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

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Editors’ key points
- Findings indicate a potential indirect pharmacodynamic response for propofol on haemodynamics rather than a direct response at the biophase.
- This study investigated the effects of propofol on systolic, diastolic and mean arterial blood pressure (SAP, DAP, MAP) by means of pharmacokinetic-/pharmacodynamic modelling.
- The time course of SAP, DAP and MAP was best fitted by models with two effect compartments with the direct response model.

Background. Concentration effect relationships are commonly described with a direct response model as for example the sigmoid $E_{\text{max}}$ model with one effect compartment as site of action. In this study we investigated whether models with more than one effect site, or indirect response, or counter-regulatory response models may be more appropriate for modelling the propofol effect on arterial blood pressure.

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. Arterial blood pressure was measured invasively at radial artery site. Pharmacokinetic-/pharmacodynamic modelling was performed by population analysis with MONOLIX, testing different direct, indirect and counter-regulatory response models.

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

Conclusions. Two effect sites were needed to describe the propofol effect on arterial blood pressure. This may reflect different pathways of arterial blood pressure response to propofol.

Keywords: arterial pressure; models; pharmacodynamics; propofol

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The haemodynamic effect of commonly used anaesthetics 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 modelled by linear or sigmoid $E_{\text{max}}$ 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 blood plasma and biophase. 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.

Previous studies regarding propofol induced changes in arterial blood pressure expressed the relationship between effect site concentration and drug effect by a sigmoid $E_{\text{max}}$ 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. It also has been shown that propofol reduces cardiac output and systemic vascular resistance, and therefore reduces arterial blood pressure. 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 modelling is nowadays considered as state of the art in population-based PKPD modelling. It provides estimates for inter- and intraindividual variability and limits the influence of outlying samples and individuals. The population-based analysis presented here was performed on invasive arterial blood pressure data recorded at the radial artery site during experimental propofol anaesthesia in volunteers.

Methods

We reanalysed arterial blood pressure data recorded at the radial artery site before, during and after target controlled...
infusion (TCI) of propofol in 9 healthy volunteers (5 female and 4 male) aged between 18 and 40 yrs, with a weight of 70 (10) kg and a height of 179 (9) cm (mean (standard deviation)). The data were part of a neurophysiologic and haemodynamic investigation performed in June 2006 at the Department of Anaesthesia, University Hospital Erlangen, after approval of the local Ethics Committee and written informed consent from participants, and were presented in part at the World Congress on Medical Physics and Biomedical Engineering 2009.\(^7\)

**Study design**

No premedication was given prior to the experiments. After overnight fasting, the volunteers came to the investigation room and lay quietly in supine position with the head of the bed raised to 45 degrees above the level. A cannula (BD Angiocath\(^\text{TM}\) 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 anaesthesia with 0.5–1 ml mepivacain 1%, an intra-arterial catheter (Leader Cath 20G, Vygon, Aachen, Germany) was inserted into the left arterial radialis for measuring arterial blood pressure and blood sampling. The catheter was connected to a transducer (xtransw, CODAN pvb Critical Care GmbH, Forstinning, Germany) by a low-volume, non-compliant length of tubing (CODAN pvb Critical Care GmbH) after careful de-airing. After inspection of the waveform quality (sharp upslope and downslope) the arterial signal was zero-referenced and the pressure dome was placed at the height of the breast position.

Invasive arterial blood pressure, heart rate, finger pulse oximetry, and ECG were monitored continuously throughout the study with a Siemens SC9000 monitor (Siemens, Erlangen, Germany). The volunteers remained breathing spontaneously throughout the trial. In case of a depressed spontaneous breathing or a decrease of arterial oxygen saturation measured by finger pulse oximetry (\(\text{SO}_2\)) below 97%, the volunteers received 4 litre min\(^{-1}\) oxygen via a face mask.

Blood pressure data were read from the analogue interface of the Siemens SC9000 monitor into the Task Force Monitor\(^\text{®}\) device (CNSystems Medizintechnik AG, Graz, Austria) and digitized with 100 samples per second. After skin preparation, EEG silver/silver chloride gel filled electrodes were placed to the left and right frontal regions and referenced to a central vertex electrode. Impedance was maintained at less than 3 k\(\Omega\), and the EEG was recorded and analysed continuously throughout the study using an A1000 EEG monitor (software version 3.12, Aspect Medical Systems, Natick, MA). Blood pressure and ECG measurements were stopped 10 min after the volunteer had regained consciousness. The study trial was ended after the last blood sample had been obtained.

**Propofol infusion**

Propofol was administered as TCI using the pharmacokinetic model of Marsh and colleagues\(^8\) to achieve predetermined increasing plasma concentrations of 0.5, 1, 1.5, 2, 2.5, 3 and 4.5 \(\mu\text{g ml}^{-1}\). Each target was maintained for 15 min. 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 \(\mu\text{g ml}^{-1}\), respectively. This higher initial target was maintained for 1 min, subsequently the target was reduced to the intended plasma concentration. After the last step of 4.5 \(\mu\text{g ml}^{-1}\) the propofol plasma target was further linearly increased by 0.5 \(\mu\text{g ml}^{-1}\) min\(^{-1}\), until one of the following endpoints was reached: EEG burst suppression patterns longer than 2 s, depressed spontaneous breathing with apnoea and need of assisted ventilation, or decrease 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 \(\mu\text{g ml}^{-1}\) and maintained for further 5 min. Subsequently the plasma target concentration was reduced to 3, 2.5, 2 and 1.5 \(\mu\text{g ml}^{-1}\), maintaining each target for 15 min. 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 \(\mu\text{g ml}^{-1}\), respectively. As soon as this concentration was reached, the target was increased to the intended plasma concentration. After the last step of 1.5 \(\mu\text{g ml}^{-1}\), 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 obtained 2, 5, 10 and 15 min after the end of the step with the highest target. Subsequently, one sample was again obtained at the end of each of the following target steps. After end of the last step with a target of 1.5 \(\mu\text{g ml}^{-1}\), further samples were obtained 15, 30, 90, and 150 min after stop of infusion. To determine the arterial propofol concentration, 2.5 ml blood were obtained per sample (S-Monovette\textsuperscript{TM} Kalium EDTA, Sarstedt, Nünnbrecht, Germany), after 1 ml blood had been obtained 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.\(^7\) 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.

**Data processing**

Episodes of blood sampling and moving artefacts were first identified by offline visual inspection of the digitized pulse pressure signal of the Task Force Monitor\(^\text{®}\) and the corresponding values of systolic, diastolic and mean arterial blood pressure (SAP, DAP and MAP, respectively) were discarded from further analysis. Previous work has shown that time periods of 1 min can be considered as short enough to obtain constant invasive estimates of arterial blood pressure and as long enough to be
representative for continuous measurements during general anaesthesia. Therefore, in order to reduce the computation time needed for modelling purposes, we decided to use a time grid with a resolution of 1 min and down-sampled the digitized data by picking one value of SAP, DAP and MAP per minute that was closest to the defined time point.

Pharmacokinetic/dynamic modelling

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 analysed first. The individual pharmacokinetic parameters obtained in this step were then used in the pharmacodynamic analysis.

Pharmacokinetic modelling

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 \( \omega^2 \). A combined proportional and additive model with means of zero and variances \( \sigma^2_1 \) and \( \sigma^2_2 \) was used to assess the intraindividual residual error. Population as well as individual pharmacokinetic parameters were obtained by population analysis using the software MONOLIX. Model selection was based on the value of \(-2 \times \text{log-likelihood}\) (see below: Model implementation and evaluation).

Pharmacodynamic modelling

In a second step, the effect of propofol on SAP, DAP and MAP was analysed. Three different types of pharmacodynamic models of increasing complexity were fitted to the data: direct response models, indirect response models, and counter-regulatory models.

Direct response models used a sigmoid \( E_{\text{max}} \) model with one or two effect compartments linked to the central compartment for the relationship between propofol concentration and arterial blood pressure:

\[
E = E_0 - E_{\text{max}} \cdot \frac{C}{C + \text{EC}_{50}} \cdot \frac{dC}{dt} = k_0 \cdot (C_p - C_E)
\]

where \( E_0 \) is the baseline value, \( E_{\text{max}} \) is the maximum reduction of arterial blood pressure from the baseline value, \( \text{EC}_{50} \) is the concentration for half-maximum effect, \( \gamma \) is the Hill exponent describing the steepness of the concentration effect curve and \( k_0 \) 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.

In the indirect response models, the rate of change in the effect variable \( E \) over time when no drug is present was expressed as following:

\[
\frac{dE}{dt} = k_{\text{in}} - k_{\text{out}} \cdot E
\]

where \( k_{\text{in}} \) and \( k_{\text{out}} \) are parameters describing generation and loss of arterial blood pressure response. At baseline, the system is assumed to be stationary with \( (dE/dt) = 0 \), and the baseline value of the effect variable is given as \( E_0 = (k_{\text{in}}/k_{\text{out}}) \).

We assumed that the response of arterial 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 \( k_{\text{in}} \):

\[
\frac{dE}{dt} = k_{\text{in}} \cdot I(t) - k_{\text{out}} \cdot E
\]

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 (e.g. baroreflex control). This approach has been tested previously for modelling the effect of ketamine on cardiac output and for the haemodynamic effect of nitroglycerin.

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

Model 1: a sigmoid \( E_{\text{max}} \) model with one effect compartment as stated above.

Model 2: a sigmoid \( E_{\text{max}} \) model with a central and a peripheral effect compartment, and the effect linked to the central effect compartment:

\[
E = E_0 - E_{\text{max}} \cdot \frac{C}{C + \text{EC}_{50}} \cdot \frac{C_{E}}{C_{E} + \text{EC}_{50}} . C_E = \frac{m_{E1}/V_{1}}{1 + \alpha} , C_p = \frac{m_{E2}/V_{1}}{1 + \alpha}
\]

\[
\frac{dm_{E1}}{dt} = k_{e0} \cdot (m_{1} - m_{E1}) - k_{e12} \cdot m_{E1} + k_{e21} \cdot m_{E2}
\]

\[
\frac{dm_{E2}}{dt} = k_{e12} \cdot m_{E1} - k_{e21} \cdot m_{E2}
\]

where the time constants \( k_{e12} \) and \( k_{e21} \) describe the transfer between the central and the peripheral effect site compartment.

Model 3: a sigmoid \( E_{\text{max}} \) model with two effect compartments and an interaction term:

\[
E = E_0 - E_{\text{max}} \cdot \frac{1}{1 + \left( \frac{C_{E1}}{\text{EC}_{50,1} + \text{EC}_{50,2}} + \alpha \cdot \frac{C_{E2}}{\text{EC}_{50,1} + \text{EC}_{50,2}} \right)^{\gamma}}
\]

\[
1 + \left( \frac{C_{E1}}{\text{EC}_{50,1} + \text{EC}_{50,2}} + \alpha \cdot \frac{C_{E2}}{\text{EC}_{50,1} + \text{EC}_{50,2}} \right)^{\gamma}
\]

\[
\gamma
\]
where the coefficient $\alpha$ defines the type of interaction between the effect compartments: $\alpha = 0$ means additive, $\alpha < 0$ means infra-additive and $\alpha > 0$ means supra-additive interaction.

Model 4: a sigmoid $E_{\text{max}}$ model with two effect compartments:

$$E = E_0 - E_{\text{max}} \cdot \left(\frac{C_{E.1}}{EC_{50.1}}\right)^{\gamma_1} + \left(\frac{C_{E.2}}{EC_{50.2}}\right)^{\gamma_2} \left(\frac{1}{1 + \left(\frac{C_{E.1}}{EC_{50.1}}\right)^{\gamma_1} + \left(\frac{C_{E.2}}{EC_{50.2}}\right)^{\gamma_2}}\right)$$

Model 5: a sigmoid $E_{\text{max}}$ model with two sequentially connected effects of different magnitude:

$$E = E_0 - E_{\text{max.1}} \cdot \left(\frac{C_{E.1}}{EC_{50.1}}\right)^{\gamma_1} - E_{\text{max.2}} \cdot \left(\frac{C_{E.2}}{EC_{50.2}}\right)^{\gamma_2} \left(\frac{1}{1 + \left(\frac{C_{E.1}}{EC_{50.1}}\right)^{\gamma_1} + \left(\frac{C_{E.2}}{EC_{50.2}}\right)^{\gamma_2}}\right)$$

with

$$\frac{dC_{e.1}}{dt} = k_{e0.1} \cdot (C_p - C_{E.1}), \quad \frac{dC_{e.2}}{dt} = k_{e0.2} \cdot (C_p - C_{E.2})$$

for models 2, 3 and 4.

Model 6: an indirect response model linked to propofol plasma concentration:

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

Model 7: a sigmoid indirect response model linked to propofol plasma concentration:

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

Model 8: a sigmoid indirect response model linked to an effect-site concentration:

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

Model 9: a sigmoid indirect response model with two effect sites:

$$I(t) = 1 - \frac{I_{\text{max}} \cdot \left(\frac{C_{E.1}}{IC_{50.1}}\right)^{\gamma_1} + \left(\frac{C_{E.2}}{IC_{50.2}}\right)^{\gamma_2}}{1 + \left(\frac{C_{E.1}}{IC_{50.1}}\right)^{\gamma_1} + \left(\frac{C_{E.2}}{IC_{50.2}}\right)^{\gamma_2}}$$

Model 10: a counter-regulatory model with two counteracting effects $E_A$ and $E_H$, which are connected by the time constant $k_{\text{off}}$:

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

$$E_A = \frac{C_E^g}{C_e + IC_{50}} \cdot \frac{dC_e}{dt} = k_{e0} \cdot (C_p - C_E), \quad \frac{dE_H}{dt} = k_{\text{off}} \cdot (E_A - E_H)$$

Model 11: a counter-regulatory model with two counteracting effects $E_A$ and $E_H$, which are connected by the time constants $k_1$ and $k_{\text{off}}$:

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

$$E_A = \frac{C_E^g}{C_e + IC_{50}} \cdot \frac{dC_e}{dt} = k_{e0} \cdot (C_p - C_E), \quad \frac{dE_H}{dt} = k_1 \cdot E_A - k_{\text{off}} \cdot E_H$$

$I_{\text{max}}$ is the maximum fractional ability of propofol to affect arterial 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 $k_{\text{eq}}$ between plasma and effect site.

In invasive arterial blood pressure measurements, DAP and SAP are usually measured at the beginning and the peak of the pulse pressure wave, respectively, whereas MAP is calculated from SAP and DAP by some formulae. In this study, each model was simultaneously fitted to SAP, MAP, and DAP data of the Task Force Monitor® device. In each iterative step, SAP and DAP values were predicted by the pharmacodynamic model and the model predictions of MAP were calculated by $MAP = DAP + (SAP - DAP)/3$. In order to avoid physiologically inconsistent predictions (e.g. SAP < DAP), we assumed that the pharmacodynamic parameters $EC_{50}, \gamma$ and $k_{\text{eq}}$ were identical for both SAP and DAP, whereas $E_0$ and $E_{\text{max}}$ of SAP and DAP were different. The interindividual variability of the PD parameters was estimated using log-normal distributions with mean zero and variance $\sigma^2$. An additive model with mean of zero and variance $\sigma^2$ was used to model the residual error.

For testing covariate effects, age and body weight were incorporated into the basic structural model by the following log-linear relationship:

$$\ln(\phi_{mi}) = \ln(\mu_m) + b_{\text{cov.m}} \times \text{cov}_i$$

where $\phi_{mi}$ is the $m$ pharmacodynamic parameter in individual $i$, $\mu_m$ is the corresponding pharmacodynamic parameter in the population, $b_{\text{cov.m}}$ is the covariate coefficient for the $m$ pharmacodynamic parameter and $\text{cov}_i$ is the covariate in individual $i$. The covariate was included into the model, if the 95% confidence interval of the covariate coefficient did not include zero.
Simulations
In order to illustrate the findings for clinical interpretation, we performed simulations with the final pharmacokinetic and pharmacodynamic models, predicting the time courses of SAP, MAP and DAP for a propofol infusion scheme as suggested by Roberts and colleagues, consisting of a bolus dose of 1.5 mg kg\(^{-1}\), 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 modelling 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 order (FO) or first order conditional estimates (FOCE) approach, which are commonly used for population analysis. All pharmacokinetic and pharmacodynamic models were expressed in the form of differential equations and implemented in MLXTRAN. The likelihood ratio test was used to compare nested models using the difference in the \(-2\times\log\text{-likelihood (A} - \text{2LL)}\) at a significance level of \(P<0.05\). For non-nested models, the model selection was based on the Bayesian information criterion \(\text{BIC} = -2\times\text{LL} + \text{Ln}(N_s)\times N_p\) where \(N_s\) is the number of subjects and \(N_p\) is the number of model parameters. The best model was selected as that one with the smallest value of BIC.

Statistics
Goodness of fit was evaluated by visual inspection of the diagnostic plots and the median prediction error. Diagnostic plots were plots of measured divided by or vs individual and population predictions, as well as individual weighted residuals (IWRES) and population weighted residuals (PWRES) vs time. For both individual and population predictions of the pharmacokinetic models as well as for the predictions by the Marsh model, the median prediction error and the median absolute prediction error were calculated as \(\text{MDPE} = \text{median}(\text{MEASURED-CPREDICTED})/\text{CPREDICTED}\) and \(\text{MDAPE} = \text{median}(\text{MEASURED-CPREDICTED})/\text{CPREDICTED}\). For arterial blood pressure, the MDPE was defined as \(\text{MDPE} = \text{median}(\text{MEASURED-EPREDICTED})/\text{EPREDICTED}\) and the MDAPE was defined as \(\text{MDAPE} = \text{median}(\text{MEASURED-EPREDICTED})/\text{EPREDICTED}\) with \(E=\{\text{SAP, MAP, DAP}\}). The final pharmacodynamic model was internally validated by visual predictive checks with 1000 simulated data sets and by the cross-validation technique. For this purpose we split the data into five different estimation sets and five different test sets. Each estimation set consisted of data from seven volunteers, the corresponding test set contained the data from the remaining two volunteers, except for the last test set, which contained the data from one volunteer. The final pharmacodynamic model was fitted to each of the estimation data sets and then the parameter estimates were used to predict the SAP, DAP and MAP values for each test set. The results obtained from the estimation and test sets were treated as independent estimates of model parameters and prediction errors and pooled. Statistical analysis and graphical representation were performed with R 2.12.2 (The R Foundation for Statistical Computing). 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 target peak concentration when one of the defined endpoints was reached was 7.2 (1.1) \(\mu\)g ml\(^{-1}\), and the target concentration of the following plateau was 5.9 (0.6) \(\mu\)g ml\(^{-1}\). The measured propofol plasma concentration increased up to 5.8 (1.9) \(\mu\)g ml\(^{-1}\) (Fig. 1A). The target peak concentration was limited in all volunteers by achieving the clinical endpoint of EEG burst suppression patterns longer than 2 s. No volunteer developed a clinical relevant depression of spontaneous breathing with apnoea and need of assisted ventilation, two volunteers developed snoring periods near target peak concentrations. The volunteers received oxygen supply via face mask at 2.9 (0.9) \(\mu\)g ml\(^{-1}\). The Marsh model overpredicted the measured propofol concentrations with MDPE = −12.3% and MDAPE = 23.0%.

Pharmacokinetic modelling
The propofol concentration time courses were best described with a three-compartment model, which was significantly better than a two-compartment model (\(\Delta -2\times\text{LL} = -39, P<0.001\)). Figure 2 shows the ratio of measured to predicted propofol concentrations for individual and population model predictions. 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 modelling. The interindividual variances of \(V_2\) and \(V_3\) showed very small estimates with large standard errors and were therefore fixed to zero.

Pharmacodynamic modelling of arterial blood pressure
SAP, DAP, and MAP dropped from baseline values of 140 (25), 58 (11) and 82 (14) mm Hg, respectively to minimum values of 77 (10), 32 (8) and 49 (9) mm Hg, respectively (Fig. 1E–F). Age showed a significant effect on base line estimates of SAP and DAP in each model \(P=0.0057\) and \(P=0.033\), respectively. Table 2 shows the goodness of fit values for the various tested direct response, indirect response and counter-regulatory models with \(\text{Ln}(E_0)\) linearly scaled on age. Within the direct response models, model 4 with two parallel effect site compartments performed better than model 1 with one effect compartment, and also better than model 2 with a peripheral effect site compartment. Assuming two sequentially connected effects of different magnitude in model 5 did not improve the goodness of fit. The interaction coefficient \(\alpha\) of model 3 was −0.7, indicating
an infra-additive interaction between the effect compartments. However, model 3 performed not better than model 4 or 5. Within indirect response models, model 9 with two effect site compartments linked to a sigmoid inhibitory function showed more reduction in BIC than model 6 with one effect site compartment linked to a simple inhibitory function. However, the BIC value of model 9 was higher than the BIC value of the direct response model 4 with two effect site compartments. For the two counter-regulatory models, the BIC value of model 10 was higher than the BIC values of the direct response model 4 and the indirect response model 9. Introducing different time delays between the counteracting effect sites in model 11 did not improve the goodness of fit.

Therefore, the direct response model 4 with two effect site compartments and age as covariate was chosen as the final pharmacodynamic model:

\[
SAP = SAP_0 - E_{\max}SAP \cdot \frac{C_E 1 \cdot (EC_{50.1})^{\gamma_1} + C_E 2 \cdot (EC_{50.2})^{\gamma_2}}{1 + (C_E 1 \cdot (EC_{50.1})^{\gamma_1} + C_E 2 \cdot (EC_{50.2})^{\gamma_2})}
\]

\[
DAP = DAP_0 - E_{\max}DAP \cdot \frac{C_E 1 \cdot (EC_{50.1})^{\gamma_1} + C_E 2 \cdot (EC_{50.2})^{\gamma_2}}{1 + (C_E 1 \cdot (EC_{50.1})^{\gamma_1} + C_E 2 \cdot (EC_{50.2})^{\gamma_2})}
\]

\[
MAP = DAP + \frac{SAP - DAP}{3}
\]

with

\[
\text{Ln}(SAP_0) = \text{Ln}(E_0SAP) + \beta_{ageSAP} \cdot \text{age}
\]

and

\[
\text{Ln}(DAP_0) = \text{Ln}(E_0DAP) + \beta_{ageDAP} \cdot \text{age}
\]

The parameter estimates and the prediction errors obtained for this final model are summarized in Tables 3 and 4. The quality of fit for this model was reasonable with median prediction errors within 5 mm Hg (Table 4) and randomly distributed.
population weighted residuals around zero line (Fig. 3). The amount of unexplained variability was only 7.9 mm Hg, 5.2 mm Hg and 4.6 mm Hg for SAP, MAP and DAP, respectively, which represent 7, 7.1 and 7.7% of the range of SAP (66 to 179 mm Hg), MAP (41 to 106) and DAP (26 to 86), respectively. The visual predictive check revealed a good agreement between the population predictions (median and 90% confidence interval) and the measured values (Fig. 4). Figure 5 illustrates the relationship between the effect site concentration of propofol in the two effect compartments and the decrease in blood pressure. Figure 6 shows the simulated time courses of plasma and effect site concentrations of propofol, and the resulting time courses of SAP, MAP and DAP as obtained with the final model during 80 min propofol infusion according to the Roberts infusion scheme.

Discussion

It was the aim of this study to characterize the effects of propofol on arterial blood pressure by means of pharmacokinetic-pharmacodynamic modelling. Concentration-effect relationships are commonly described with a direct response model as for example the sigmoid $E_{\text{max}}$ model with one 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 haemoglobin, can be derived from drug-receptor kinetics.

Whereas this concept seems reasonable for the hypnotic effect of propofol, which is assumed to be mediated by interaction with the GABA receptor, 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. In addition, it does not consider the physiologic interaction between

![Diagram](https://via.placeholder.com/150)

**Fig 2** Time course of measured divided by predicted plasma concentrations of propofol for individual (a) and population (a) model predictions. Each blue line depicts the data of one volunteer.

**Table 1** Results of the pharmacokinetic modelling. $CL_1$, elimination clearance; $CL_2$, $CL_3$, intercompartmental clearances; $V_1$, volume of central compartment; $V_2$, $V_3$, volumes of peripheral compartments; $\sigma_1^2$, interindividual variance; $\sigma_2$, variance of the proportional residual error; $\sigma_3$, variance of the constant residual error

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (%SE)</th>
<th>$\sigma_1^2$ (%SE)</th>
<th>$\sigma_2$ (%SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$CL_1$ (litre min$^{-1}$)</td>
<td>1.97 (14)</td>
<td>0.039 (49)</td>
<td></td>
</tr>
<tr>
<td>$V_1$ (litre)</td>
<td>7.24 (17)</td>
<td>0.18 (67)</td>
<td></td>
</tr>
<tr>
<td>$CL_2$ (litre min$^{-1}$)</td>
<td>1.67 (9)</td>
<td>0 (fixed)</td>
<td></td>
</tr>
<tr>
<td>$V_2$ (litre)</td>
<td>35.2 (15)</td>
<td>0.065 (89)</td>
<td></td>
</tr>
<tr>
<td>$CL_3$ (litre min$^{-1}$)</td>
<td>0.85 (24)</td>
<td>0.083 (65)</td>
<td></td>
</tr>
<tr>
<td>$V_3$ (litre)</td>
<td>264 (73)</td>
<td>0 (fixed)</td>
<td></td>
</tr>
<tr>
<td>$\sigma_1^2$</td>
<td>0.013 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma_2$</td>
<td>0.0009 (84)</td>
<td></td>
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</tbody>
</table>

**Table 2** Comparison of the goodness of fit for the different pharmacodynamic models of arterial blood pressure. $-2\log$ likelihood; BIC, Bayes information criterion; $N_p$, total number of parameters, given as the number of model parameters + number of covariate parameters + the number of interindividual variances + the number of intraindividual variances
cardiac output and peripheral resistance determined by major cardiovascular reflexes. Therefore, models with more than one effect site may be more plausible for the propofol 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 $E_{\text{max}}$ model with a Hill exponent $\gamma = 1$. In this study we tested also inhibition functions with a sigmoid $E_{\text{max}}$ 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 by major cardiovascular reflexes such as baroreflex control. Therefore, we additionally tested counter-regulatory models of increasing complexity.

Pharmacokinetic/dynamic modelling 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 with 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.

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.

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 arterial blood pressure 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. In the model by Marsh and colleagues 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 $C_{L1} = 1.83$ litre min$^{-1}$, $V_1 = 15.4$ L, $C_{L2} = 1.72$ litre min$^{-1}$, $V_2 = 31.4$ L, $C_{L3} = 0.65$ litre min$^{-1}$ and $V_3 = 196$ L. In the propofol model published by Schnider and colleagues the corresponding parameters were $1.74$ litre min$^{-1}$, $4.3$ L, $1.96$ litre min$^{-1}$, $29.8$ L, $0.84$ litre min$^{-1}$ 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 blood sampling. The fact that $V_1$ was estimated with a large standard error may be mainly explained by the relative short post infusion sampling in our study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>$\omega^2$</th>
<th>CV Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{0,\text{SAP}}$ (mm Hg)</td>
<td>101 (13)</td>
<td>0.00979</td>
<td>102 (5)</td>
</tr>
<tr>
<td>$\beta_{\text{age, SAP}}$</td>
<td>0.0132 (36)</td>
<td>–</td>
<td>0.0131 (12)</td>
</tr>
<tr>
<td>$E_{\text{max,SAP}}$ (mm Hg)</td>
<td>54.8 (10)</td>
<td>0.0871</td>
<td>57.3 (5)</td>
</tr>
<tr>
<td>$E_{0,\text{DAP}}$ (mm Hg)</td>
<td>44.3 (14)</td>
<td>0.0121</td>
<td>44.9 (5)</td>
</tr>
<tr>
<td>$\beta_{\text{age, DAP}}$</td>
<td>0.0113 (47)</td>
<td>–</td>
<td>0.0113 (13)</td>
</tr>
<tr>
<td>$E_{\text{max,DAP}}$ (mm Hg)</td>
<td>18.1 (16)</td>
<td>0.207</td>
<td>18.9 (5)</td>
</tr>
<tr>
<td>$E_{E_{50,1}}$ ($\mu$g·ml$^{-1}$)</td>
<td>1.96 (16)</td>
<td>0.165</td>
<td>2.04 (5)</td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>4.77 (73)</td>
<td>4.15</td>
<td>5.59 (15)</td>
</tr>
<tr>
<td>$k_{0,1}$ (min$^{-1}$)</td>
<td>0.0540 (44)</td>
<td>1.50</td>
<td>0.0528 (11)</td>
</tr>
<tr>
<td>$E_{E_{50,2}}$ ($\mu$g·ml$^{-1}$)</td>
<td>2.20 (14)</td>
<td>0.148</td>
<td>2.04 (4)</td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>8.49 (78)</td>
<td>5.13</td>
<td>6.33 (9)</td>
</tr>
<tr>
<td>$k_{0,2}$ (min$^{-1}$)</td>
<td>0.0695 (43)</td>
<td>1.48</td>
<td>0.0607 (14)</td>
</tr>
<tr>
<td>$\sigma_{\text{SAP}}$</td>
<td>7.88 (2)</td>
<td>–</td>
<td>7.87 (4)</td>
</tr>
<tr>
<td>$\sigma_{\text{MAP}}$</td>
<td>5.21 (2)</td>
<td>–</td>
<td>5.20 (1)</td>
</tr>
<tr>
<td>$\sigma_{\text{DAP}}$</td>
<td>4.64 (2)</td>
<td>–</td>
<td>4.64 (1)</td>
</tr>
</tbody>
</table>

Table 3 Pharmacodynamic parameters of the final pharmacodynamic model: sigmoid $E_{\text{max}}$ model with two effect compartments and age as covariate. $E_{0,\text{SAP}}$, baseline effect for systolic arterial blood pressure; $\beta_{\text{age, SAP}}$, coefficient for age effect on the baseline of systolic arterial blood pressure; $E_{\text{max,SAP}}$, maximum reduction from baseline systolic arterial blood pressure; $E_{0,\text{DAP}}$, baseline effect for diastolic arterial blood pressure; $\beta_{\text{age, DAP}}$, coefficient for age effect on the baseline of diastolic arterial blood pressure; $E_{\text{max,DAP}}$, maximum reduction from baseline diastolic arterial blood pressure; $E_{E_{50,1}}$, propofol effect site concentration for half-maximum effect in the first and second effect compartment; $\gamma_1$, Hill exponent for the first and second effect compartment; $k_{0,1}$, transfer rate constant between central compartment and effect site for the first and second effect compartment; $\omega^2$, interindividual variance; $\sigma$, standard deviation of the residual intraindividual error; CV, cross validation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>$\omega^2$</th>
<th>CV Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDPEind (mm Hg)</td>
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<td>–</td>
<td>1</td>
</tr>
<tr>
<td>MDPEind (mm Hg)</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>MDPEind (mm Hg)</td>
<td>2</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>MDPEind (mm Hg)</td>
<td>12</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>CV MDPEind (mm Hg)</td>
<td>–4</td>
<td>–3</td>
<td>3</td>
</tr>
<tr>
<td>CV MDPEind (mm Hg)</td>
<td>17</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 4 Predictions errors of the final pharmacodynamic model of arterial blood pressure. MDPEind, median prediction error of the individual estimates; MDPEind, median absolute prediction error of the individual estimates; MDPEind, median prediction error of the population estimates; MDPEind, median absolute prediction error of the population estimates; CV, cross validation.
Pharmacodynamics: SAP, DAP and MAP

Previous studies have shown that 99% of the variability of MAP can be explained by the combined influence of SAP and DAP, thus establishing a link between the steady and pulsatile component of arterial blood pressure by estimating MAP from SAP and DAP. In peripheral systemic arteries, MAP is usually estimated by adding one-third pulse pressure to DAP. Therefore, we fitted each pharmacodynamic model simultaneously to SAP, MAP and DAP data by determining the objective function with SAP and DAP model predictions and MAP estimations given the formula above. This concept takes into consideration independent changes in cardiac output and peripheral resistance and captures their simultaneous impact on MAP in each pulse pressure wave. Moreover, it may reasonably predict MAP from both invasive and noninvasive SAP and DAP measurements.

The time course of SAP, DAP and MAP was best fitted by models with two effect compartments with the direct response model being superior to the other response models. The selected model shows a small amount of unexplained variability of the data and a reasonable description of the time structure of propofol induced changes in arterial blood pressure. All parameters were estimated with reasonable precision, as indicated by the standard errors. Whereas the predictions with the individual posthoc parameters fit the data quite

![Fig 3 Goodness-of-fit plots: measured arterial blood pressure vs the individual Bayesian (A, D and G) and the population predictions (B, E and H), and the population-weighted residuals vs time after start of the infusion of propofol at time zero (C, F and I) as obtained with the final pharmacodynamic model (direct response model 4 with two effect compartments). The solid black diagonal line represents the line of identity (measured = predicted). PWRES, population-weighted residuals.](http://bja.oxfordjournals.org/)

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well, indicating that there is no general model misspecification, the predictions with the typical population parameters showed a greater deviation from the individual measured arterial blood pressure, because of the large interindividual variability of the pharmacodynamic parameters. However, the observed prediction errors of the population predictions lower than 5 mm Hg can be considered as clinically acceptable disagreement. Moreover, the estimates of pharmacodynamic...
parameters (Table 3) and the prediction errors (Table 4) obtained by cross-validation showed no relevant differences to the results of the main analysis, indicating a reasonable validity of the final pharmacodynamic model.

We found that two effect site compartments were necessary both in the direct response model (model 4) and also in the indirect response model (model 9). A model that assumed a second effect site compartment which was however not linked to the effect but served only as peripheral compartment (model 2) was inferior, whereas it has been used successfully for modelling the propofol effect on the bispectral index of the EEG.12 This may indicate that in contrast to the sedative/hypnotic effect the propofol effect on arterial blood pressure is mediated by two pathways. If one considers that the change of arterial blood pressure under propofol administration is a result of changes in cardiac output and systemic vascular resistance,4 the need of two effect sites seems to be reasonable. Differences between the effect compartments regarding propofol sensitivity, rate of change and equilibration time between central and effect compartment (as depicted in Fig. 6A) may not only be explained by the individual physiological status of the heart and the peripheral arterial vascular system, but also may reflect the impact of major cardiovascular reflexes on cardiac output and peripheral resistance.23 One possible clinical interpretation of the two effect compartments of the pharmacodynamic model may be that the first effect compartment reflects...
changes in peripheral vascular resistance, which may be more sensitive to propofol (i.e. $EC_{50,1}$ lower than $EC_{50,2}$) than changes in cardiac output reflected by the second effect compartment that shows a faster equilibration with the central compartment (i.e. $k_{e0,2}$ higher than $k_{e0,1}$) and a steeper rate of response to changes of effect site concentration of propofol (i.e. $\gamma_2$ higher than $\gamma_1$). These changes simultaneously modulate the magnitude and time course of arterial blood pressure (Fig. 6a).

In the literature on indirect response models, an inhibitory function is typically linked to the plasma concentration using a simple $E_{\text{max}}$ model (as in model 6 in our study). This model was not able to adequately describe the propofol induced changes in arterial blood pressure. A significant improvement of the quality of fit was first obtained by linking a sigmoid inhibitory function not to the plasma but to the effect site concentrations of two effect compartments (model 9). However, this model did not perform better than the direct response model with two effect compartments (model 4).

Interestingly, the counter-regulatory models 10 and 11 showed a poorer fit performance than direct or indirect response models with two effect compartments. A possible explanation for this finding may be that the counter-regulatory effect exerted by major cardiovascular reflexes may better be reflected by the differences in pharmacodynamic parameters between the two effect compartments of the models 4 and 9.

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 arterial blood pressure was measured. As these measurements lasted only about 240 min, the late elimination phase of the pharmacokinetics was
not so important. For pharmacodynamic modelling we used the pharmacokinetic predictions based on the individual pharmacokinetic parameters, and these predictions showed a high precision (MDPE = 0.6%, MDAPE = 7.5%).

The down sampling of arterial blood pressure measurements to one value per minute may introduce some type of upper limit for the estimation of $k_{e0}$ as very fast changes may not be detectable. For the slower reacting arterial blood pressure when compared with other effect variables such as processed EEG, the time resolution of one value per minute should be sufficient. Besides, the selected time resolution also fitted reasonably the tradeoff between number of measurements, model complexity and computation time for robust model development.

Previous studies in healthy volunteers have shown that acute hypercapnia induced by breathing a mixture of CO2 and medical air to attain an end-tidal CO2 of 7 kPa (53 mm Hg) for 30 min may not directly alter the myocardial contractility or relaxation and the systemic vascular resistance. However, the investigators reported an increase in respiration rate of 8 breaths per minute and in DAP and SAP of 5 and 10 mm Hg, respectively. Unfortunately, the end-tidal carbon dioxide tension was not monitored in our study. Therefore, a possible increase in arterial carbon dioxide partial pressure may have influenced the decrease in arterial blood pressure at propofol peak concentrations.

Age had a significant impact on the estimates of the baseline values of SAP and DAP. The observed increase of blood pressure with age has been reported previously. However, the relatively small population of 9 volunteers aged between 18 and 40 yrs may not be as representative as a larger patient population for this age group. Therefore, the baseline values of SAP and DAP found in this study may not be representative for a patient population aged between 18 to 40 yrs and should also not be extrapolated for other age groups. Additionally, the population size in our study may not have been sufficient to detect age influences on other pharmacodynamic parameters as reported by Kazama and colleagues for SAP, who found an increased sensitivity (expressed as smaller EC50) and a delayed response (expressed as shorter k_e0) in elderly compared with young patients. Further, the measured SAP and DAP were not uniformly distributed over all possible combinations of $C_{E,1}$ and $C_{E,2}$ (Fig. 5). This indicates that the pharmacodynamic model appropriately describes only the part of the effect concentration plane that contains the measured data, but not all possible combinations of $C_{E,1}$ and $C_{E,2}$. Therefore, the best pharmacodynamic model obtained with this investigation should be validated in larger patient populations including elderly.

In conclusion, we have investigated the effect of propofol on arterial blood pressure comparing different direct, indirect and counter-regulatory response models. We found that changes in SAP, DAP and MAP were best described by a sigmoid $E_{max}$ model with two effect site compartments. This may reflect different pathways of arterial blood pressure response to propofol. As the haemodynamic side effects of propofol are crucial in daily clinical practice, a pharmacodynamic model for these effects may be helpful not only for procedural sedation with propofol but also for the design of drug delivery systems with multiple inputs and multiple outputs.

Authors’ contributions
C.J.: designed the study, performed the volunteer recruitment, study execution and data acquisition, developed and implemented the PK/PD models in MONOLIX. He performed data analysis and interpretation, graphical representation with R, and wrote the first draft of the manuscript. M.L., J.S. and H.I.: performed data analysis and interpretation, revised critically the manuscript for content and gave final approval to the manuscript version submitted for publication. Additionally, H.I. also worked on the development of PK/PD models.

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Declaration of interest
None declared.

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