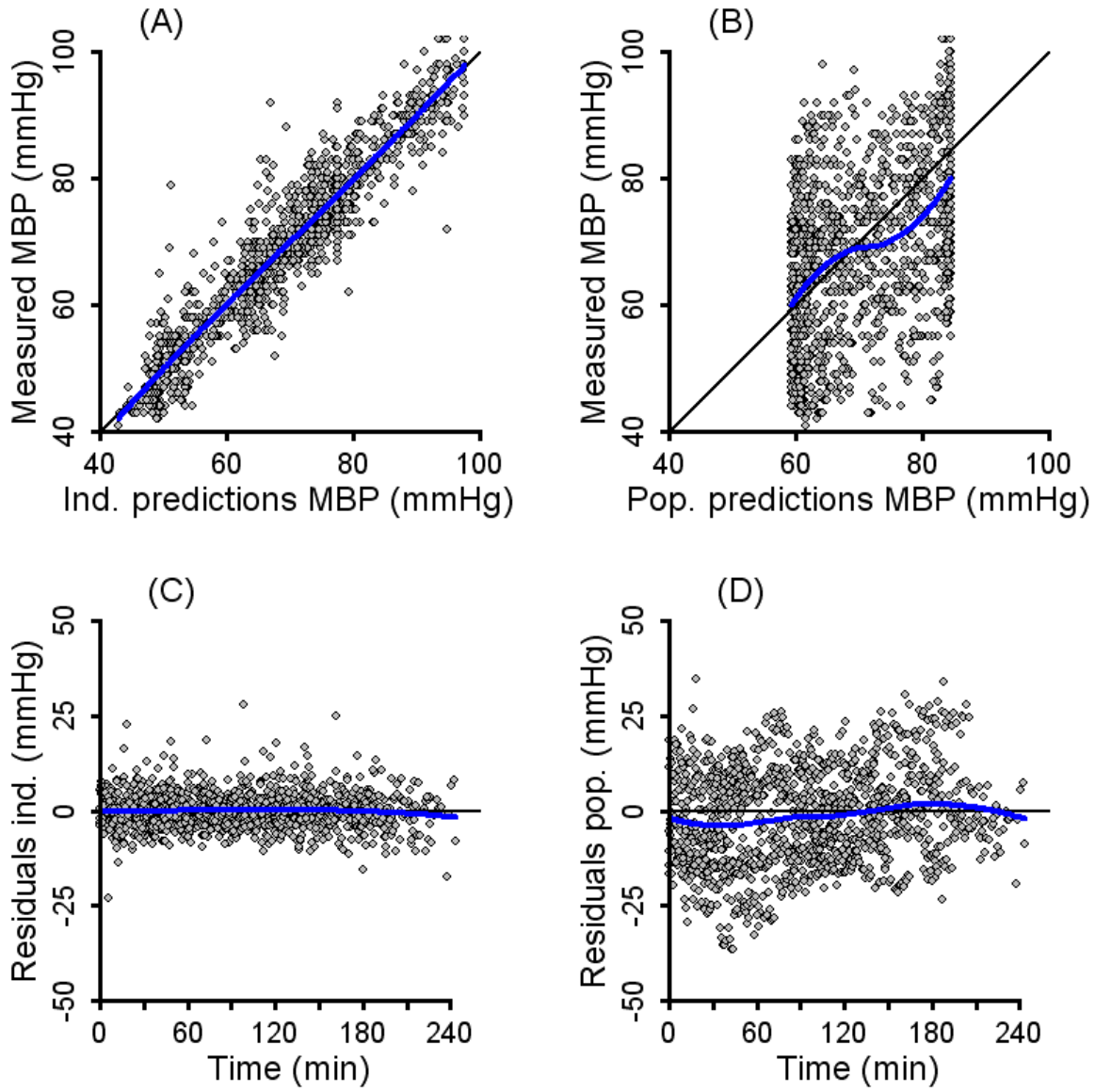

(A)
Measured MBP (mmHg)
40
60
80
100
Ind. predictions MBP (mmHg)
(B)
Measured MBP (mmHg)
Pop. predictions MBP (mmHg)
(C)
Residuals ind. (mmHg)
-50
-25
0
25
50
0
60
120
180
240
Time (min)
(D)
Residuals pop. (mmHg)
Time (min)

Fig. 8

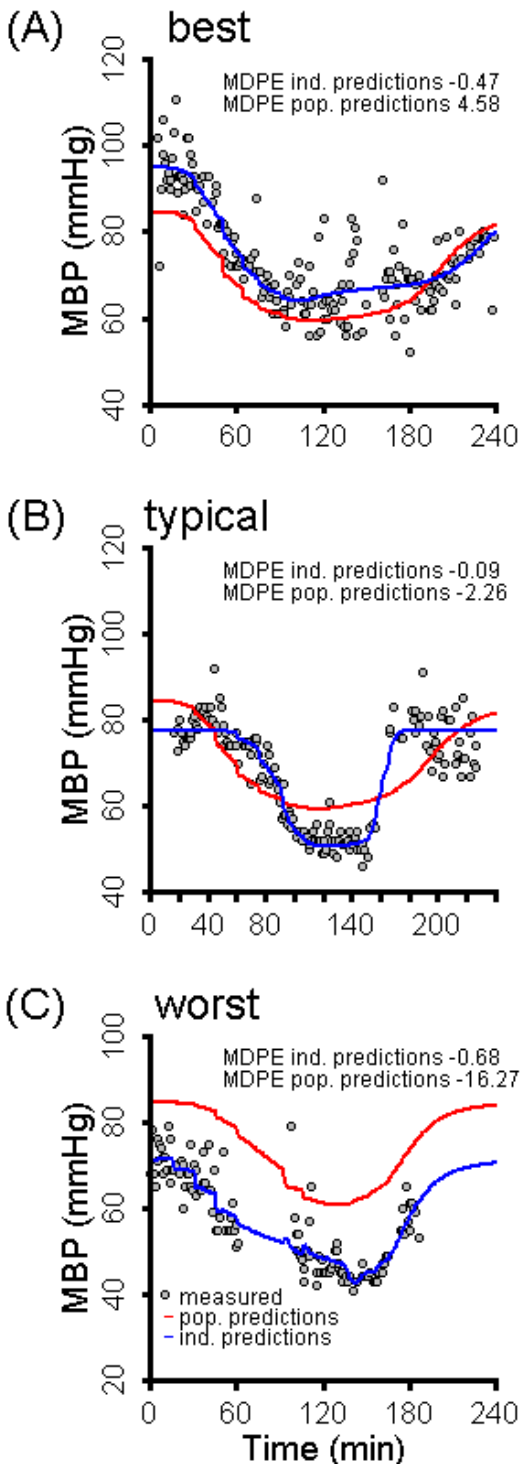
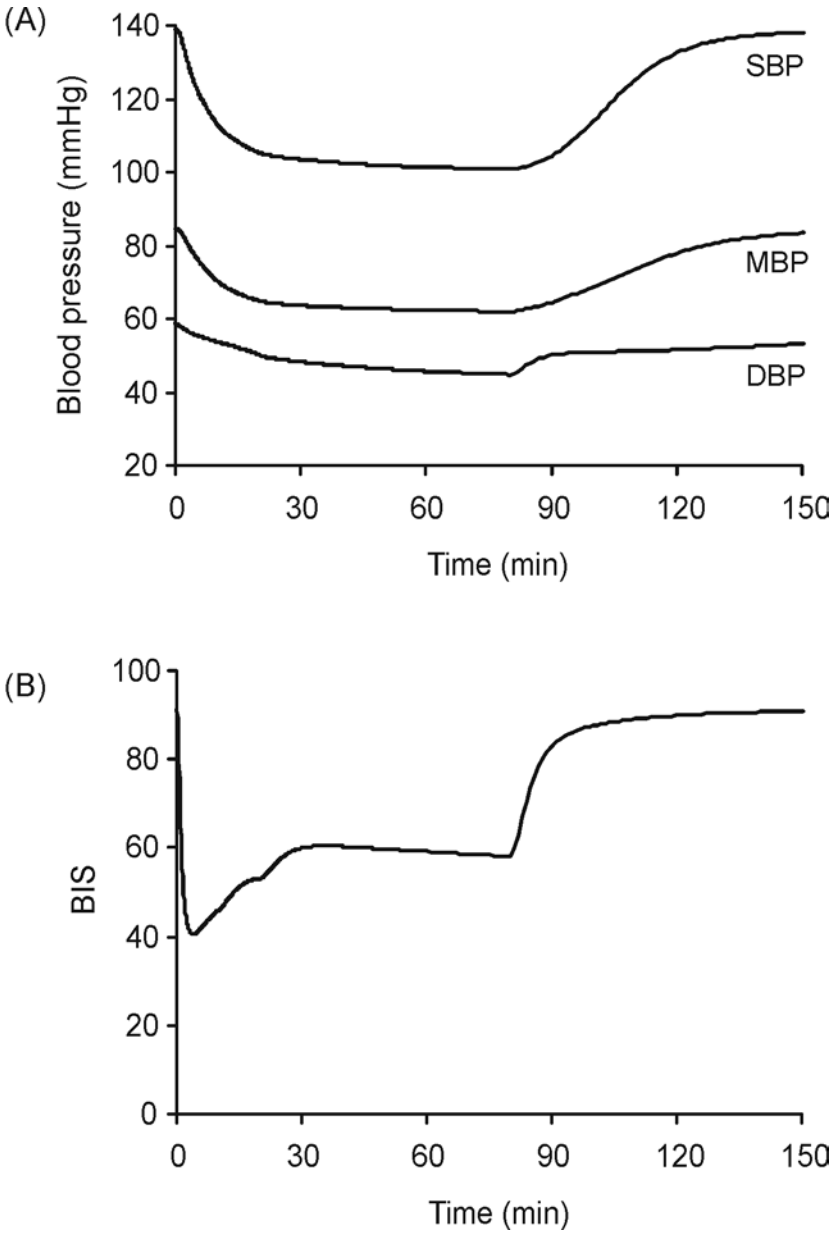

(A)
best
MDPE ind. predictions -0.47
MDPE pop. predictions 4.58
MBP (mmHg)
40
60
80
100
120
0
60
120
180
240
(B)
typical
MDPE ind. predictions -0.09
MDPE pop. predictions -2.26
MBP (mmHg)
40
60
80
100
120
0
40
80
140
200
(C)
worst
MDPE ind. predictions -0.68
MDPE pop. predictions -16.27
MBP (mmHg)
20
40
60
80
100
measured
pop. predictions
ind. predictions
0
60
120
180
240
Time (min)

Fig. 9


(A)
Blood pressure (mmHg)
140
120
100
80
60
40
20
SBP
MBP
DBP
0
30
60
90
120
150
Time (min)
(B)
BIS
100
80
60
40
20
0
0
30
60
90
120
150
Time (min)