ANESTHESIOLOGY

Modeling the Effect of Excitation on Depth of Anesthesia Monitoring in γ-Aminobutyric Acid Type A Receptor Agonist ABP-700

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The γ-aminobutyric acid type A receptor agonist cyclopropyl-methoxycarbonyl metomidate (ABP-700), a second-generation analog of etomidate, produces a rapid onset of sedation and deep general anesthesia
- Side effects of ABP-700 include excitatory phenomena such as involuntary muscle movements

What This Article Tells Us That Is New

- The effects of involuntary muscle movement on pharmacokinetic-pharmacodynamic models of the effects of ABP-700 on the Bispectral Index (BIS) and the Modified Observer's Assessment of Alertness/Sedation scores were studied using data from 266 individuals
- In the ABP-700 pharmacokinetic-pharmacodynamic model, a secondary disinhibitory effect-site for BIS that functions in opposition to drug effects underlying suppression of the BIS signal was associated with involuntary muscle movements
- The ABP-700 pharmacokinetic-pharmacodynamic model of its effects on Modified Observer's Assessment of Alertness/Sedation scores did not indicate a relationship between involuntary muscle movement and clinical hypnosis

ABSTRACT

Background: γ-Aminobutyric acid type A ($GABA_A$) receptor agonists are known to cause involuntary muscle movements. The mechanism of these movements is not known, and its relationship to depth of anesthesia monitoring is unclear. We have explored the effect of involuntary muscle movement on the pharmacokinetic-pharmacodynamic model for the $GABA_A$ receptor agonist ABP-700 and its effects on the Bispectral Index (BIS) as well as the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores.

Methods: Observations from 350 individuals (220 men, 130 women) were analyzed, comprising 6,312 ABP-700 concentrations, 5,658 ABP-700 metabolite (CPM-acid) concentrations, 25,745 filtered BIS values, and 6,249 MOAA/S scores, and a recirculatory model developed. Various subject covariates and pretreatment with an opioid or a benzodiazepine were explored as covariates. Relationships between BIS and MOAA/S models and involuntary muscle movements were examined.

Results: The final model shows that the pharmacokinetics of ABP-700 are characterized by small compartmental volumes and rapid clearance. The BIS model incorporates an effect-site for BIS suppression and a secondary excitatory/disinhibitory effect-site associated with a risk of involuntary muscle movements. The secondary effect-site has a threshold that decreases with age. The MOAA/S model did not show excitatory effects.

Conclusions: The $GABA_A$ receptor agonist ABP-700 shows the expected suppressive effects for BIS and MOAA/S, but also disinhibitory effects for BIS associated with involuntary muscle movements and reduced by pretreatment. Our model provides information about involuntary muscle movements that may be useful to improve depth of anesthesia monitoring for $GABA_A$ receptor agonists.

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Involuntary muscle movements are frequently observed after administration of γ-aminobutyric acid type A ($GABA_A$) receptor agonists such as the widely used sedative and general anesthetic agents etomidate[1] and propofol,[2,3] but also novel anesthetic agents such as AZD3043[4] and ABP-700.[5] The presentation and nature of the involuntary muscle movements are diverse, ranging from isolated twitching of a finger to whole-body movements that may mimic tonic-clonic seizure activity, and given the unknown origin of these movements, they can be alarming for clinicians. Furthermore, subjects receiving ABP-700[5] and AZD3043[6] who exhibited involuntary muscle movements sometimes showed elevated Bispectral Index (BIS) values, although they were deeply anesthetized as judged clinically using the Modified Observer's Assessment of Alertness/

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Sedation (MOAA/S) scale. This discrepancy between processed electroencephalogram and clinical monitoring signs and scores remains unexplained for $GABA_A$ receptor agonists and complicates the assessment of the cerebral drug effect.

Cyclopropyl-methoxycarbonyl metomidate (CPMM or ABP-700) is a $GABA_A$ receptor agonist and a second-generation analog of etomidate. It is under development for use as an induction agent for general anesthesia.[7] First-in-human studies showed that ABP-700 has a rapid onset of action and recovery from sedation and deep general anesthesia.[5] This clinical profile is attributed to an ester bond that undergoes rapid hydrolysis by nonspecific tissue esterases and generates a metabolite, CPM-acid, that is approximately 1,000-fold less potent than ABP-700 as a $GABA_A$ receptor agonist. A preliminary three-compartmental pharmacokinetic-pharmacodynamic model was previously published as a part of the article on the first-in-human, bolus only study on ABP-700. Of note was the steep relationship between effect-site concentration of ABP-700 and the cerebral drug effect as measured by both BIS and MOAA/S.[5]

Notable side effects of ABP-700 include the occurrence of excitatory phenomena such as involuntary muscle movements, tachycardia, and tachypnea.[5,8] Although recent preclinical studies showed that CPM-acid can inhibit the $GABA_A$ receptor, a potential mechanism for seizure induction,[9] this effect was only seen at concentrations two orders of magnitude greater than those achieved clinically.

To better understand the relationship between clinical anesthesia pharmacodynamic measurements and involuntary muscle movements for $GABA_A$ receptor agonists, and to better characterize the pharmacokinetics of ABP-700, we developed a recirculatory pharmacokinetic-pharmacodynamic model of ABP-700 as a prototype $GABA_A$ receptor agonist based on data from five phase 1, single-center studies. We developed a recirculatory model because it allows arterial and venous concentrations of both ABP-700 and CPM-acid to inform pharmacokinetic model development. Addition of a pharmacodynamic component to model the relationships between plasma ABP-700 concentrations and BIS and MOAA/S observations allows for inferences of the physiologic mechanisms underlying these measures of drug effect.

Materials and Methods

In total, data from 350 individuals (220 men, 130 women) were analyzed. The data of three subjects were removed due to dosing errors, such as an erroneous subcutaneous infusion, or a faulty cannula. Weight range was from 51 to 108 kg, age range was from 18 to 55 yr, and height range was from 151 to 200 cm. For ABP-700, 6,312 observations (3,310 arterial, 3,002 venous) were analyzed. For the development of the CPM-acid, BIS, and MOAA/S models, we only used data from studies in which individualized arterial concentration profiles were available. Hence, CPM-acid pharmacokinetic model development and pharmacodynamic model development were performed using data from 266 individuals. For the CPM-acid pharmacokinetic model, 5,658 observations (3,199 arterial, 2,459 venous) were analyzed. For BIS, 25,745 (median filtered) observations were analyzed, and for MOAA/S, 6,249 observations were analyzed.

Study Execution

This analysis involves data from five studies of the safety and tolerability of ABP-700 (see Supplemental Digital Content 1, http://links.lww.com/ALN/C493): ANVN-01[5] (bolus-only dose escalation study), ANVN-02[8] (infusion dose escalation study), ANVN-03 (bolus-only dose optimization study, venous samples only), ANVN-04 (infusion dose optimization study), and ANVN-05 (induction dose study). In various cohorts, pretreatment in the form of an opioid agent or benzodiazepine was administered before administration of ABP-700. The pretreatments fentanyl (ranging from 0.5 to 2 $\mu g \cdot kg^{-1}$), sufentanil (0.2 $\mu g \cdot kg^{-1}$), and midazolam (ranging from 15 to 30 $\mu g \cdot kg^{-1}$) were administered as a bolus 5 min before administration of ABP-700. Remifentanil (ranging from 0.05 to 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was administered as a continuous infusion, starting 5 min before the administration of ABP-700 and ending when the administration of ABP-700 was halted.

These studies were performed at the QPS Early Phase I unit, Groningen, The Netherlands, in cooperation with the Department of Anesthesiology at the University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, in accordance with the Declaration of Helsinki, in compliance with Good Clinical Practice and applicable regulatory requirements. They were approved by the ethics committee (Medical Ethics Review Committee, Bebo Foundation, Assen, The Netherlands, NL48312.056.14) and were registered at the Dutch Trial Register (NTR4545, NTR4735, NTR5173, NTR5231, and NTR5442).

Healthy subjects aged between 18 and 55 yr were eligible for these studies. Inclusion criteria were an American Society of Anesthesiologists (Schaumburg, Illinois) physical status score of I and no risk of a difficult airway (modified Mallampati score I or II). Exclusion criteria were a body mass index less than 17.5 or above 30.0, significant medical history, chronic use of medication (oral contraceptives excluded), alcohol, drugs, or tobacco, and having previously received ABP-700. For the first two studies, women had to be of nonchildbearing potential (*i.e.*, to have been sterilized at least 6 months before the first dose, or to have been postmenopausal with amenorrhea for at least 1 yr before the first dose with a measured follicle-stimulating hormone level less than 30 U/l).

During the study execution, an attending anesthesiologist was present throughout the conduct of the study until the full recovery of the subject. Safety and tolerability of

ABP-700 were assessed as described by Struys *et al.*[5] and Valk *et al.*,[8] by assessment of adverse events, safety laboratory tests, intermittent 12-lead electrocardiograms, temperature, and infusion site reaction monitoring. Continuous monitoring of three-lead electrocardiogram, heart rate, pulse oximetry, noninvasive blood pressure (every minute), continuous arterial blood pressure, respiration rate and pattern, and end-tidal carbon dioxide were monitored in all subjects using a Philips MP50 monitor (Philips, The Netherlands). As the investigators had not fully anticipated the extent of the involuntary muscle movements, no standardized scoring system was implemented *a priori* in the study protocol. Instead, the responsible clinicians recorded their observations on the character and extent of the involuntary muscle movements electronically. Involuntary muscle movement severity was evaluated by *post hoc* analysis of the recorded observations as described by Struys *et al.*[5] and Valk *et al.*[8] Involuntary muscle movements were defined as "extensive" when they involved the whole body or a considerable part of it. Involuntary muscle movements were defined as "few movements" when they were observed in a few body parts, such as in both arms or both legs.

All BIS and MOAA/S observations and blood sampling times, as well as data on vital signs and manually written comments, were stored electronically using a dedicated and validated electronic data capturing device (RUGLOOP II, DEMED, Belgium).

Blood Sampling

For blood sampling times, see Supplemental Digital Content 2 (http://links.lww.com/ALN/C494). Blood samples were collected in pre-chilled EDTA vacutainers. Samples were stored on wet ice for no longer than 30 min until centrifuged at 5°C for 7 min at 1,800*g* to separate the plasma. Plasma was transferred using disposable pipettes into cryovials and placed immediately on dry ice until transferred to a –80°C freezer within a total allotted time of 60 min. The analysis process was identical to the methods described in a previous publication on ABP-700.[5]

In brief, high-performance liquid chromatography was used to measure plasma concentrations of ABP-700 with tandem mass spectrometric detection using a SCIEX API4000 instrument, including a Turbo Ion Spray interface in positive mode at QPS Netherlands B.V. (The Netherlands). Deuterium-labeled D5-ABP-700 and D5-CPM-acid were used as internal standards. The internal standard solution and acetonitrile were added to 0.05 ml of plasma. The supernatant was then mixed and centrifuged, and partly transferred onto the Ostro Protein Precipitation & Phospholipid Removal Plate, 25 mg (Waters Chromatography B.V., The Netherlands). The supernatant was eluted using positive pressure and consecutively collected in a 96-well plate. A dilution step with Milli-Q ultrapure water (Merck Milliport, The Netherlands) and acetonitrile was applied before analysis.

On a C18 column (ACE 3μm column, 50 x 3.0 mm, Advanced Chromatography Technologies, Aberdeen, United Kingdom), mounted in line with a 4 × 3.0 mm C18 guard column (Advanced Chromatography Technologies, United Kingdom) on an Agilent 1100/1200 LC system (Agilent Technologies, USA), liquid chromatography was performed, with the column temperature maintained at 50°C. The mobile phase A was 0.1% formic acid in water, and the mobile phase B was 0.1% formic acid in 50% acetonitrile. A gradient of 30 to 95% B was applied over a period of 1 min, at a flow rate of 1 ml · min^{-1} for sample elution. The approximate elution time for ABP-700 was 2.1 min. The nominal mass transitions monitored had mass-to-charge-ratios of 315.2 to 211.1. The method was validated over a concentration range of 5 to 1,250 ng · ml^{-1} for ABP-700 and 25.0 to 6,250 ng/ml for CPM-acid. Both within a single run of 6 aliquots (within-run for repeatability) and between different runs (between-run for reproducibility) distributed over at least 2 days, precision and accuracy were demonstrated for the validation samples. Validation samples were prepared in blank human NaF/NaEDTA plasma by spiking known concentrations of ABP-700 and CPM-acid. The acceptance criterion for precision, the percentage of the coefficent of variation (CV%) not to exceed 20.0% at the lower limit of quantification or 15% at all other levels, was met for all samples. The acceptance criterion for accuracy of the percentage of the relative error (%RE). not to exceed 20.0% at the lower limit of quantification or 15% at all other levels, was also met for all samples. The lower limits of quantification for ABP-700 and CPM-acid were determined at 5 ng · ml^{-1} and 25 ng · ml^{-1}, respectively.

Model Development

For pharmacokinetic and pharmacodynamic model development, NONMEM version 7.4 (Icon Development Solutions, USA) was used for model estimation and simulations, and R version 2.14.1[10] (available at https://www.R-project.org/, accessed January 2020) was used for performance estimation and generation of diagnostic plots. Model parameters were calculated relative to a reference individual,[11] a 70-kg, 35-yr-old, 170-cm man. Interindividual variability in model parameters was assumed to be log-normally distributed across the population. The ABP-700 pharmacokinetic model was developed first, and afterward the pharmacodynamic and CPM-acid models were developed using the individual predictions from the final ABP-700 pharmacokinetic model. This is known as the "sequential method."[12,13] Initial models assumed the theoretical allometric scaling exponents,[14] volumes scaling linearly with weight, clearances to the three-fourths power, and rate constants to negative one-fourth power. Compartmental allometry[15–17] was applied to peripheral compartments, which includes interindividual variability of peripheral compartment volume as a contributor to variability in the associated compartmental clearance. This

arises when a peripheral compartmental clearance is considered a property of the associated volume as well as the body as a whole. Observations lower than the reported limit-of-quantification of an assay were not used. Individual variability (η) values obtained from NONMEM estimation were examined for potential covariate relationships, which were subsequently tested in the model. Inclusion of a parameter in the model required an improvement of at least 9.21 in the corrected Akaike Information Criterion (AIC). For estimates of logarithmic interindividual variability, we report the estimated variance and the coefficient of variation using the equation

$$CV\left(\%\right) = \sqrt{e^{\omega^2} - 1} \cdot 100\%$$

where ω^2 is the estimated parameter population variance. For the sake of brevity, we do not describe all models tested during model development, and report only those that led to the final models.

The pharmacokinetic model development focused on a mammillary recirculatory structural model for ABP-700 and CPM-acid, similar to that used for another drug, AZD3043.[6] We used a recirculatory pharmacokinetic model structure because it is a classical pharmacometrical approach,[18] which allows simultaneous fitting of arterial and venous concentrations with a recognizable mechanistic basis. From dosing, drug initially appears in a depot compartment and is then transported to arterial and then to venous compartments *via* peripheral compartments and a nondistributive pathway. Drug transport through the central circulation was a flow representing the rate of venous-arterial circulation of drug mass in the model. We refer to this as the apparent cardiac output because of its structural similarity to cardiac output in circulation models. Apparent cardiac output is estimated from the data and does not represent blood pumped by the heart over time as we did not have measurements of cardiac output.

A similar arterial-venous-peripheral compartmental model structure was used for the CPM-acid. All of the drug transport determined by ABP-700 elimination clearance was assumed to result in CPM-acid production. Residual observation error (ε) was assumed to be proportional to the predicted concentrations, separately for ABP-700 and CPM-acid.

BIS Model Development

Initially, BIS values were modeled as a sigmoidal *Emax* function of effect-site compartment concentrations (*Ce*), which in turn were driven by concentration in the arterial compartment *V1* (C_{V1}) and a first-order rate constant ($ke0_{BIS}$). The equation of the initial pharmacodynamic model was

$$ke0_{BIS} = ke0_{BIS,ref} \cdot \exp\left(\eta 1\right)$$

$$EC_{50,BIS} = EC_{50,BIS,ref} \cdot exp\left(\eta 2\right)$$

$$\delta Ce / \delta t = ke0_{BIS} \cdot \left(C_{V1} - Ce\right)$$

$$BIS_{observed} = \left(BIS_{baseline} + \eta 3\right) \cdot \left(1 - EC^{\gamma} / \left(EC^{\gamma} + EC_{50}{}^{\gamma}\right)\right) + \varepsilon$$

where $BIS_{baseline}$ is the baseline pharmacodynamic measure when no drug is present, $EC_{50,BIS}$ is the effect-site concentration associated with 50% of the maximum drug effect, γ is the steepness of the concentration *versus* response relation, and ε represents additive residual error. During model development, we also considered a second sigmoidal function causing increased BIS values. The equations are detailed in the Results section. To reduce estimation times, we median-filtered BIS observations every 30 s with a filter width of 30 s. Due to the large variability in pretreatment agents and their dosing regimens, we considered the absence or presence of pretreatment as a binary variable when assessing the influence of pretreatment on predicted BIS. As such, we did not analyze their effect according to individual pretreatment drug and/or dosing regimen. This binary approach has been successfully applied previously for other drugs such as propofol.[19]

Modified Observer's Assessment of Alertness/Sedation Model Development

MOAA/S observations were treated as ordered categorical responses and modeled using a proportional-odds method. Based on the predicted effect-site concentration, the model estimates the cumulative probabilities of MOAA/S scores. Let *S* denote an observed score, the logits *lx*, of the probabilities that $S = 0$, $S \le 1$, $S \le 2$, $S \le 3$, $S \le 4$, are

$$l_{S=0} = b_0 + DEFF \cdot Ce$$

$$l_{S\le1} = b_0 + b_1 + DEFF \cdot Ce$$

$$l_{S\le2} = b_0 + b_1 + b_2 + DEFF \cdot Ce$$

$$l_{S\le3} = b_0 + b_1 + b_2 + b_3 + DEFF \cdot Ce$$

$$l_{S\le4} = b_0 + b_1 + b_2 + b_3 + b_4 + DEFF \cdot Ce$$

where b_0 is a fixed effect parameter representing the logit of the probability for score 0, and b_1 through b_4 represent the differences in logits between the scores. The parameter for drug effect (*DEFF*) is a fixed effect for the model, and *EC* represents the effect-site concentration of ABP-700, calculated using a first-order rate constant ($ke0_{MOAA/S}$) in a similar manner as done for BIS. The corresponding probabilities are given by

$$PC_x = e^{l_x} / \left(1 + e^{l_x}\right)$$

The actual probabilities, p_x, of observing a particular score are $P_{S=0} = \mathrm{PC}_{S=0}$, $P_{S=1} = PC_{S\le1} - PC_{S=0}$, $P_{S=2} = PC_{S\le2} - PC_{S\le1}$, $P_{S=3} = PC_{S\le3} - PC_{S\le2}$, $P_{S=4} = PC_{S\le4} - PC_{S\le3}$, $P_{S=5} = 1 - PC_{S\le4}$.

Simulations

To illustrate the characteristics of the final pharmacokinetic model, as well as the BIS and MOAA/S models, we performed simulations of a short infusion for illustrative individuals to demonstrate expected drug concentrations and the influence of pretreatment, age, weight, and infusion rate on predicted BIS and MOAA/S.

Results

Pharmacokinetic Model Development

First, the ABP-700 pharmacokinetic model was developed, and incorporating two peripheral compartments performed better than one (Δ AIC = –464.08). Decreasing clearance with age improved the model (Δ AIC = –12.46). Removing compartmental allometry from the model does not change the number of estimated model parameters and caused poorer model fit (Δ AIC = –31.90), so compartmental allometry was retained in the model. To obtain sufficient estimation stability, interindividual variability was fixed to 0 for the depot compartment volume, peripheral compartment clearances, and apparent cardiac output. Doing so obtains the expected smooth parabolic shape of the likelihood profiles, indicating reliable estimates for parameters and their confidence limits. The equations for the final ABP-700 pharmacokinetic model are as follows:

$$Fsize = WGT / 70$$

$$CL = CL_{ref} \cdot Fsize^{0.75} \cdot \exp\left(\theta_1 \cdot (AGE - 35)\right) \cdot \exp(\eta 1)$$

$$V_{arterial} = V_{arterial,ref} \cdot Fsize \cdot \exp(\eta 2)$$

$$V_{venous} = V_{venous,ref} \cdot Fsize \cdot \exp(\eta 3)$$

$$V_{P1} = V_{P1,ref} \cdot Fsize \cdot \exp(\eta 4)$$

$$V_{P2} = V_{P2,ref} \cdot Fsize \cdot \exp(\eta 5)$$

$$Q_{ND} = Q_{ND,ref} \cdot Fsize^{0.75} \cdot \exp(\eta 6)$$

$$Q_{CO} = Q_{CO,ref} \cdot Fsize^{0.75}$$

$$Q_{P1} = Q_{P1,ref} \cdot \left(V_{P1} / V_{P1,ref}\right)^{0.75}$$

$$Q_{P2} = Q_{P2,ref} \cdot \left(V_{P2} / V_{P2,ref}\right)^{0.75}$$

$$V_{depot} = V_{depot,ref} \cdot Fsize$$

Symbols with the subscript *ref* and θ represent estimated parameters and η estimated variances, WGT is weight in kg, and AGE is age in years.

Subsequently, the CPM-acid pharmacokinetic model was developed. All of the ABP-700 eliminated was assumed to produce CPM-acid, appearing in the CPM-acid depot compartment. To reduce the number of parameters, the apparent cardiac output from the ABP-700 pharmacokinetic model was transferred to the CPM-acid model, and interindividual variability of the depot compartment time constant and intercompartmental clearance were fixed to zero as in the ABP-700 pharmacokinetic model. Using a single peripheral compartment did not show bias in the diagnostic plots, and a second peripheral compartment was not tested. Decreasing apparent clearance of CPM-acid with age improved model fit (Δ AIC = –9.53). The equations for the final CPM-acid pharmacokinetic model are as follows:

$$CL_{CPM-A} = CL_{CPM-A,ref} \cdot Fsize^{0.75} \cdot \exp\left(\theta_1 \cdot (AGE - 35)\right) \cdot \exp(\eta 1)$$

$$V_{CPM-A,arterial} = V_{CPM-A,arterial,ref} \cdot Fsize \cdot \exp(\eta 2)$$

$$V_{CPM-A,venous} = V_{CPM-A,venous,ref} \cdot Fsize \cdot \exp(\eta 3)$$

$$V_{CPM-A,P} = V_{CPM-A,P,ref} \cdot Fsize \cdot \exp(\eta 4)$$

$$Q_{CPM-A,ND} = Q_{CPM-A,ND,ref} \cdot Fsize^{0.75} \cdot \exp(\eta 5)$$

$$Q_{CPM-A,P} = Q_{CPM-A,P1,ref} \cdot \left(V_{CPM-A,P} / V_{CPM-A,P,ref}\right)^{0.75}$$

$$K_{CPM-A,depot} = K_{CPM-A,depot,ref} \cdot Fsize^{-0.25}$$

The estimated parameters of the final ABP-700 and CPM-acid pharmacokinetic models are shown in table 1. NONMEM codes for the model differential equations are shown in Supplemental Digital Content 3 (http://links.lww.com/ALN/C495).

Diagnostic plots for the ABP-700 model are shown in figure 1 (arterial) and figure 2 (venous), and for the CPM-acid are shown in figure 3 (arterial) and figure 4 (venous). The structure of the final ABP-700 and CPM-acid pharmacokinetic models is shown in figure 5. The best, typical, and worst fit of arterial and venous ABP-700 predictions to the data are included in Supplemental Digital Content 4 (http://links.lww.com/ALN/C496) and 5 (http://links.lww.com/ALN/C497), respectively. Similarly, for CPM-acid predictions, these are included in Supplemental Digital Content 6 (http://links.lww.com/ALN/C498) and 7 (http://links.lww.com/ALN/C499), respectively. An expanded view of the initial arterial and venous concentration predictions for bolus dosing (ANVN-01) and infusion (ANVN-02) are shown in Supplemental Digital Content 8 (http://links.lww.com/ALN/C500). The final model for ABP-700 shows some overprediction for early arterial and venous samples and underprediction for late venous observations. Misfit in the early samples shows limitations of the model for front-end kinetics. Misfit in the late venous samples suggests limitations of the model for how the peripheral compartments interact with the venous compartments.

BIS Model Development

The initial BIS pharmacodynamic model varied $EC_{50,BIS}$, $ke0_{BIS}$, and $BIS_{baseline}$ across individuals with $ke0_{BIS}$ scaling to its theoretical allometric exponent (–0.25) and removing allometric scaling of $ke0_{BIS}$ resulted in slightly worse model

Table 1. Model Parameters for the Final Pharmacokinetic Model for ABP-700 and CPM-Acid

		Confidence Limits			Variability	
Parameter	**Estimated**	**Lower 1%**	**Upper 99%**		**Variance (σ^2)**	**Coefficient of Variation (%)**
ABP-700						
CL_{ref} (l · min^{-1})	1.95	1.86	2.05	η1	0.0443	21.3
$V_{arterial,ref}$ (l)	4.54	3.70	5.28	η2	0.652	95.9
$V_{venous,ref}$ (l)	7.01	5.64	8.25	η3	0.222	49.9
$V_{P1,ref}$ (l)	3.43	3.02	3.94	η4	0.115	34.9
$V_{P2,ref}$ (l)	6.10	5.06	7.43	η5	0.563	86.9
$Q_{ND,ref}$ (l · min^{-1})	1.12	0.933	1.27	η6	0.0824	29.3
$Q_{CO,ref}$ (l · min^{-1})	2.41	2.25	2.55			
$Q_{P1,ref}$ (l · min^{-1})	0.372	0.259	0.495			
$Q_{P2,ref}$ (l · min^{-1})	0.104	0.0775	0.130			
$V_{depot,,ref}$ (l)	0.463	0.342	0.568			
Θ_1	–0.00568	–0.00975	–0.00187			
Residual error				ε	0.0627	25.4
CPM-acid						
$CL_{CPM-A,ref}$ (l · min^{-1})	0.769	0.732	0.808	η1	0.0466	21.8
$V_{CPM-A,arterial,ref}$ (l)	3.47	3.00	4.00	η2	0.423	72.6
$V_{CPM-A,venous,ref}$ (l)	2.50	2.18	2.86	η3	0.493	79.9
$V_{CPM-A,VP,ref}$ (l)	17.0	16.0	18.1	η4	0.115	34.9
$Q_{CPM-A,ND,ref}$ (l · min^{-1})	2.23	2.19	2.28	η6	0.00622	7.9
$Q_{CPM-A,P1,ref}$ (l · min^{-1})	0.525	0.489	0.562			
$K_{CPM-A,depot,ref}$ (min^{-1})	0.0760	0.0720	0.0803			
Θ_1	–0.00575	–0.00987	–0.00163			
Residual error				ε	0.0209	14.5

The role of each parameter in the model structure is shown in figure 5.
CL, clearance; K, rate constant; QCO, apparent cardiac output; QND, non-distributive flow; QP, peripheral flow; V, volume of distribution.

fit (Δ AIC = 2.72). For the model, periods of high drug concentration were poorly predicted. Adding a nonzero limit to the BIS pharmacodynamic model (lower limit to BIS value) showed considerable improvement to model fit. However, there was insufficient model stability for reliable parameter estimates. We also considered a secondary pharmacodynamic effect-site that functions in opposition to the primary effect-site, *i.e.*, reducing predicted drug effect as concentrations increased. If the primary effect-site is interpreted as drug effect causing suppression of the electroencephalogram processes underlying the BIS value, *i.e.*, BIS suppression, then the secondary effect-site would be interpreted as drug effect causing the apparent excitation of said electroencephalogram processes, leading to increased BIS values, *i.e.*, disinhibition of BIS. The equations of this pharmacodynamic model were

$$EC_{50,suppres} = EC_{50,suppres,ref} \cdot exp(\eta 1)$$

$$ke0_{suppres} = ke0_{suppres,ref} \cdot Fsize^{-0.25}$$

$$\delta Ce_1 / \delta t = ke0_{suppres} \cdot (C_{Varterial} - Ce_1)$$

$$Supression = EC_1^{\lambda_{suppress}} / \left(EC_1^{\lambda_{suppress}} + EC_{50,suppres}^{\lambda_{suppress}}\right)$$

$$EC_{50,excite} = EC_{50,excite,ref} \cdot \exp(\eta 2)$$

$$ke0_{excite} = ke0_{excite,ref} \cdot Fsize^{-0.25}$$

$$\delta Ce_2 / \delta t = ke0_{excite} \cdot (C_{Varterial} - Ce_2)$$

$$Excitation = EC_2^{\lambda_{excite}} / \left(EC_2^{\lambda_{excite}} + EC_{50,excite}^{\lambda_{excite}}\right)$$

$$BIS_{obs} = (BIS_{baseline} + \eta 3) \cdot \left(1 - \left(1 - Excitation\right) \cdot Supression\right) + \varepsilon$$

where EC_1, $EC_{50,suppres}$, $ke0_{suppress}$, and $\lambda_{suppress}$ represent effect-site concentration, concentration for 50% effect, effect-site time constant, and sigmoidicity parameters, respectively, for an effect-site that represents suppression of BIS. Parameters EC_2, $EC_{50,excite}$, $ke0_{excite}$, and λ_{excite} represent equivalent parameters for a secondary effect-site that causes increases in BIS values. An increase in excitation in the presence of constant suppression effects would be associated with an increase in observed BIS values. The balance of these suppression and disinhibitory effects determines the overall BIS value.

Inclusion of this secondary excitatory pharmacodynamic effect resulted in a very large improvement in model fit (Δ AIC = –6,176.39). However, interindividual variability could not be reliably estimated for the *ke0* values, and these were fixed to zero. Estimating a shared *ke0* for both suppression and excitation resulted in a poorer fit (Δ AIC = 39.62). Higher $EC_{50,excite}$ values were found in the presence of pretreatment, and incorporating

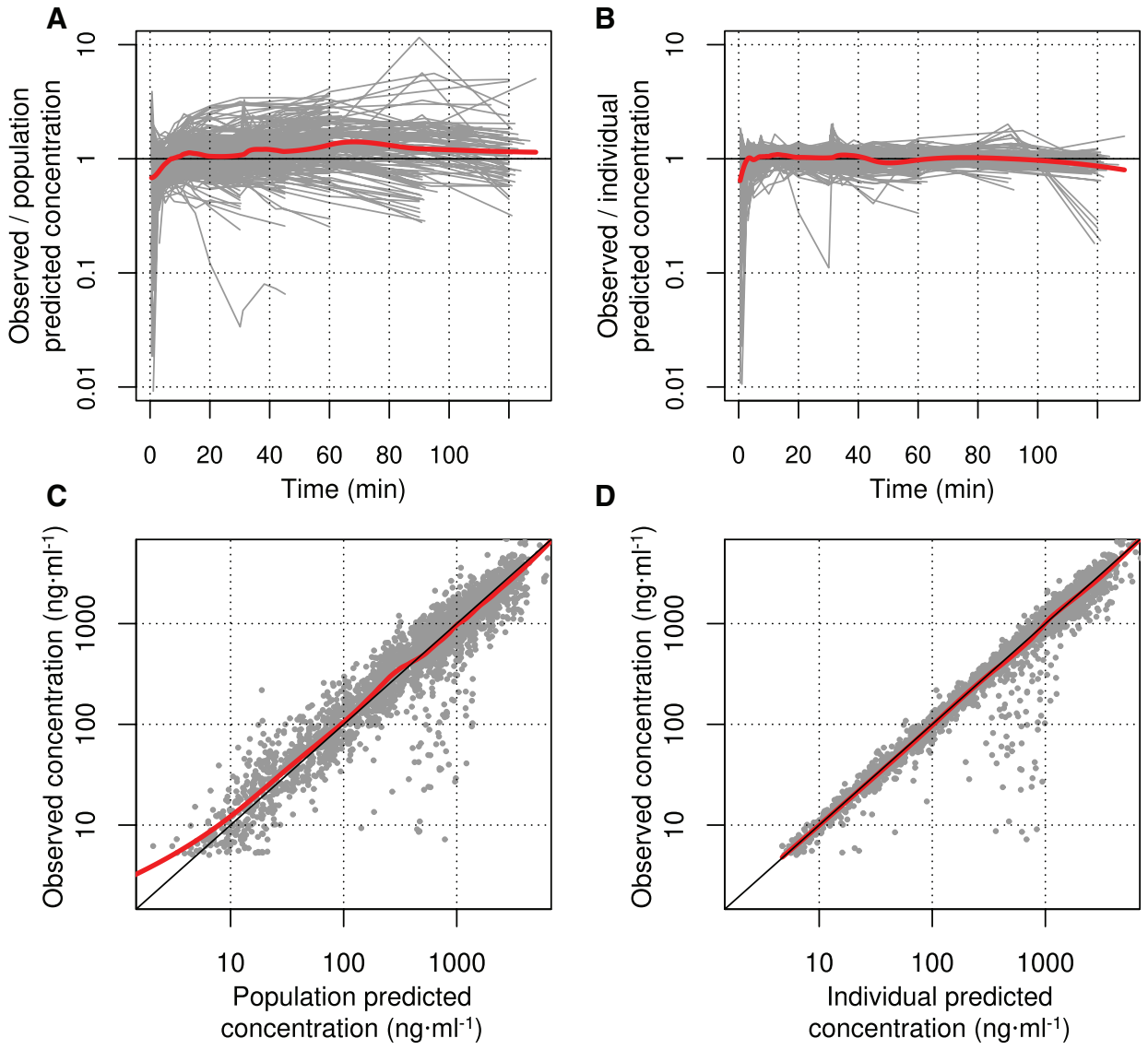

Fig. 1. Diagnostic plots for ABP-700 arterial samples. *Red line*: Smoother. (*A*) Population-observed/-predicted arterial plasma ABP-700 concentrations *versus* time. (*B*) *Post hoc* individual-observed/-predicted arterial plasma ABP-700 concentrations *versus* time. (*C*) Population-observed *versus* population-predicted arterial plasma ABP-700 concentrations. (*D*) *Post hoc* individual-observed *versus* individual-predicted arterial plasma ABP-700 concentrations.

this into the model resulted in improved model fit (Δ AIC = –34.62). Lower individual $EC_{50,excite}$ values were estimated with increasing age and adding an age covariate for $EC_{50,excite}$ improved model fit (Δ AIC = –13.58). The final equation for $EC_{50,excite}$ was

$$EC_{50,excite} = EC_{50,excite,ref} \cdot exp(\eta 2) \cdot \begin{cases} 1, & no\ pretreatment \\ \theta_1, & pretreatment \end{cases} \cdot exp\left(\theta_2 \cdot (AGE - 35)\right)$$

The estimated model parameters are shown in table 2, and diagnostic plots are shown in figure 6. Interestingly, low $EC_{50,excite}$ values were associated with involuntary muscle movements scored as "extensive" (P = 1.95e-6), while increased $EC_{50,excite}$ values were associated with involuntary muscle movements scored as "few" (P = 8.58e-4). No role of CPM-acid was found in the BIS model.

Modified Observer's Assessment of Alertness/Sedation Model Development

The initial MOAA/S pharmacodynamic model scales $ke0_{MOAA/S}$ by its theoretical exponent of –0.25, and removing this scaling did not improve model fit (Δ AIC = –0.05). An age relationship was found between age and the *DEFF*

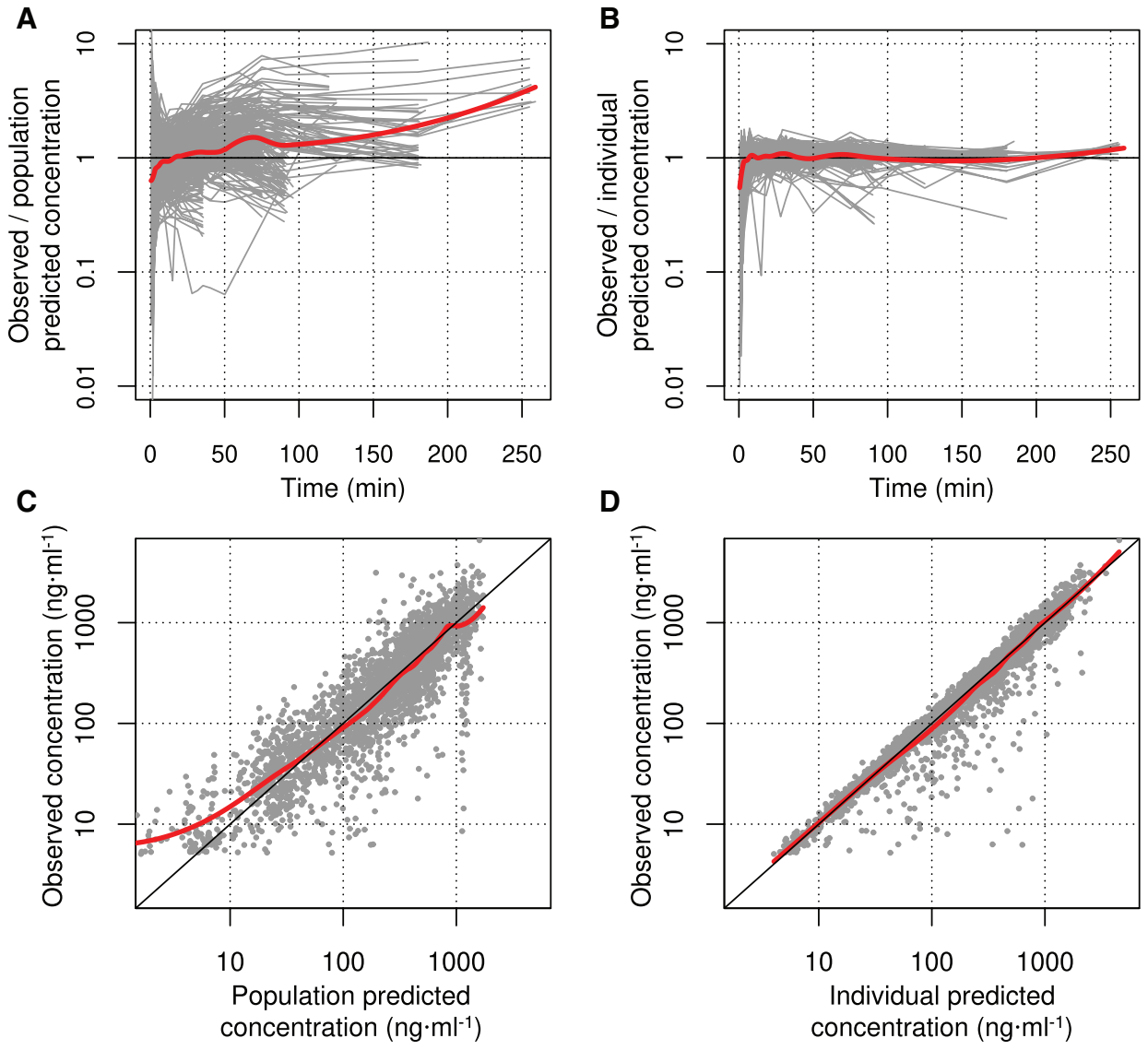

Fig. 2. Diagnostic plots for ABP-700 venous samples. *Red line*: Smoother. (*A*) Population-observed/-predicted venous plasma ABP-700 concentrations *versus* time. (*B*) *Post hoc* individual-observed/-predicted venous plasma ABP-700 concentrations *versus* time. (*C*) Population-observed *versus* population-predicted venous plasma ABP-700 concentrations. (*D*) *Post hoc* individual-observed *versus* individual-predicted venous plasma ABP-700 concentrations.

parameter, improving model fit (Δ AIC = –123.41). The equation for DEFF for the final MOAA/S model was

$$DEFF = DEFF_{ref} \cdot \exp\left(\theta_1 \cdot \left(AGE - 35\right)\right)$$

The final model parameters are shown in table 2. No role of the CPM-acid was found in MOAA/S model.

Simulation of Pharmacokinetic and Pharmacodynamic Model Characteristics

To explore the characteristics of the final models, we performed simulations of a 7-min infusion at 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for a 70-kg, 35-yr-old individual. The dose was based on simulations from preliminary pharmacokinetic-pharmacodynamic models,[5] and the results are shown in figure 7. Arterial and venous ABP-700 concentrations rise and fall rapidly when starting and stopping the infusion. The predicted BIS shows the interaction of the suppression and disinhibition component effects of the BIS. At low effect-site concentrations, suppressive effects dominate, lowering BIS values from the baseline. As effect-site concentrations increase further, disinhibitory effects cause BIS to reverse its downward trend and return toward baseline. Time to peak effect for BIS suppressive effects is 1.6 min, and for

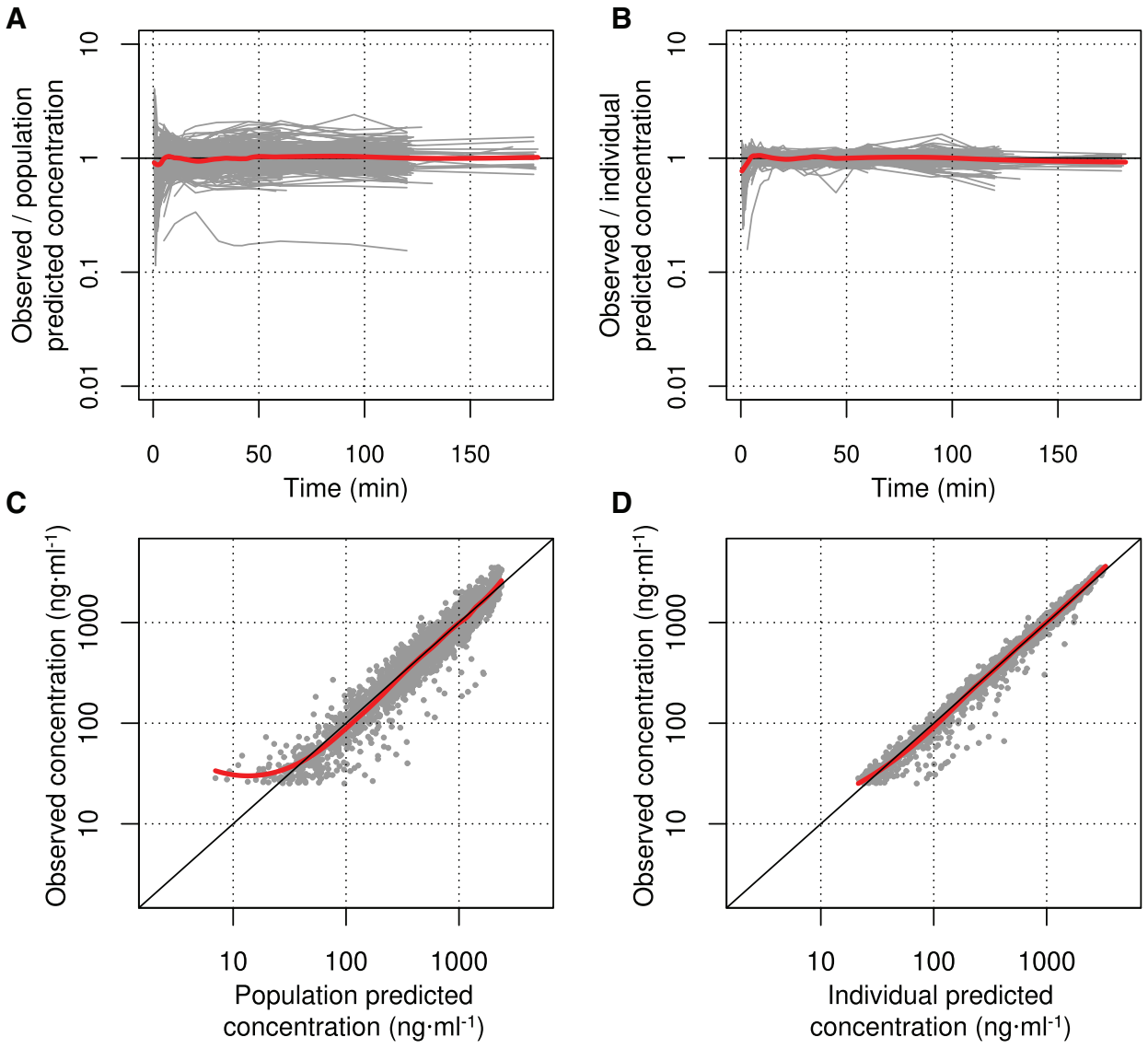

Fig. 3. Diagnostic plots for CPM-acid arterial samples. *Red line*: Smoother. (*A*) Population-observed/-predicted arterial plasma CPM-acid concentrations *versus* time. (*B*) *Post hoc* individual-observed/-predicted arterial plasma CPM-acid concentrations *versus* time. (*C*) Population-observed *versus* population-predicted arterial plasma CPM-acid concentrations. (*D*) *Post hoc* individual-observed *versus* individual-predicted arterial plasma CPM-acid concentrations.

BIS disinhibition effects is 1.5 min. The presence of pretreatment reduced disinhibitory effects and thus lowers the obtained BIS values for the same dose. These opposing disinhibitory effects are not evident in the time course of the MOAA/S score, where the MOAA/S score decreases monotonically with increasing effect-site concentrations.

To explore the influence of patient covariates and infusion rate for the final models, we performed simulations shown in figure 8. The overall influence of age on BIS and MOAA/S appear to be opposing. With advancing age, BIS values decrease less from baseline whereas the MOAA/S shows more rapid, deeper, and longer-duration effects. For weight, the covariate relationships are more canonical, with both BIS and MOAA/S showing slightly less drug effect and shorter duration for smaller individuals when dosed on a per-kilogram basis. For different infusion rates, BIS again shows paradoxical characteristics. Higher infusion rates result in more rapid initial onset but may stabilize at higher BIS values than lower infusion rates do. The MOAA/S shows more canonical monotonic dose-response characteristics, with higher infusion rates resulting in more rapid, greater, and longer duration decreases in the MOAA/S.

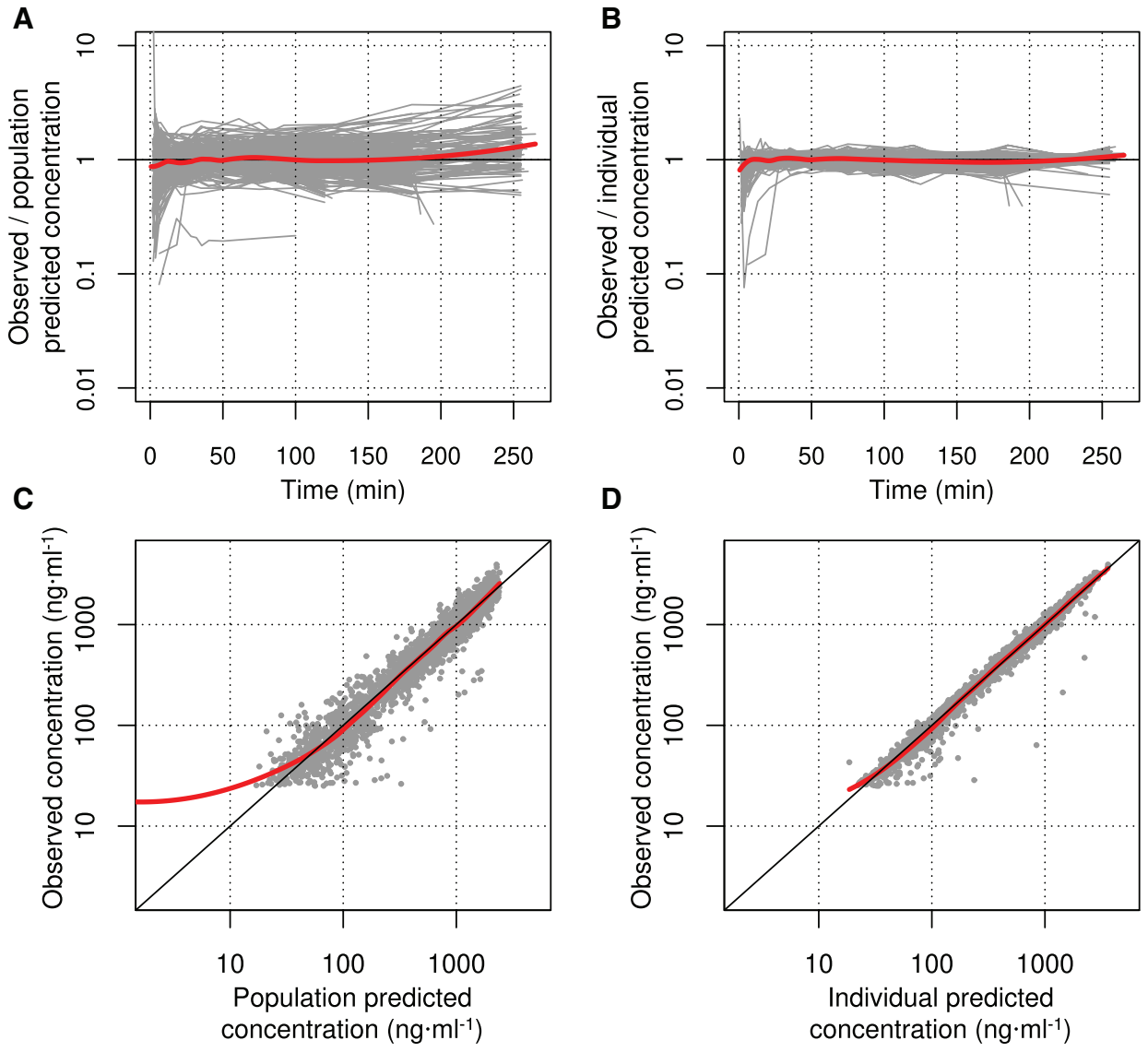

Fig. 4. Diagnostic plots for CPM-acid venous samples. *Red line*: Smoother. (*A*) Population-observed/-predicted venous plasma CPM-acid concentrations *versus* time. (*B*) *Post hoc* individual-observed/-predicted venous plasma CPM-acid concentrations *versus* time. (*C*) Population-observed *versus* population-predicted venous plasma CPM-acid concentrations. (*D*) *Post hoc* individual-observed *versus* individual-predicted venous plasma CPM-acid concentrations.

Discussion

We present a recirculatory mammillary pharmacokinetic-pharmacodynamic model to predict arterial and venous concentrations of ABP-700 and its metabolite, CPM-acid, as well as BIS and the MOAA/S. The recirculatory ABP-700 pharmacokinetic model's characteristics are roughly similar to a previously developed three-compartmental model after bolus administration[5] with an elimination clearance of 1.95 *versus* 1.66 l · min^{-1}. The small distribution volumes, indicating a small amount of body distribution and accumulation of the drug, and rapid clearance result in drug concentrations that stabilize rapidly after a change in drug administration rate and decrease rapidly after the cessation of infusions. The CPM-acid estimated apparent clearance of 0.769 l · min^{-1} is low compared to that of ABP-700, so high CPM-acid plasma concentrations may occur with prolonged infusions. As reported by Valk *et al.*,[9] very high concentrations of CPM-acid can cause inhibition of the $GABA_A$ receptor, potentially resulting in epileptic seizure activity. However, the maximum CPM-acid concentration observed during all phase 1 studies of ABP-700 in any individual was about 3,000 ng · ml^{-1}. This is approximately two orders of magnitude lower than the

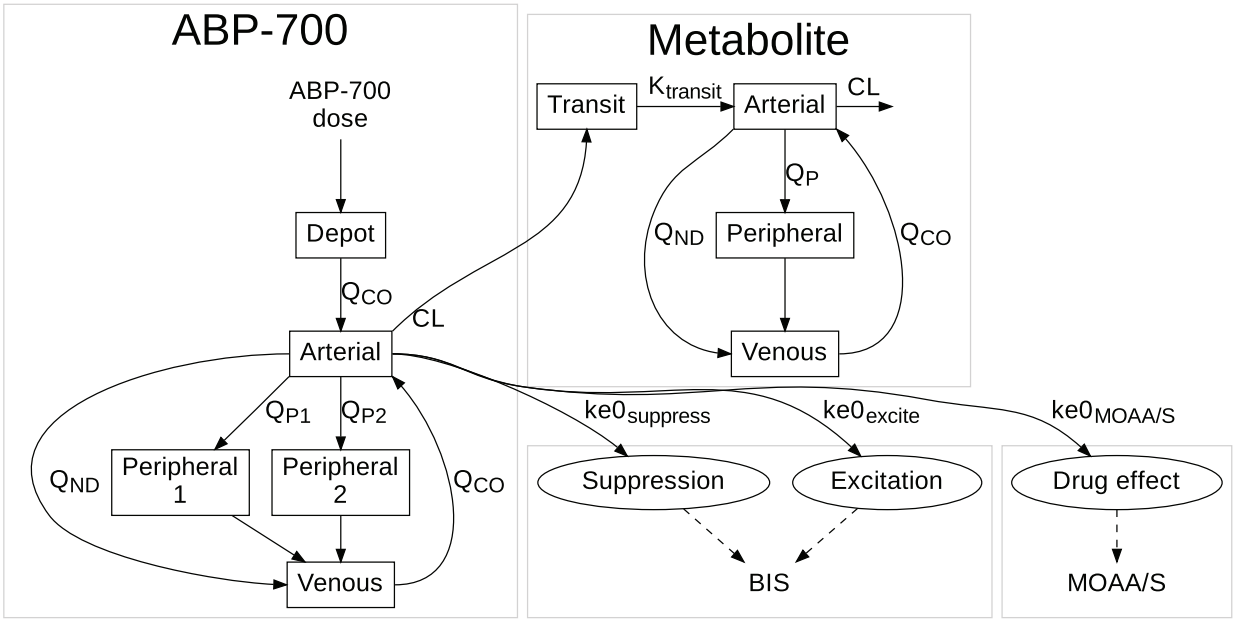

Fig. 5. Structural model for the recirculatory pharmacokinetic model for ABP-700 and CPM-acid and the pharmacodynamic models for the Bispectral Index and the Modified Observer's Assessment of Alertness/Sedation. The estimated value for each model parameter is shown in tables 1 and 2. BIS, bispectral index; CL, clearance; $K_{transit}$, transit rate constant; $ke0_{excite}$, effect-site rate constant for BIS disinhibition; $ke0_{MOAA/S}$, effect-site rate constant for MOAA/S; $ke0_{suppress}$, effect-site rate constant for BIS suppression; MOAA/S, Modified Observer's Assessment of Alertness/Sedation; QCO, apparent cardiac output; QP, peripheral flow; QND, non-distributive flow.

Table 2. Model Parameters for the Final Bispectral Index and Modified Observer's Assessment of Alertness/Sedation Model

		Confidence Limits			Variability	
Parameter	**Estimated**	**Lower 1%**	**Upper 99%**		**Variance (σ^2)**	**Coefficient of Variation (%)**
BIS						
$EC_{50,suppress,ref}$ (ng · ml^{-1})	1,041	986	1,100	η1	0.0995	32.3
$ke0_{suppress,ref}$ (1 · min^{-1})	0.844	0.823	0.865			
$\lambda_{suppress}$	4.45	4.27	4.63			
$EC_{50,excite,ref}$ (ng · ml^{-1})	1,230	943	1,590	η2	0.560	86.6
$ke0_{excite,ref}$ (1 · min^{-1})	1.03	0.934	1.14			
λ_{excite}	1.12	1.00	1.25			
$BIS_{Baseline}$	88.3	87.6	89.1	η3	20.7	—
Θ_1	2.00	1.52	2.67			
Θ_2	–0.0226	–0.0376	–0.00798			
Residual error				ε	42.3	—
Modified Observer's Assessment of Alertness/Sedation						
DEFF	3.35	3.17	3.53			
$ke0_{MOAA/S}$	0.848	0.795	0.907			
b0	–5.38	–5.65	–5.12			
b1	0.186	0.145	0.234			
b2	0.190	0.148	0.238			
b3	0.385	0.326	0.449			
b4	0.941	0.856	1.03			
Θ_1	0.00846	0.00657	0.0103			

The role of each parameter in the model structure is shown in figure 5.

BIS, bispectral index; DEFF, drug effect scaling constant; $EC_{50,excite}$, effect-site concentration producing 50% of maximal BIS suppression; $EC_{50,suppress}$, effect site concentration producing 50% of maximal BIS suppression; $ke0_{excite}$, effect-site rate constant for BIS disinhibition; $ke0_{MOAA/S}$, effect-site rate constant for the Modified Observer's Assessment of Alertness/Sedation (MOAA/S); $ke0_{suppress}$, effect-site rate constant for BIS suppression; λ_{excite}, slope for BIS disinhibition; $\lambda_{suppress}$, slope for BIS suppression.

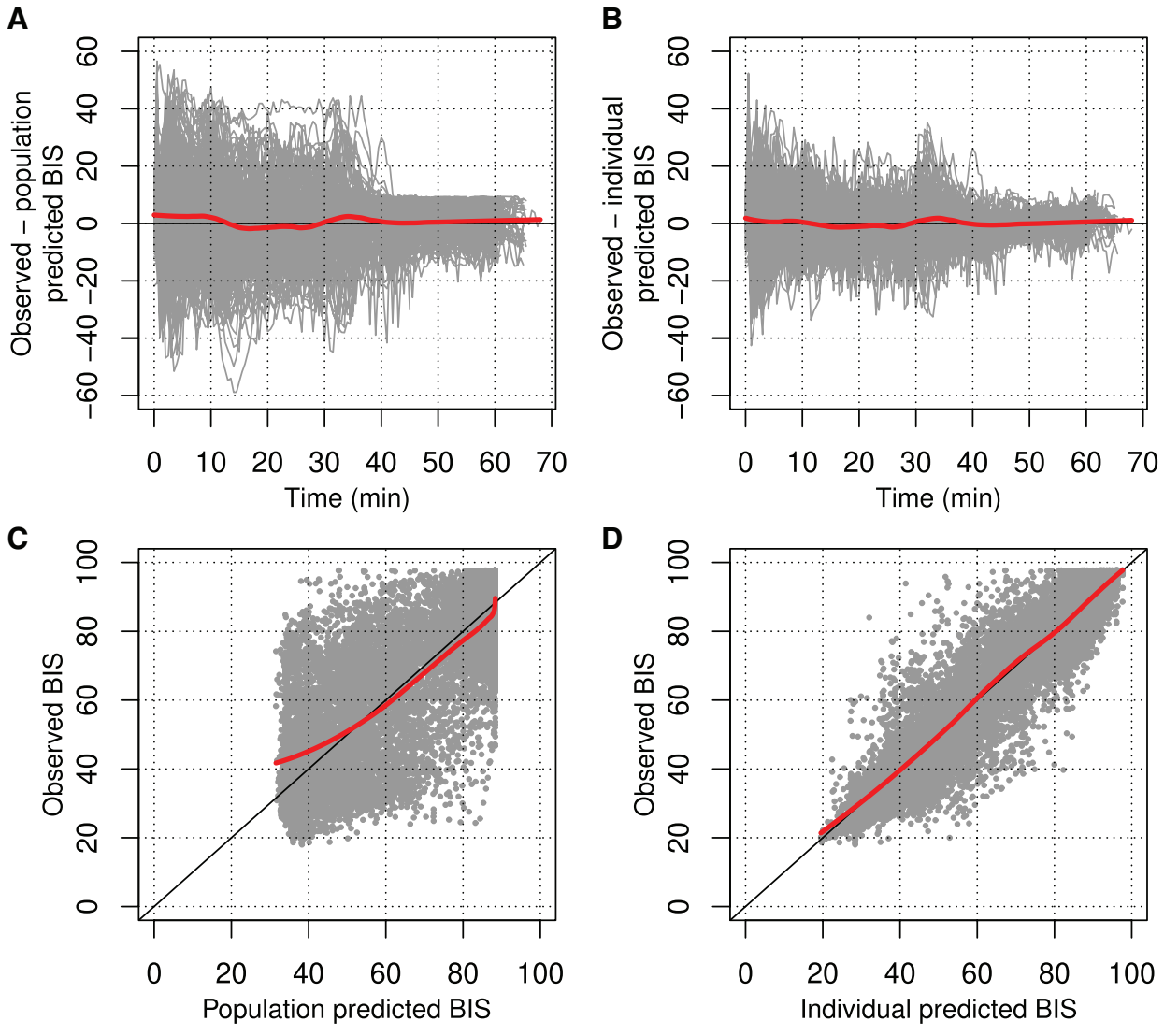

Fig. 6. Diagnostic plots for the Bispectral Index (BIS) model. *Red line*: Smoother. (*A*) Population-observed/-predicted BIS values *versus* time. (*B*) *Post hoc* individual-observed/-predicted BIS values *versus* time. (*C*) Population-observed *versus* population-predicted BIS values. (*D*) *Post hoc* individual-observed *versus* individual-predicted BIS values.

CPM-acid concentration associated with the $GABA_A$ current inhibition *in vitro*, and with occurrence of seizures in dogs,[9] rendering it unlikely that the involuntary muscle movements observed in humans during the phase 1 studies were of convulsive etiology. A simulation of a 5-h infusion of 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ shows that CPM-acid concentrations reach a steady-state plasma concentration after about 3 to 4 h at a concentration around 10,000 $ng \cdot ml^{-1}$ (30 μM; Supplemental Digital Content 9, http://links.lww.com/ALN/C501). This is also well below the concentration of CPM-acid that would cause $GABA_A$ receptor inhibition,[9] and thus, it is not expected that this is a mechanism that could cause seizure activity in humans receiving ABP-700. However, this simulation is a considerable extrapolation from the kind of data we had available for model development, and as such, interpretation of these data should be done with caution.

Compared to the previous investigation of ABP-700, more informative covariate relationships could also be discerned because of the larger and more diverse dataset. We found that clearance decreases with age, and thus, older individuals require lower maintenance infusion rates to achieve the same drug concentrations. A similar decrease of apparent clearance of CPM-acid with age was found.

As we developed the BIS model, we found that the initial model did not have a satisfactory fit. Based on our observation that increased BIS values were reported in subjects experiencing severe involuntary muscle movements,[5,8] we then decided to separate the BIS effect into a suppression

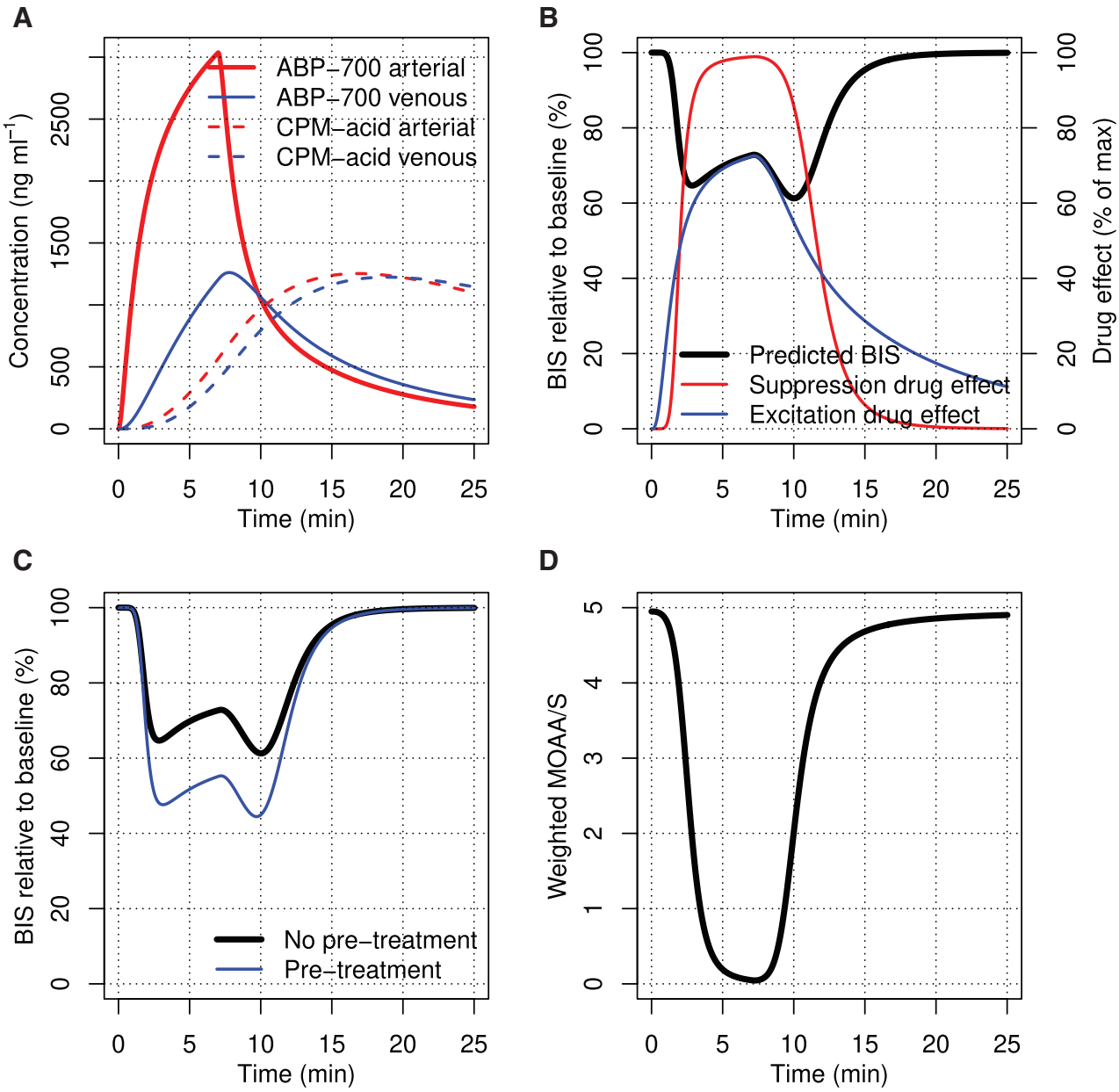

Fig. 7. Simulation of a 70-kg, 35-yr-old individual with and without pretreatment receiving 120 μg · kg^{-1} · min^{-1} ABP-700 for 7 min. (*A*) Plasma concentrations, arterial and venous, of ABP-700 and CPM-acid. (*B*) Time course of Bispectral Index (BIS) in the absence of pretreatment. (*C*) Time course of BIS in the absence *versus* in the presence of pretreatment. (*D*) Time course of the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores weighted by the predicted probability of each score.

and a disinhibition, or excitation, component. The final BIS model thus contains effect-sites for both suppression and disinhibition as pharmacodynamic endpoints of a $GABA_A$ receptor agonist. We found lower values of $EC_{50,excite}$ in individuals where involuntary muscle movement was noted as extensive. This conforms with the idea that involuntary muscle movement interferes with BIS as a method to monitor depth of anesthesia. The threshold for disinhibition decreases with increasing age, and this results in apparently paradoxical BIS behavior; the pharmacodynamic effect of ABP-700 appears to diminish with increasing age and plateau for high effect-site concentrations, resulting in high BIS values. For our model, the threshold for disinhibition is increased in the presence of pretreatment, reflecting the apparently reduced disinhibitory drug effect pathways for a given drug concentration.

Consistent with our observations during the clinical studies of ABP-700, our pharmacodynamic model shows a

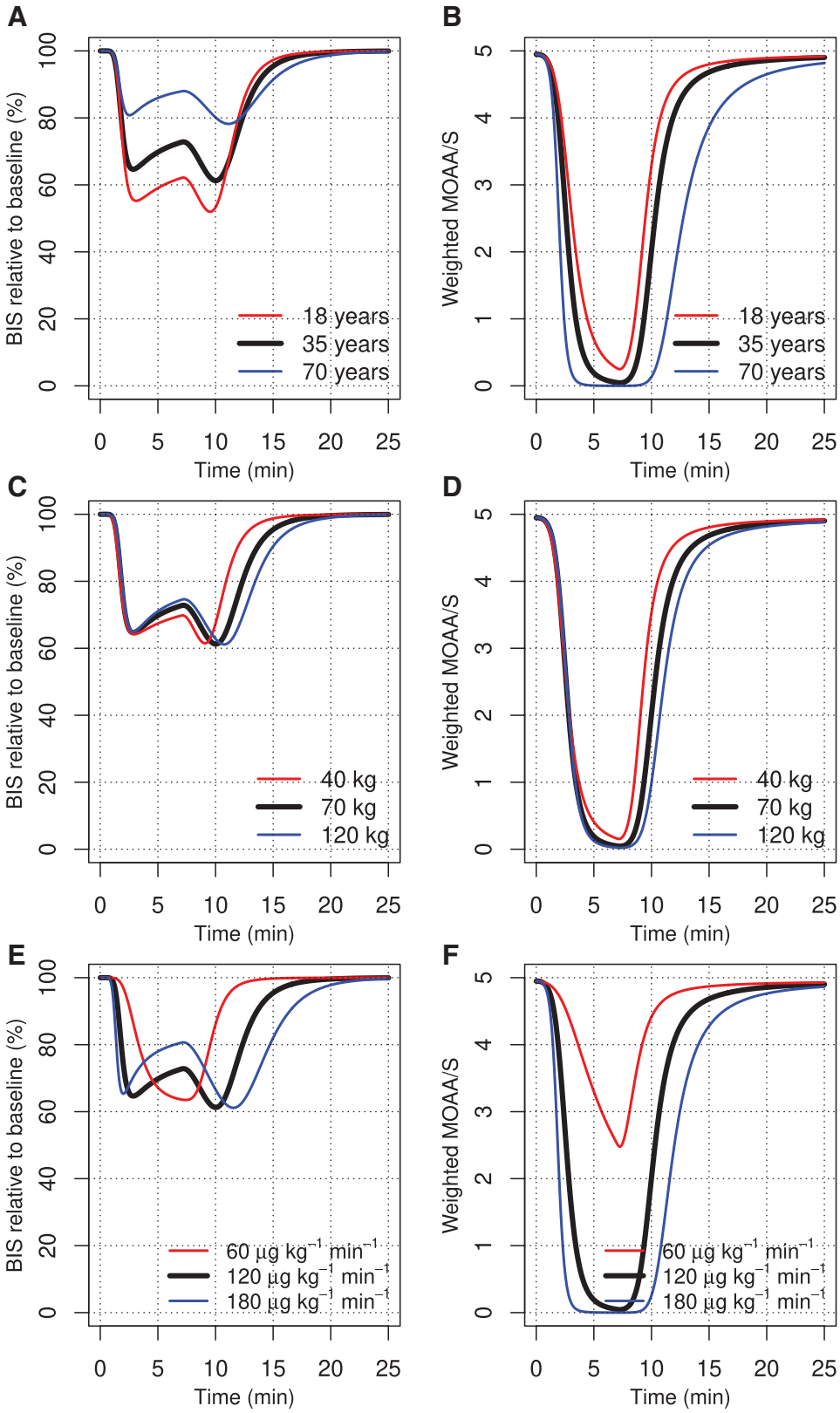

Fig. 8. The influence of age (*A and B*), weight (*C and D*), and infusion rate (*E and F*) for a 70-kg, 35-yr-old individual receiving ABP-700 without pretreatment on Bispectral Index (BIS; *A, C, and E*) and Modified Observer's Assessment of Alertness/Sedation (MOAA/S) (*B, D, and F*).

very fast-acting drug, with an "on-off switch"–like action on clinical effect. This is illustrated by the quite steep slope of the sigmoid model for BIS suppression, having a $\gamma_{suppression}$ value of 4.45. This is steeper than another hypnotic drug, propofol, for which $\gamma_{suppression}$ values between 1.86 and 2.17[19–21] were found. The $ke0_{suppression}$ is also quite fast at 0.844 min^{-1}, considerably faster than that of other hypnotic drugs.

It is not clear whether the disinhibitory submodel influences the actual depth of hypnosis in the clinical sense. A possible explanation is that in the presence of involuntary muscle movements, the BIS monitor is reporting a higher BIS value than would be expected based on drug effect as measured by the MOAA/S, because of the interference of electromyography frequencies, which are misinterpreted by the BIS algorithm,[22] thus masking the presence of sufficient anesthetic depth. If this mechanism is correct, then individuals receiving ABP-700 may show BIS values higher than clinically acceptable, but still have sufficient suppressive cerebral drug effect. This separation of hypnotic effects and clinically excitatory effects is partially supported by the developed pharmacodynamic model for the clinical MOAA/S score. Our model shows a high probability of a MOAA/S value of 0 at high effect-site concentrations, and we did not find a biphasic relationship in the MOAA/S with a "return of responsiveness" at higher concentrations. This suggests that cerebral drug effect as measured by the MOAA/S is not affected when involuntary muscle movement is present. If BIS values can increase while the MOAA/S score remains unchanged, then this would potentially reduce the utility of BIS monitoring for detecting insufficient anesthetic states for $GABA_A$ receptor agonists such as ABP-700 in the presence of involuntary muscle movements.

For most anesthetic drugs, elderly patients experience a greater drug effect, *e.g.*, there is more BIS suppression for a given dose and achieved drug concentration. Figure 8 shows that the influence of age, weight, and dose on predicted BIS is not straightforward: BIS does not always diminish with increasing age and dose. Elevated BIS values could be caused by (1) inadequate ABP-700 concentrations resulting in insufficient hypnosis or (2) excessively high ABP-700 concentrations resulting in disinhibition of BIS and excessive clinical excitation. This discrepancy could potentially cause a dilemma in clinical practice: If clinicians focus on achieving BIS values in the usual hypnotic range of 40 to 60, they may tend to increase drug administration when BIS values above this range are observed. In the case of ABP-700, this could result in further disinhibition, further increasing BIS values, and a failure to achieve the target BIS values. It is unknown whether this applies to other $GABA_A$ receptor–modulating agents.

We found lower values of $EC_{50,excite}$ in individuals where involuntary muscle movement was scored as extensive. In other words, there seems to be an intrinsic factor that makes some individuals more prone to disinhibition, clinically presenting as involuntary muscle movements. Our model, combined with our observations from the clinical studies, in which there was a notable interindividual variability in severity of involuntary muscle movements within dosing cohorts,[5] suggests that there is considerable interindividual susceptibility for this pharmacodynamic effect. We can only speculate what might cause this interindividual susceptibility. As it is probable that involuntary muscle movements are modulated by the $GABA_A$ receptor, various $GABA_A$ receptor subtypes might have a slightly different effect on disinhibition of BIS, and thus, a different distribution of $GABA_A$ receptor subtypes might cause a higher susceptibility to involuntary muscle movements. There is also interindividual variability in speed and extent of drug distribution, which may be most evident for rapid-onset drugs, such as $GABA_A$ receptor agonists ABP-700, etomidate, and, albeit to a smaller extent, propofol. This variability may result in unsynchronized onset of drug action at different sites in the central nervous system resulting in transient disinhibition of the subcortical excitatory neuronal circuits and involuntary muscle movements.[23] This hypothesis is supported to an extent by the $ke0_{excitation}$ (1.03) and the $ke0_{suppression}$ (0.844), showing that the onset of excitation/disinhibition is faster than the onset of BIS suppression, potentially resulting in a temporary disequilibrium in which clinical excitation has the upper hand.

The limitations of the study are similar to the ones reported in previous work by Struys *et al.*[5] and Valk *et al.*[8] While the covariate range for age and weight is broader than in those studies, it remains rather limited, and thus, the ability of the study to identify relevant covariate relationships is not as strong as it would have been had the study considered broader, stratified covariate ranges. While the recirculatory model does address arterial-venous differences, it does not fully address front-end kinetics. Especially for drugs with such a rapid onset and offset of effect, the front-end kinetics may play a considerable role in the pharmacologic action of the drug. Our blood sampling schedule did not include intense early sampling, so the front-end-kinetics structural model is rather simple, consisting of only a single depot compartment. Pharmacokinetic models developed with more extensive early sampling typically include more complex structural models incorporating multiple depot compartments.[6,24] So, our pharmacokinetic model only provides limited information on drug concentration prediction in the very early phase of drug distribution. During the study design, we did not consider the possibility of dual pharmacodynamic effects causing both BIS suppression and excitation. If this had been suspected *a priori*, we would have considered changes to the study design, such as measuring raw electroencephalographic waves using a full-montage electroencephalogram, to determine if differences in electroencephalographic activity can be observed between subjects experiencing clinical excitation *versus* subjects not experiencing clinical excitation.

Conclusions

Our model shows that, in a recirculatory mammillary pharmacokinetic-pharmacodynamic model, ABP-700

pharmacokinetics are characterized by a small amount of body distribution and rapid clearance. A secondary disinhibitory effect-site for BIS was associated with clinical excitation and involuntary muscle movements. This disinhibition functions in opposition to drug effects underlying suppression of the BIS signal and thus affects BIS monitoring. It is not known whether the presence of this disinhibition indicates insufficient actual anesthetic depth, or whether it is a separate signal, only interfering with values produced the BIS monitor. Our MOAA/S model does not indicate a relationship between disinhibition and clinical hypnosis. There are potential implications for the reliability of the BIS monitor, and indeed of other electroencephalogram-based monitors of depth of anesthesia, for ABP-700 and other $GABA_A$-ergic anesthetic agents. An interindividual susceptibility to excitation seems to exist, and the threshold for experiencing involuntary muscle movements decreases with increasing age. The mechanisms for this variability are unclear and warrant further investigation, as they might provide insight into the nature of the phenomenon of involuntary muscle movements and may improve the predictability of depth of anesthesia monitoring during excitation in $GABA_A$ receptor agonists.

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This study was a sponsor-initiated study by the then-owner of the molecule, The Medicines Company, Parsippany, New Jersey. The sponsor covered the costs related to this study.

Competing Interests

Dr. den Daas is an employee of QPS Netherlands, BV (Groningen, The Netherlands). Dr. Campagna is a former employee of The Medicines Company (Parsippany, New Jersey). S.P. Sweeney is a former employee of The Medicines Company and Annovation Biopharma (Cambridge, Massachusetts). Dr. Absalom's research group/department received grants and funding from The Medicines Company, Becton Dickinson (Eysins, Switzerland), Dräger (Lübeck, Germany), Paion (Aachen, Germany), and Rigel (San Francisco, California), and he has received honoraria from The Medicines Company, Janssen Pharmaceutica NV (Beerse, Belgium), Becton Dickinson (Eysins, Switzerland), Paion, Rigel, Philips (Eindhoven, Netherlands), and Ever Pharma (Unterach, Austria). Dr. Struys's research group/department received grants and funding from The Medicines Company, Masimo (Irvine, California), Fresenius (Bad Homburg, Germany), Acacia Design (Maastricht, The Netherlands), and Medtronic (Dublin, Ireland), and he has received honoraria from The Medicines Company, Masimo, Fresenius, Baxter (Deerfield, Illinois), Medtronic, and Demed Medical (Temse, Belgium). The other authors declare no competing interests.

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References

1. Yelavich PM, Holmes CM: Etomidate: A foreshortened clinical trial. Anaesth Intensive Care 1980; 8:479–83
2. Walder B, Tramèr MR, Seeck M: Seizure-like phenomena and propofol: A systematic review. Neurology 2002; 58:1327–32
3. Li Y, Flood P, Cornes S: Electroencephalography of seizure-like movements during general anesthesia with propofol: Seizures or nonepileptic events? A A Case Rep 2015; 5:195–8
4. Kalman S, Koch P, Ahlén K, Kanes SJ, Barassin S, Björnsson MA, Norberg Å: First human study of the investigational sedative and anesthetic drug AZD3043: A dose-escalation trial to assess the safety, pharmacokinetics, and efficacy of a 30-minute infusion in healthy male volunteers. Anesth Analg 2015; 121:885–93
5. Struys MMRF, Valk BI, Eleveld DJ, Absalom AR, Meyer P, Meier S, den Daas I, Chou T, van Amsterdam K, Campagna JA, Sweeney SP: A phase 1, single-center, double-blind, placebo-controlled study in healthy

subjects to assess the safety, tolerability, clinical effects, and pharmacokinetics-pharmacodynamics of intravenous cyclopropyl-methoxycarbonylmetomidate (ABP-700) after a single ascending bolus dose. Anesthesiology 2017; 127:20–35
6. Björnsson MA, Norberg Å, Kalman S, Simonsson US: A recirculatory model for pharmacokinetics and the effects on Bispectral Index after intravenous infusion of the sedative and anesthetic AZD3043 in healthy volunteers. Anesth Analg 2015; 121:904–13
7. Campagna JA, Pojasek K, Grayzel D, Randle J, Raines DE: Advancing novel anesthetics: Pharmacodynamic and pharmacokinetic studies of cyclopropyl-methoxycarbonyl metomidate in dogs. Anesthesiology 2014; 121:1203–16
8. Valk BI, Absalom AR, Meyer P, Meier S, den Daas I, van Amsterdam K, Campagna JA, Sweeney SP, Struys MMRF: Safety and clinical effect of i.v. infusion of cyclopropyl-methoxycarbonyl etomidate (ABP-700), a soft analogue of etomidate, in healthy subjects. Br J Anaesth 2018; 120:1401–11
9. Valk BI, McGrath M, Lehoux D, Zerler B, Marota JJA, Raines DE: Toxicologic and inhibitory receptor actions of the etomidate analog ABP-700 and its metabolite CPM-acid. Anesthesiology 2019; 131:287–304
10. R Foundation for Statistical Computing: R Development Core Team: R: A language and environment for statistical computing.
11. Holford NH: A size standard for pharmacokinetics. Clin Pharmacokinet 1996; 30:329–32
12. Zhang L, Beal SL, Sheiner LB: Simultaneous vs. sequential analysis for population PK/PD data I: Best-case performance. J Pharmacokinet Pharmacodyn 2003; 30:387–404
13. Zhang L, Beal SL, Sheinerz LB: Simultaneous vs. sequential analysis for population PK/PD data II: Robustness of methods. J Pharmacokinet Pharmacodyn 2003; 30:405–16
14. Anderson BJ, Holford NH: Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008; 48:303–32
15. Hannivoort LN, Eleveld DJ, Proost JH, Reyntjens KM, Absalom AR, Vereecke HE, Struys MM: Development of an optimized pharmacokinetic model of dexmedetomidine using target-controlled infusion in healthy volunteers. Anesthesiology 2015; 123: 357–67
16. Eleveld DJ, Proost JH, Cortínez LI, Absalom AR, Struys MM: A general purpose pharmacokinetic model for propofol. Anesth Analg 2014; 118:1221–37
17. Eleveld DJ, Proost JH, Vereecke H, Absalom AR, Olofsen E, Vuyk J, Struys MMRF: An allometric model of remifentanil pharmacokinetics and pharmacodynamics. Anesthesiology 2017; 126:1005–18
18. Upton RN: The two-compartment recirculatory pharmacokinetic model–An introduction to recirculatory pharmacokinetic concepts. Br J Anaesth 2004; 92:475–84
19. Eleveld DJ, Colin P, Absalom AR, Struys MMRF: Pharmacokinetic-pharmacodynamic model for propofol for broad application in anaesthesia and sedation. Br J Anaesth 2018; 120:942–59
20. Cortínez LI, Sepúlveda P, Rolle A, Cottin P, Guerrini A, Anderson BJ: Effect-site target-controlled infusion in the obese: Model derivation and performance assessment. Anesth Analg 2018; 127:865–72
21. Araújo AM, Machado H, de Pinho PG, Soares-da-Silva P, Falcão A: Population pharmacokinetic-pharmacodynamic modeling for propofol anesthesia guided by the Bispectral Index (BIS). J Clin Pharmacol 2020; 60:617–28
22. Dahaba AA: Different conditions that could result in the Bispectral Index indicating an incorrect hypnotic state. Anesth Analg 2005; 101:765–73
23. Kugler J, Doenicke A, Laub M: The EEG after etomidate, Etomidate: An Intravenous Hypnotic Agent. Edited by Doenicke A. Berlin Heidelberg, Springer Verlag, 1977, pp 31–48
24. Masui K, Kira M, Kazama T, Hagihira S, Mortier EP, Struys MM: Early phase pharmacokinetics but not pharmacodynamics are influenced by propofol infusion rate. Anesthesiology 2009; 111:805–17