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Modeling respiratory depression induced by remifentanil and propofol during sedation and analgesia using a continuous noninvasive measurement of pCO_2

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Running title: A model for propofol-remifentanil respiratory depression

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Nonstandard abbreviations:

BIS	Bispectral index
EEG	electroencephalograph
IC_{50}	concentration that causes 50% of the maximal inhibition
IMP	importance sampling
I_{MAX}	maximal inhibition
OBJ	objective function
Ce	predicted concentration in the effect site
pc-VPC	prediction-corrected visual predictive checks
SNP	single nucleotide polymorphism
SAEM	stochastic approximation expectation maximization
TCI	targeted controlled infusion

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Abstract

Background: Respiratory depression is a common adverse effect of propofol and remifentanil. We aimed to develop a model for respiratory depressant effects of propofol with remifentanil in patients undergoing endoscopy with sedation. **Methods:** Data were available for 136 patients undergoing endoscopy with sedation. Participants randomly received infusions of propofol and remifentanil. Predicted plasma concentrations, outputted by infusion pumps, were available. Transcutaneous arterial pressure of carbon dioxide (pCO_2) was measured. Data were analyzed using nonlinear mixed effects modeling methods. Covariate relationships were investigated for age, noxious stimuli (endoscopy tube insertion) and A118G genotype for the μ-opioid receptor (OPRM1). **Results:** Participants had a median (range) age of 64.0 (25.0-88.0) years, weight of 70.0 (35.0-98.0) kg and height of 164.0 (147.0-190.0) cm. Seven percent were recessive homozygous for OPRM1 polymorphism. An indirect effect model with "modulator" compartment best described pCO_2 data (***P<0.001) over a direct effect model. Remifentanil inhibited pCO_2 removal with an IC_{50} of 1.13 ng/ml and k_{e0} of 0.28 min^{-1}. Propofol affected the modulator compartment with an IC_{50} of 4.97 μg/ml (no effect-site compartment). Propofol IC_{50} and remifentanil k_{e0} were reduced with increasing age. Noxious stimuli and genotype were not significant covariates. **Conclusions:** An indirect effect model with rebound mechanism can describe remifentanil and propofol induced changes in pCO_2 in patients undergoing noxious procedures. The model may be useful for identifying optimal dosing schedules for these drugs in combination that provide adequate sedation but avoid respiratory depression.

Introduction

Sedation with analgesia is used as an anesthetic technique to allow diagnostic or therapeutic procedures without pain or distress for patients. Combining sedation and analgesia provides optimal conditions for endoscopic diagnosis and intervention, and better success rates.(Ootaki et al., 2012) Anesthesiologists must administer hypnotic and/or analgesic drugs, observe the effect induced, evaluate possible unwanted side effects, take action if required and adjust dosing to the individual's response. While being sedated patients breathe spontaneously with little airway support, and recover quickly to their pre-procedure conditions. Most drugs used for sedation and analgesia also have respiratory depressant effects that occur in a concentration-dependent fashion.

Several methods of measuring ventilatory depression are currently available but all have advantages and disadvantages: oxygen saturation might show adequate levels during severe apnea; respiratory rate is difficult to measure objectively clinically, and without an accurate evaluation of tidal volume is hardly effective in assessing adequate ventilation; pCO_2 changes reflect respiratory function but must be measured by arterial blood sampling (invasive and non-continuous) or through capnography, which may be susceptible to false negatives. Transcutaneous CO_2 monitors are based on arterialization of the capillary bed through the local application of heat. The use of Stow–Severinghaus electrodes provide information on the transcutaneous CO_2 tension continuously and non-invasively and with good correlation with arterial pCO_2. Transcutaneous measurement of arterial pCO_2 allows us to study respiratory depression by analyzing the time course of pCO_2 in individual patients undergoing sedation-analgesia with propofol and remifentanil. Measuring and predicting pCO_2 levels is clinically relevant since pCO_2 reflects the level of respiratory depression. Very high levels of pCO_2 may be associated to severe consequences like narcosis or cerebral edema.(Joyce and McGee, 2011; Spindelboeck and Moser, 2012)

Several models of respiratory effects have been reported for individual drugs commonly used during sedation (propofol, and the opioids remifentanil and alfentanil).(Bouillon et al., 1999; Bouillon et al., 2003; Bouillon et al., 2004a; Caruso et al., 2007) Few reports exist for models of combined effects for propofol with remifentanil on respiratory depression, despite the frequency with which agents are combined in anesthesia, and those that do are based on data derived in healthy volunteers.(Nieuwenhuijs et al., 2003; Olofsen et al., 2010) Respiratory control is determined by multiple processes, in which intrinsic feedback is provided by arterial pH levels and concentrations of O_2 and CO_2.(Dahan et al., 1990; Lloyd et al., 1958; Ward and Karan, 2002) Feedback mechanisms regulate respiratory drive which changes the alveolar minute ventilation. This makes it difficult to isolate and quantify key components of the system and consequently, many of the current models have been developed in highly controlled conditions (Bouillon et al., 1999) and in healthy volunteers.(Bouillon et al., 2003; Bouillon et al., 2004a; Caruso et al., 2007; Olofsen et al., 2010) This may limit their ability to predict respiratory depression in patient populations and the clinical environment.

A model has previously been reported for the effects of propofol and remifentanil on bispectral index (BIS) in patients undergoing endoscopy under sedation and analgesia.(Borrat et al., 2013) In that study, the effect of noxious stimulation on BIS was quantified, and the influence of the A118G single nucleotide polymorphism (SNP) of the OPRM1 gene (which encodes the μ-opioid receptor) on remifentanil potency investigated. In the present study, we aimed to develop a model to describe respiratory changes during propofol-remifentanil sedation in the same patients using continuously and noninvasively measured levels of pCO_2. A secondary aim was to test the influence of noxious stimulation on CO_2 elimination and of the A118G SNP genotype on respiratory changes in response to remifentanil.

Materials and Methods

This study was approved by the Institutional Review Board of the Hospital CLINIC de Barcelona, Spain (reference 2007/3664). All participants gave written, informed consent before being enrolled in the project. The data were a subset of a larger study in which the influence of the A118G SNP genotype on opioid requirements during sedation for endoscopy was investigated.(Borrat et al., 2013) Study methods are described in brief below, and have been reported in detail previously.(Borrat et al., 2013)

Patients and drug administration

Two hundred and seven patients undergoing sedation and analgesia for ultrasonographic upper gastrointestinal endoscopy were enrolled with the aim to include between 20 and 40 patients who could have the A118G SNP since the expected prevalence of A118G in the OPRM1 gene has been estimated to be around 10–19% in general population.(Lotsch and Geisslinger, 2005) All patients received a combination of propofol and remifentanil.

Participants were randomized to one of four groups. Each group received a fixed targeted controlled infusion (TCI) of either propofol 2.0 µg/ml, propofol 3.0 µg/ml, remifentanil 1.0 ng/ml or remifentanil 2.0 ng/ml. Infusions were given *via* a TCI system (Base Primea, Fresenius Kabi AG, Bad Homburg, Germany) set to target the desired concentration in the effect compartment. Parameter estimates as reported by Schnider et al.,(Schnider et al., 1998; Schnider et al., 1999) and Minto et al.,(Minto et al., 1997) were used for propofol and remifentanil infusions respectively. For each participant, the infusion of the second drug began after some data collection with the allocated drug only. The target effect site concentration of the second drug was then determined by the nausea (or "GAG") response of the previous participant according to the Dixon up-down method,(Dixon, 1991) and the second infusion started. GAG response to insertion of the endoscopy tube was considered positive when nausea, cough and/or

fight against the introduction of the endoscopy probe were observed (evaluated by the endoscopist responsible for the procedure). In the two propofol groups, a positive response resulted in an increase of the target remifentanil concentration by 0.5 ng/ml. In the remifentanil groups the corresponding increase in targeted propofol concentration was 0.5 µg/ml. A negative response to endoscopy tube insertion resulted in a reduction of the targeted concentration in the subsequent participant by the same magnitude. Once the response to endoscopy was observed, TCI targets for both drugs were altered according to clinical requirements as per standard clinical practice.

Response measurements

Arterial blood pressure, pulse oximetry data and respiratory rate were monitored noninvasively for all participants. In addition, electroencephalograph (EEG) data from BIS (Bispectral Index A2000, Covidien, Boulder, CO) were recorded.

Transcutaneous arterial pressure of carbon dioxide (pCO_2) was measured using a SENTEC Digital Monitor (Therwil, Arlasheim, BL, Switzerland). pCO_2 is measured with a sensor containing a Severinghaus type pH-sensitive electrode bathed in an electrolytic solution protected by a permeable membrane. The sensor is warmed to a constant surface temperature of 42°C increasing CO_2 permeability. CO_2 crosses the sensor membrane and modifies the pH in the electrolyte solution which is sensed by the Severinghaus electrode. pH changes and therefore proportional electrode signal are directly related to pCO_2 concentration. The sensor was calibrated and prepared according to the manufacturer recommendations, then placed in the earlobe of the patient and secured with special adhesive and an ear clip. An equilibration period of about five minutes was observed before the monitor was ready to give accurate measures. Measurements were recorded online every second using specific software.

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Data from pCO_2, drug infusion, predicted plasma concentrations, BIS, hemodynamics, noxious stimulation and other relevant events were synchronized off line for further analysis with a resolution of one data every 30 seconds. Before beginning the study, a single venous blood sample was drawn for genotyping of the A118G SNP as described elsewhere.(Borrat et al., 2013) Prior to any drug administration, a five minute period was observed in which the patient rested in a quiet environment while baseline data were collected.

Data analysis

Data were analyzed using a population approach in NONMEM version 7.2 (Icon Development Solutions, Ellicott City, MA). The stochastic approximation expectation maximization (SAEM) algorithm, followed by importance sampling (IMP), was used. Model selection was based on inspection of visual plots (including prediction-corrected visual predictive checks, or "pc-VPCs")(Bergstrand et al., 2011) and the change in the minimum value of the objective function (OBJ) provided by NONMEM. The minimum OBJ approximately equals the -2 x log likelihood (-2LL). A reduction in the OBJ between nested models suggests an improvement in model fit. A statistically significant improvement was required for inclusion of one additional parameter (one degree of freedom), equating to a reduction > 3.84 based on a Chi square distribution ($\alpha < 0.05$). Inter-individual variability (IIV) was modeled exponentially and residual error using an additive error model. Subject-specific magnitude of residual error and the non-diagonal elements of the Ω variance co-variance were also tested for significance.

Model building

Plasma drug concentration data were not available, so TCI system predicted plasma concentrations were used as the pharmacokinetic basis of the model. For each drug, we tested the inclusion of a hypothetical effect site compartment to describe the delay in effect

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onset.(Sheiner et al., 1979) Thus the time course of the predicted concentrations in the effect site was described as:

$$\frac{dCe}{dt} = k_{e0} \times (Cp - Ce)$$

Equation 1

where Cp is the concentration predicted by the TCI system, Ce is the predicted concentration in the effect site and k_{e0} is the first order rate constant governing the disequilibrium in drug distribution between the central (plasma) and effect site compartments. For both drugs the presence of the effect compartment has been widely documented.(Babenco et al., 2000; Bouillon et al., 2003; Bouillon et al., 2004a; Minto et al., 1997; Schnider et al., 1999)

In the current evaluation the framework of the indirect and turn-over response models including rebound mechanisms (Dayneka et al., 1993; Wakelkamp et al., 1996) was used to describe the time course of pCO_2 as the pharmacodynamic endpoint. pCO_2 levels are the result of the contribution of (i) CO_2 production and removal (i.e. removal from the lung alveolar *via* the process of respiration) rates, as represented by the zero and first order rate constants K_{in} and K_{deg}, respectively, as well as (ii) feedback mechanisms represented by the modulator M (equations 2 and 3).

$$\frac{dpCO_2}{dt} = K_{in} - K_{deg} \times M \times pCO_2$$

Equation 2

$$\frac{dM}{dt} = K_{mod} \times \left(\frac{pCO_{2_t}}{pCO_{2_0}}\right)^{\alpha} - K_{mod} \times M$$

Equation 3

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where K_{mod} is the turnover rate constant governing M dynamics, and α scales the effect of the change in pCO_2 over time (pCO_{2t}) with respect to baseline (pCO_{20}) on the production rate of M. In baseline conditions, the rate of CO_2 production is in equilibrium with its removal, then $dpCO_{20}/dt = 0$, $K_{in} = pCO_{20} \times K_{deg}$, and pCO_{2t} equals pCO_{20}.

The amount in the modulator compartment feeds back to the pCO_2 compartment to modulate the rate of pCO_2 removal (for example, *via* increasing or decreasing respiratory rate). Note that in this model, rebound is parameterized as a fraction from baseline, so that in homeostatic conditions ($t = 0$) the amount in the modulator compartment is equal to 1 and no modulation of pCO_2 removal occurs.

Drug effects were modeled as follows. Remifentanil is known to suppress ventilation,(Babenco et al., 2000; Dershwitz et al., 1996) and this mechanism of action was incorporated in the model as a reduction on the K_{deg} parameter as represented in equation 4.

$$\frac{dpCO_2}{dt} = K_{in} - \left(K_{deg} \times M \times pCO_2 \times E_{REM}\right)$$

Equation 4

E_{REM}, represents a function accounting for the remifentanil drug effects which takes the general form represented by equation 5:

$$E_{REM} = 1 - I_{MAX} \frac{{Ce_R}^{\gamma}}{{Ce_R}^{\gamma} + {IC_{50R}}^{\gamma}}$$

Equation 5

where IC_{50R} is the concentration of remifentanil in the effect site (C_{eR}) that causes 50% of the maximal inhibition in K_{deg} (I_{MAX}), and γ is a slope parameter governing the slope of the K_{deg} vs.

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C_{eR} relationship. I_{MAX} was constrained between 0 and 1, and during model development other models for drug effects, such as the linear model, were also tested.

Propofol effects (E_{PROP}) were incorporated in the model as modifying the feedback mechanism affecting removal of pCO_2 (represented in equation 6) following the observation that propofol alters the slope of the ventilation response to rising arterial CO_2.(Blouin et al., 1991) Subsequently, we incorporated propofol effects through the modulator compartment as inhibition of K_{mod}.

$$\frac{dM}{dt} = K_{mod} \times E_{PROP} \times \left(\frac{pCO_{2_t}}{pCO_{2_0}}\right)^{\alpha} - K_{mod} \times M$$

Equation 6

E_{PROP} has a structure similar to E_{REM} in equation 5, and as in the case of remifentanil, additional models for E_{PROP} were tested during the model building process. In addition, propofol has been shown to suppress CO_2 production in tissues by up to 30% in steady state, controlled respiratory studies.(Pavlin et al., 1996) To avoid bias in our parameter estimates, we included a correction factor on CO_2 production as suggested by Bouillon et al.,(Bouillon et al., 2004a) and Caruso et al,(Caruso et al., 2007; Caruso et al., 2008) assuming an I_{MAX} of 0.3 for propofol effects on K_{in} (equation 7):

$$\frac{dpCO_2}{dt} = (K_{in} \times E_{PROP}) - \left(K_{deg} \times M \times pCO_2\right)$$

Equation 7

The model described in equations 1-7 resembles the observations that both drugs independently cause depression of the respiratory system. A schematic representation of the model developed for respiratory depression effects of remifentanil and propofol in combination is provided in Figure 1.

Covariate model selection

Effects of several covariates were explored for significance. We tested the effect of age on the IC_{50} parameters of both drugs, and on the k_{e0} of remifentanil, based on the results obtained from previous analyses performed by Minto et al (Minto et al., 1997) and Schnider et al.(Schnider et al., 1999) A118G SNP was tested as a binary covariate for an influence on the IC_{50} of remifentanil, as individuals carrying the A118G genotype are known to display reduced sensitivity to opioids for some endpoints.(Borrat et al., 2013; Klepstad et al., 2004; Skarke et al., 2003) The third covariate explored was that of noxious stimulation ("NOX"). We hypothesized that noxious stimulation, or pain, is likely to increase respiration rate and therefore we explored NOX effects as an increase in the K_{deg} parameter. NOX was introduced as a binary covariate (endoscopy tube inserted or not inserted) that varied within the period of endoscopy, as done in previous work focusing on sedation levels in which a significant influence of this covariate was detected on propofol and remifentanil requirements.(Borrat et al., 2013) We tested each covariate individually, requiring a statistically significant improvement ($\alpha < 0.05$) in model fit as judged by the -2LL value for inclusion. For the final model, all significant covariates were included and the model reduced by removing those that failed to contribute to model fit. In addition to investigating covariates as described above, we also checked to see whether scaling to body weight was required for any parameters (this did not require the addition of a parameter to be estimated, so model improvement was evaluated using vpc's).

Results

Data were available for 136 of the 207 participants studied, providing a total of 38,761 pCO_2 observations. Seventy-one participants were excluded due to inadequate recordings of pCO_2 levels for the following reasons: unfinished signal stabilization despite more than 10 minutes waiting, sensor dislodged from the earlobe, excessive movement of the patient, poor quality of the signal and problems with the data collection software. The final number of participants by group were N=36 in the propofol 2.0 µg/ml group, N=29 in the propofol 3.0 µg/ml group, N=29 in the remifentanil 1.0 ng/ml group and N=31 in the remifentanil 2.0 ng/ml group. Demographic characteristics for the group are summarized in Table 1, while characteristics of the data are summarized in Table 2.

Model building

Given the complexity of the mechanisms involved in the regulation of the respiratory depression as represented in previous published PKPD models, and the observational characteristics of our data, during the model building process we used the following techniques/approaches to develop our selected model: (i) deterministic simulations with the aid-software Berkeley-Madonna(Macey and Oster, 2010) to find proper initials estimates of the model parameters, and (ii) sequential model building where data from each drug was analysed separately first, and combination data were then incorporated into the analysis. In addition we experienced convergence issues with several models. All model features represented in equations 1-6 were supported by a significant reduction in -2LL. The main results obtained during model building ranked on the absolute decrease in -2LL, and the results of sensitivity analysis using simulation for each parameter in the final model, are provided in the Supplemental Data.

Considering the presence of an effect site compartment for remifentanil reduced the value of -2LL by over 500 points (***$p<0.001$). On the other hand our data did not support the prediction of effect site concentrations of propofol ($p>0.05$), therefore E_{PROP} on K_{mod} and K_{in} (equations 6 and 7) is driven by predicted plasma concentrations of propofol. With respect to the pharmacodynamic relationships (i.e., equation 5), I_{MAX} was not found to be significantly different from 1 for the effects of remifentanil and propofol on K_{deg} and K_{mod} respectively ($p>0.05$). As explained in the methods section the I_{MAX} corresponding to E_{PROP} on K_{in} was fixed (i.e., not estimated) to 0.3 according to literature estimates.(Bouillon et al., 2004a; Caruso et al., 2007; Caruso et al., 2008) Sigmoidicity was absent in the pharmacodynamic relationship of propofol (γ parameter not significant different from 1; $p>0.05$), in the case of remifentanil the estimate of γ was 2.75.

The inclusion of a modulator compartment (represented by equations 2 and 3) was highly significant indicating a strong regulatory mechanism. The final model uses the ratio between current and baseline value of pCO_2 as the driving force triggering the regulatory mechanism. Other parameterizations were tested, such as that used by Olofsen et al., (2010)(Olofsen et al., 2010) but in our case it worsened the fit. In addition we got an estimate of the α parameter significantly different from 1 (***$p<0.001$). E_{PROP} effects on K_{mod} also resulted in significance, supporting the observation that propofol by itself has an effect of respiratory function. During model building, other model alternatives were also explored, for example, including propofol effects on K_{deg} (with and without an interaction term between propofol and remifentanil) and as an allosteric modulator of E_{REM}, but as these did not result in model improvements they were not investigated further.

The following parameters in the model were associated with inter-patient variability: pCO_{20}, K_{deg}, and IC_{50R}. IIV was not supported by the data for the remaining parameters despite

individual testing. As stated in the methods section, IIV was described with an exponential model. However the distribution of the random effect for pCO_{20} was better described using the Box-Cox transformation,(Box and Cox, 1964) which improved model performance as judged by visual inspection of the predictive checks. Results also indicated a significant patient-specific magnitude of residual error. The population model selected included covariance for the random effects associated pCO_{20}, K_{deg}, and IC_{50R}. We scaled pCO_{20} by weight, as this corrected a persistent misspecification in our vpc's.

A118G SNP in the OPRM1 genotype caused a small increase in the remifentanil IC_{50}, from 1.12 ng/ml in normal patients to 1.32 ng/ml (18%) in those who were recessive homozygous for the GG SNP on the OPRM1 gene. However this effect was neither statistically, nor clinically, significant. When introduced individually, significant covariate effects were identified for age on remifentanil IC_{50} and k_{e0}, age on propofol IC_{50}, and noxious stimuli (NOX) on K_{deg} (see Supplemental Data 1). All significant covariates were included and those that failed to estimate (indicating no effect) were removed. The final selected model included covariate effects for age on remifentanil k_{e0} (Age_k_{e0R}) and propofol IC_{50} (Age_$IC_{50,P}$).

Table 3 lists the model parameter estimates corresponding to the selected model for the interaction of propofol and remifentanil on respiratory depression. Some parameters (α, Age_k_{e0R} and Age_IC_{50p}) showed a high standard error indicating that they were not fully identifiable. Percentage of η- and ε-shrinkage was lower than 5 %.

Figure 2 shows the results of model performance. The panels corresponding to the pc-VPCs indicated that the mean tendency and the dispersion of data are well captured by the model regardless of the independent variable used to check model performance (time, or predicted concentrations). Similarly, conditional weighted residuals versus the three different independent variables reveals that there were no systematic deviations from the perfect fit (i.e., CWRES=0)

indicating an absence of major model misspecifications. CWRES versus time datapoints are visible for propofol alone, remifentanil alone and for the combination (top right plot of Figure 2).

Figure 3 gives the profiles for predicted drug plasma concentrations for both drugs, the predicted effect site concentrations for remifentanil, and the observed and model predicted pCO_2 levels for six patients selected at random.

Figure 4 demonstrates through typical simulations the contribution of the different elements of the selected model on the time course of respiratory depression. Drug pharmacokinetic profiles (panel A) are simulated using standard population models given in the literature (see methods). The kinetic profiles in panel B show that the model elements with greater impact on pCO_2 are E_{REM} and the modulator. Age appears to have a marginal effect on respiratory response as shown in panel C. The effect of remifentanil on K_{deg} is more pronounced than the effect propofol exerts on K_{Mod} and K_{in} (panel D). Note that although propofol does not affect K_{deg} directly, it indirectly reduces it through its action on M.

Figures 5 and 6 are simulations, restricted to the concentration range adequately covered by our data (remifentanil $\leq$ 3.0 ng/ml and propofol $\leq$ 4.0 mcg/ml). Figure 5 shows isobolograms corresponding to a 10% and 20% increase in pCO_2 from baseline once steady-state conditions are achieved, suggesting a synergistic relationship between propofol and remifentanil. Figure 6 gives the time course of recovery following termination of an infusion (t=0 is steady state). Note at time 0, the system is assumed to be at steady state. Predicted pCO_2 returns to near baseline levels within 30 min for most concentration combinations, although some fluctuations exist due to the effect of the modulator/feedback components of the model.

Discussion

Propofol with remifentanil is a popular hypnotic-opioid combination commonly used for anesthesia and sedation. Although several models for respiratory depression exist for healthy volunteers, or patients receiving just one of these drugs, a model for their combined effects on respiratory depression in patients undergoing noxious procedures has yet to be reported. We developed an indirect-effect model with system feedback to describe changes in pCO_2 induced by propofol and remifentanil. OPRM1 genotype and noxious stimuli were not significant covariates in our dataset. A combination of propofol 1.8 and remifentanil 1.5, that induces a sedation level of not responsive to verbal command but rousable, has an expected pCO_2 response of 55.7 mmHg (assuming steady state conditions, basal pCO_2 of 39 mmHg in a 65 y old, 70kg male).

We found remifentanil potently inhibits pCO_2 removal, with an effect-site IC_{50} of 1.13 ng/ml. This is similar to that reported in healthy volunteers (0.92-1.6 ng/ml).(Babenco et al., 2000; Bouillon et al., 2003; Olofsen et al., 2010) Onset of remifentanil effects was slow, with a k_{e0} of 0.28 min^{-1} ($t_{1/2}k_{e0}$ of 2.48 min) that increased with age. Others suggest somewhat faster onset (k_{e0} 0.34-1.3 min^{-1}, $t_{1/2}k_{e0}$ 0.53-2.03 min) for respiratory depressant effects.(Babenco et al., 2000; Bouillon et al., 2003; Olofsen et al., 2010) This difference may be partly due to our older patient population (median age of 64.0 y, in comparison to healthy volunteers aged < 45 y). Slower onset with increasing age has also been reported for remifentanil EEG pharmacodynamics.(Minto et al., 1997) Propofol had an IC_{50} of 4.97 µg/ml in plasma. Older individuals were more sensitive to propofol, with age-adjusted IC_{50} estimates of 2.65 µg/ml and 1.9 µg/ml in 50 and 65 year olds, respectively. An IC_{50} for propofol in the effect site of 1.33 µg/ml was reported in healthy young adults.(Bouillon et al., 2004a) Our estimate is higher, partly because we did not include an effect-site compartment for propofol. The corresponding IC_{50} in the effect site will be lower as drug is transferred more slowly and in smaller amounts to

this compartment (dictated by the k_{e0} parameter). Propofol effects on tidal volume have a reported IC_{50} of 3.0 µg/ml in children undergoing sedation for endoscopy.(Hahn et al., 2011) Remifentanil-propofol effects on ventilation response to stepped increases in pCO_2 have been studied in healthy volunteers.(Nieuwenhuijs et al., 2003) In these controlled, steady state conditions, propofol predominantly suppressed the slope of the ventilatory response (IC_{50} of 1.0 µg/ml) and had a much smaller effect on reducing the set-point of that response. Our estimate of baseline pCO_2 was less than that typically reported (36.4 mmHg/70kg versus 40.9-42.4 mmHg in other studies).(Bouillon et al., 2003; Bouillon et al., 2004a; Caruso et al., 2007; Nieuwenhuijs et al., 2003) Elevated ventilation rate in study participants as a result of pre-induction anxiety sometimes occurs,(Goodman et al., 1987) and may be true of our patients too, accounting for our lower baseline pCO_2. We also scaled baseline pCO_2 to weight; this was mandated by our data and a persistent misspecification in our checks of model performance. There is neither literature data nor physiological basis that we are aware of, supporting the covariate effect of body weight on the baseline pCO_2 parameter. However with this covariate in the selected model, model performance represented by visual predictive checks was greatly improved over the model without its inclusion. We recognize that such part of our model indicated some degree of model-misspecification probably at a different level than baseline that could not be handled in another way.

The remifentanil IC_{50} estimate for bispectral index suppression in the same patients was much larger than that estimated for pCO_2 (19.6 ng/ml).(Borrat et al., 2013) The inability of remifentanil to substantively impact bispectral index leading to high IC_{50} estimates is well documented(Manyam et al., 2007; Nieuwenhuijs et al., 2003) and is indicative of its low impact on sedation levels.(Bouillon et al., 2004b) Conversely we saw a smaller IC_{50} estimate for propofol for bispectral index (3.86 µg/ml in the effect site) than that estimated for pCO2, in line

with propofol's potent sedative and anesthetic effects and smaller impact on the respiratory system.

Our model most closely resembles that of Bouillon et al. They described single drug effects using CO_2 arterial and effect-site compartments.(Bouillon et al., 2003; Bouillon et al., 2004a) Drug concentration indirectly effects CO_2 elimination from the arterial compartment (estimated at 0.08-0.11 min^{-1} in volunteers, similar to our K_{deg} parameter at 0.06 min^{-1}).(Bouillon et al., 2003; Bouillon et al., 2004a) They also applied system feedback to CO_2 elimination (using an equivalent function to equation 3), the delay of which was dependent on the parameter describing the CO_2 transfer rate between compartments ($k_{el,CO2}$, 0.9 min^{-1}).(Bouillon et al., 1999; Bouillon et al., 2003; Bouillon et al., 2004a) In our model, feedback delay is described by K_{mod} (0.45 min^{-1}). Our estimate of gain in the system response to increasing pCO_2 (α), at 3.82, was close to reported values of 4.3-4.37 established in single drug studies in volunteers.(Bouillon et al., 2003; Bouillon et al., 2004a) The large confidence intervals surrounding this parameter estimate reflect the uncontrolled, non-steady state conditions of our study.

Olofsen et al also used two compartments (tissue and alveolar) to describe CO_2 pharmacokinetics, with remifentanil reducing inspired ventilation.(Olofsen et al., 2010) Their model reflects the observation that opioids alter the baseline (or set-point) of the ventilatory response to rising pCO_2 while propofol alters the slope of that response.(Nieuwenhuijs et al., 2003) They included both remifentanil and propofol effects, but delay in system feedback was not estimated and propofol was incorporated as a (binary) covariate effect on system and remifentanil parameters. Unlike these previous models, we grouped pCO_2 kinetics into a single compartment and described system modulation using compartmental kinetics. Propofol effects were applied to the rate of synthesis in the modulator compartment, thereby affecting the magnitude of the response to rising pCO_2. Remifentanil effects were applied directly to the

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parameter describing pCO_2 removal as done by others for opioids (usually minute ventilation, in our model K_{deg}).(Bouillon et al., 1999; Bouillon et al., 2003; Caruso et al., 2008; Olofsen et al., 2010) Thus we include independent, concentration-based drug effects for both propofol and remifentanil on pCO_2.

We modeled pCO_2, as an objective biomarker of respiratory depression. Previous work has established the correlation between pCO_2 and $pACO_2$.(Chhajed et al., 2010; Rollins et al., 2014) An absolute value above 75 mmHg, in the severe hypercapnia range, can affect several organs and systems and may cause decreased cerebral blood flow, increased plasma catecholamine levels and increased cardiac output and arterial blood pressure predisposing to severe arrhythmias. Hypercapnic pulmonary vasoconstriction augments hypoxic pulmonary vasoconstriction and may worsen right heart function. Values above 150 mmHg have been associated with stupor and coma. Hypercapnia cannot easily be diagnosed clinically but is obvious with the aid of a quantitative CO_2 measurement system.(Lumb, 2000) The trend of continuous measures of pCO_2 gives an idea of the global performance of the respiratory drive. Using this monitor in the clinical setting might be advantageous, particularly in patients breathing spontaneously where capnography, transthoracic impedance measurement of respiratory rate or estimation of tidal volume methods are not reliable. We found that we often had issues maintaining sensor contact in lightly sedated patients who frequently moved. Consequently data were unavailable for 71 of 207 participants, usually due to an unstable connection or signal. We note that newer sensors are now available that can be securely fixed to the chest using tape, and these may provide a more stable method of measuring transcutaneous pCO_2. Arterial blood sampling, the gold standard for pCO_2, is not a continuous measure nor is it practical in this setting for obvious reasons.

We could not detect altered pCO_2 response for A118G polymorphic patients. Similarly, Romberg et al did not detect differences in respiratory effects despite an increase in analgesic

requirements.(Romberg et al., 2005) Noxious stimulation is usually associated with increased respiratory rate which should decrease pCO_2. Although there was a trend, NOX was not included in the model based on our *a priori* criteria for covariate inclusion. The effect of age suggests that CO_2 washout is slower in older patients.

This model could be used to explore concentration ranges previously proposed as optimal for sedation, and to simulate expected pCO_2 levels while incorporating covariate and interindividual variability factors. This would help define rational and safe sedation ranges that avoid or minimize the consequences of respiratory depression and increased pCO_2. Automatic control Closed-Loop systems have already been used adjusting propofol and remifentanil to hypnotic endpoints using the BIS.(Liu et al., 2011) Sedation and analgesia techniques might benefit from an automatic system able to use two different endpoints - hypnotic level on one side and pCO_2 as Bouillon et al proposed for remifentanil and pCO_2.(Caruso et al., 2006)

Several limitations of our work should be acknowledged. Modulation of the respiratory system occurs via several physiological processes.(Dahan et al., 1990; Lloyd et al., 1958; Ward and Karan, 2002) This makes estimation of model parameters difficult, even in controlled conditions and ventilation studies. We studied patients undergoing an uncomfortable procedure with anesthetic polypharmacy in non-steady state conditions and all components of the respiratory system in play. Although an advantage in that our data reflect the clinical environment, this impedes our ability to identify and quantify system factors. Hypercarbic and hypoxic respiratory drives vary among individuals.(Sahn et al., 1977) We did not establish individual sensitivity to rising CO_2, and our population may include outlier individuals. We modeled all processes of system modulation together as one process (in one compartment), which is physiologically inaccurate but does provide an adequate description of our data. An inhibitory effect of hypnotics on CO_2 production has been documented (Pavlin et al., 1996) and should be included to avoid biased parameter estimates.(Bouillon et al., 2004a) We assumed only propofol inhibits

CO_2 production, up to 30% of baseline.(Bouillon et al., 2004a; Caruso et al., 2007; Caruso et al., 2008) Of course this assumption may be incorrect, particularly where multiple drugs are administered. We did notice parameter estimates were better aligned with literature values once this correction was included. We also had a high rate of dropouts as discussed above, although these were fairly random across the four groups (with perhaps some increased dropout in those individuals receiving remifentanil first, see results).

Using clinical data from patients undergoing sedation with analgesia, with noninvasively and continuously measured pCO_2, we developed a PKPD model characterizing a synergistic relationship for propofol and remifentanil for respiratory depression. Neither A118G SNP in the OPRM1 gene, nor noxious stimulation, influenced the respiratory effects of remifentanil in our dataset. Age significantly affected the propofol and remifentanil relationship to pCO_2, with older patients more prone to respiratory depression. Context sensitive decrement times show that recovery from hypercapnia is fast and within 15 min, pCO_2 nears baseline irrespective of the residual drug concentrations.

Authorship contributions:

Participated in research design: Borrat, Trocóniz, Castells and Gambús.

Conducted experiments: Borrat, Valencia, Jensen, Pedroso, Muñoz, Castellví-Bel, Castells, Gambús.

Performed data analysis: Hannam, Trocóniz, Valencia, Gambús.

Wrote or contributed to the writing of the manuscript: Hannam, Trocóniz, Gambús and Borrat. All authors had access to the final version of the manuscript.

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Footnotes:

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Figure legends:

Figure 1. Model of propofol and remifentanil effects on the pCO_2. The model is based on two compartments: the main compartment describing changes in CO_2, and a modulator compartment (M) representing feedback processes (such as control of ventilation rate) that work to maintain system homeostasis. Changes in CO_2 concentration in the main compartment modify the rate in to M (by K_{mod}), and changes in M modify the rate of CO_2 removal from the main compartment (by K_{deg}). These primary relationships of the system are indicated by the heavy bold arrows. The influence of CO_2 on K_{mod} is determined by the ratio of pCO_2 at time t (pCO_{2t}) to that at baseline (pCO_{20}), so during homeostasis this term is equal to 1 and no system modulation occurs. Propofol reduces K_{mod} (thereby reducing the rate in to M and inhibiting the feedback response to rising pCO_2), and has a small effect on metabolic CO_2 production (represented by K_{in}, $\leq$ 30% reduction). Remifentanil acts *via* an effect site compartment to reduce K_{deg}. Drug effects for both remifentanil (E_{REM}) and propofol (E_{PROP}) are indicated in the figure by light arrows. α is an amplification factor for the system feedback.

Figure 2. Goodness of fit plots. The left panel gives prediction-corrected visual predictive checks (pc-VPCs), while the right panel gives conditional weighted residuals (CWRES). Goodness of fit is given for pCO_2 versus time (A and B), pump-predicted remifentanil concentrations in the plasma (C and D), and pump-predicted propofol concentrations in the plasma (E and F). The pc-VPC plots show median and 90% observation intervals (solid and dashed lines respectively), overlaid with prediction percentiles (10%, 50%, and 90%, solid shaded areas). CWRES plots show the ideal fit (horizontal grey line, CWRES=0) and the actual fit (red broken line). For the CWRES v time plot, CWRES data points that pertain to propofol alone are given by red circles, remifentanil by blue circles, and the combination by open circles. VPCs were constructed using 1000 simulations.

Figure 3. Plots of individual fits for six participants, selected at random. Predicted plasma concentrations are given for propofol (yellow line), for predicted plasma and effect-site concentrations for remifentanil (blue solid and broken lines, respectively). Observed pCO_2 are open black circles, with individual model predictions in solid red lines. Durations of noxious stimuli are indicated by the horizontal black lines visible at the top of each plot.

Figure 4. Contribution of different elements of the final model over time. Simulation shows A) the time course of drug concentrations for a ten minute fixed infusion of 2.0 µg/ml propofol and 2.5 ng/ml remifentanil (based on literature population pharmacokinetic models, see methods section), B) the corresponding change in predicted pCO_2 for 1) the full model (solid black line) 2) ignoring the contribution of remifentanil, 3) ignoring the contribution of propofol, and 4) ignoring the contribution of the modulator compartment. C shows the contribution of age on pCO_2 for the same infusion inputs. D shows the percentage change from baseline value for K_{deg} and K_{mod} parameters with increasing steady state concentrations of either drug alone.

Figure 5. Isoboles for steady state concentrations of remifentanil and propofol that cause 10% and 20% increases in pCO_2 from baseline. Broken lines indicate additive effects, while solid lines show model predictions and bow toward the plot origin suggesting a synergistic relationship.

Figure 6. Simulated time to recovery following termination of drug administration, from steady state conditions. Plasma profiles for propofol (red broken lines) and remifentanil (blue broken lines) are simulated using Schnider and Minto PK models respectively. Predicted pCO_2 profiles are given by solid lines. The system is assumed to be at steady state at time=0.

Table 1. Participant demographics

Values are median (range) unless otherwise indicated. Concentrations given for propofol and remifentanil are those predicted by the TCI pump in the plasma compartment and for the full dataset.

Participants	Median (range)
Count of participants	136
Age (y)	64.0 (25.0-88.0)
Height (cm)	164.0 (147.0-190.0)
Weight (kg)	70.0 (35.0-98.0)
Gender (count, M/F)	84 / 52
OPRM1* (count, %)	7 (5.4%)
Propofol concentration (µg/ml)	2.72 (0, 13.0)
Remifentanil concentration* (ng/ml)	1.50 (0, 9.8)

*Recessive homozygous (GG) for the SNP on the OPRM1 gene.

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Table 2. Summary of baseline, infusion and noxious stimulation conditions

Values are median (range) durations, given in minutes. Median (range) predicted plasma concentrations for both drugs are also provided for each condition.

	Data points	Duration (min)	Predicted plasma concentrations*	
			Propofol (µg/ml)	Remifentanil (ng/ml)
Baseline (no drug)	970	2.5 (0 - 19.4)	-	-
Propofol infusion	2,010	1.5 (0 - 19.1)	4.2 (0.004 - 10.6)	-
Remifentanil infusion	2,647	2.9 (0 - 13.9)	-	3.1 (0.01 - 8.2)
Combination infusion	33,134	66.9 (15.1 - 142.2)	2.5 (0.002 - 13.0)	1.5 (0.004 - 9.8)
NOX=0	17,223	22.5 (4.0 - 68.1)	2.7 (0 - 13.0)	1.2 (0 - 9.8)
NOX=1	21,538	45.3 (1.85 - 126.9)	2.5 (0 - 8.9)	1.3 (0 - 5.9)

*Plasma concentrations are predicted by the TCI system used in effect site targeting mode. NOX is noxious stimulation as caused by insertion of the endoscopy tube.

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Table 3. Final parameter estimates for the final model

Inter-individual variability (IIV) is expressed as CV(%) with 95% confidence intervals given in square brackets. pCO_{20} is baseline pCO_2, estimated per kg. K_{deg} is a rate constant describing the rate of pCO_2 removal from the main system compartment, K_{mod} describes the rate of synthesis and degradation from the modulator compartment, α describes amplification of the feedback system in responding to changes in pCO_2. IC_{50P} and IC_{50R} are the concentrations of propofol and remifentanil respectively that cause 50% the maximal drug effect. γ_R is a shape parameter describing the shape of the remifentanil concentration-response curve and k_{e0R} describes the transfer of remifentanil between the plasma and effect-site compartments. *Age covariate effects, introduced as $\theta_{Ind} = \theta_{pop} - (AGE/64) * \theta_{Age}$. Minimal IIV terms were added and fixed to a low value for all parameters not already associated with IIV (indicated by - in table) to improve NONMEM efficiency during SAEM estimation methods with MU referencing.

Parameter	Estimate (CV%)	[5^{th} -95^{th}]	Shrinkage (%)	IIV (CV%)
System parameters				
pCO_{20} (mmHg/kg)	36.4 (0.52)	[0.49-0.56]	0%	29.2* (27.6%)
K_{deg} (min^{-1})	0.057 (39.1%)	[0.01-0.10]	0.4%	204.7 (32.7%)
K_{mod} (min^{-1})	0.45 (43.0%)	[0.07-0.83]	-	-
α	3.82 (94.8%)	[-3.28-10.92]	-	-
Residual error (mmHg)	1.98 (11.4%)	[1.54-2.42]	1.9%	52.82 (11.7%)
Drug parameters				
IC_{50R} (ng/ml)	1.13 (44.0%)	[0.16-2.10]	4.0%	80.0 (25.2%)
γ_R	2.75 (18.3%)	[1.77-3.73]	-	-
k_{e0R} (min^{-1})	0.28 (37.3%)	[0.07-0.48]	-	-
*Age_k_{e0R}	0.12 (73.4%)	[-0.05-0.29]	-	-
IC_{50P} (µg/ml)	4.97 (17.3%)	[3.28-6.66]	-	-

*Age_IC_{50p}	2.73 (51.3%)	[-0.01-5.47]	-	-

* IIV for pCO_{20} was best modelled using a box cox transformation, and the box cox parameter λ (CV%, 5^{th} -95^{th}) of -1.18 (11.4%, -1.43--0.92). CV, coefficient of variation.

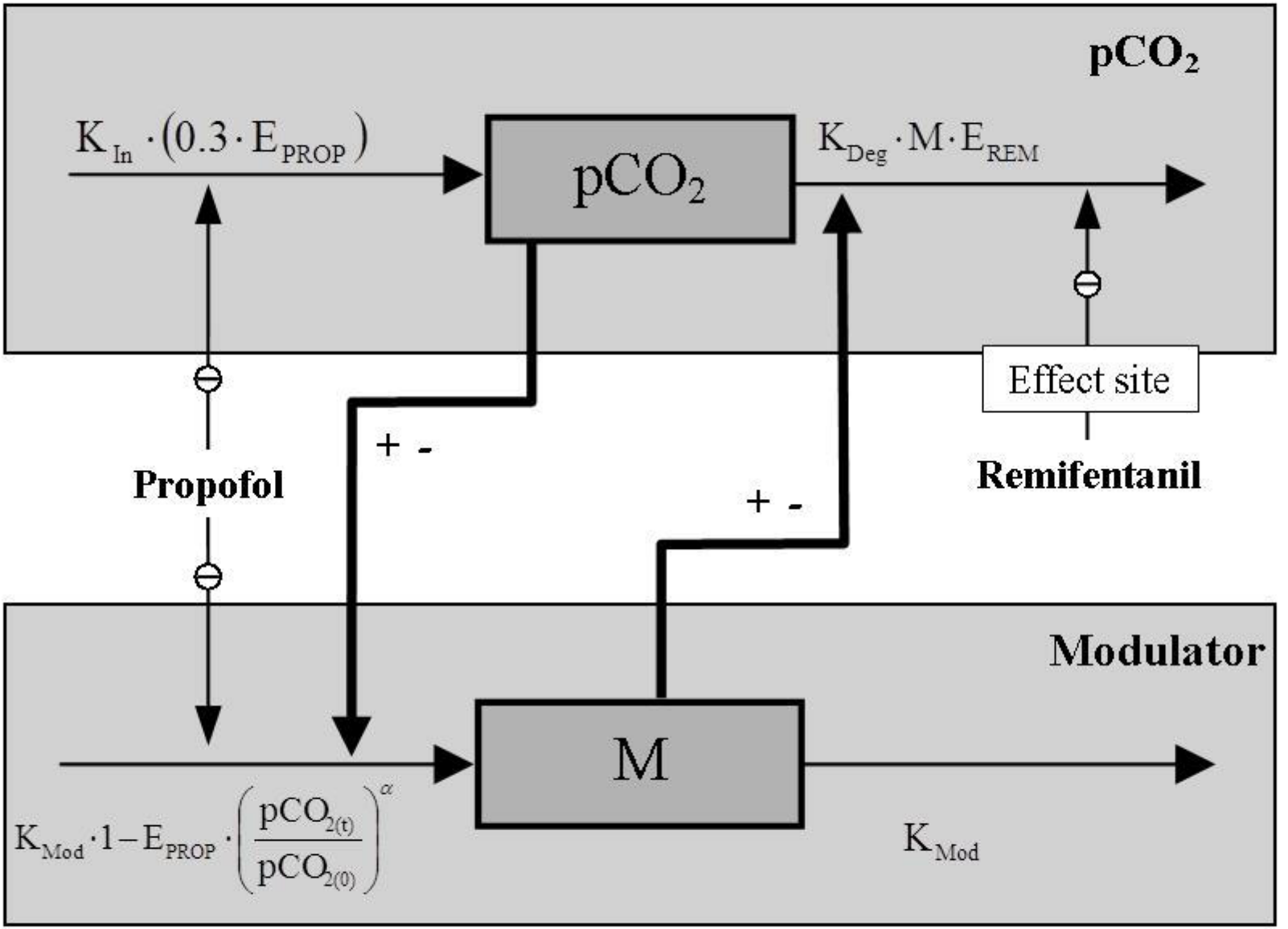
pCO2
$K_{In} \cdot (0.3 \cdot E_{PROP})$
pCO2
$K_{Deg} \cdot M \cdot E_{REM}$
Effect site
Propofol
Remifentanil
+ -
+ -
Modulator
M
$K_{Mod} \cdot 1 - E_{PROP} \cdot \left(\frac{pCO_{2(t)}}{pCO_{2(0)}} \right)^{\alpha}$
K_{Mod}

Figure 1

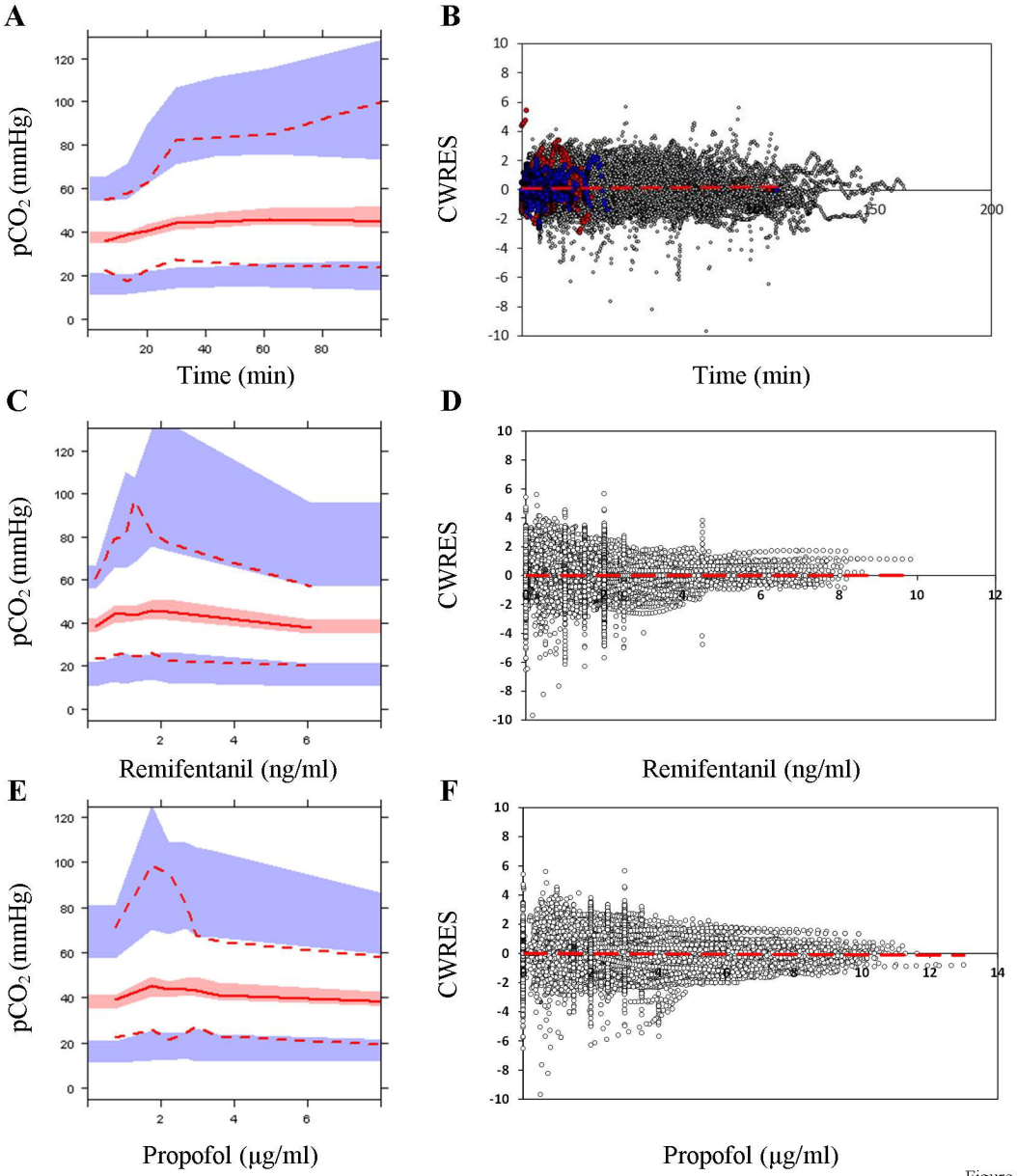
A
B
C
D
E
F
pCO2 (mmHg)
CWRES
Time (min)
Remifentanil (ng/ml)
Propofol (µg/ml)

Figure 2

JPET Fast Forward. Published on December 11, 2015 as DOI: 10.1124/jpet.115.226977
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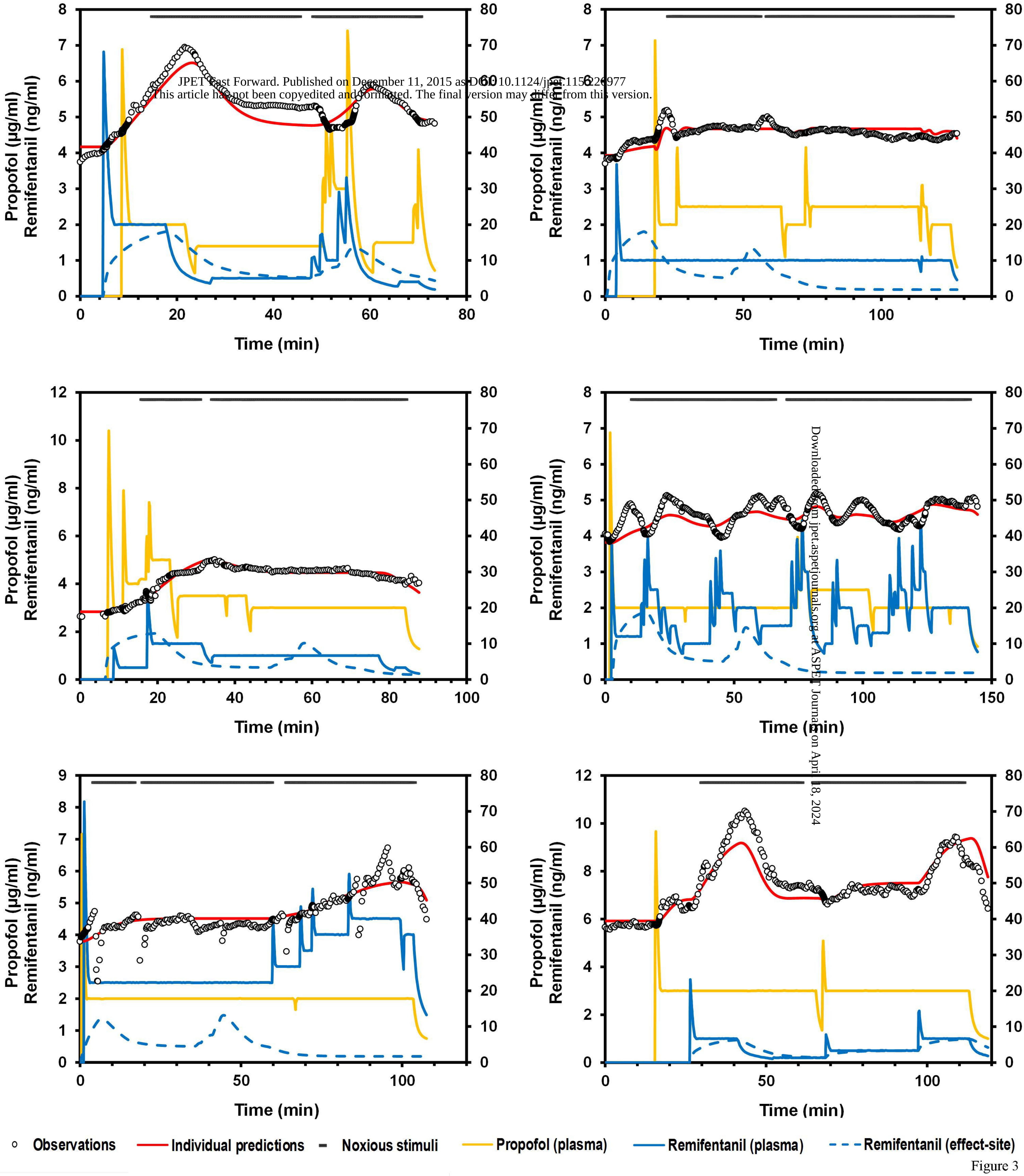

Figure 3

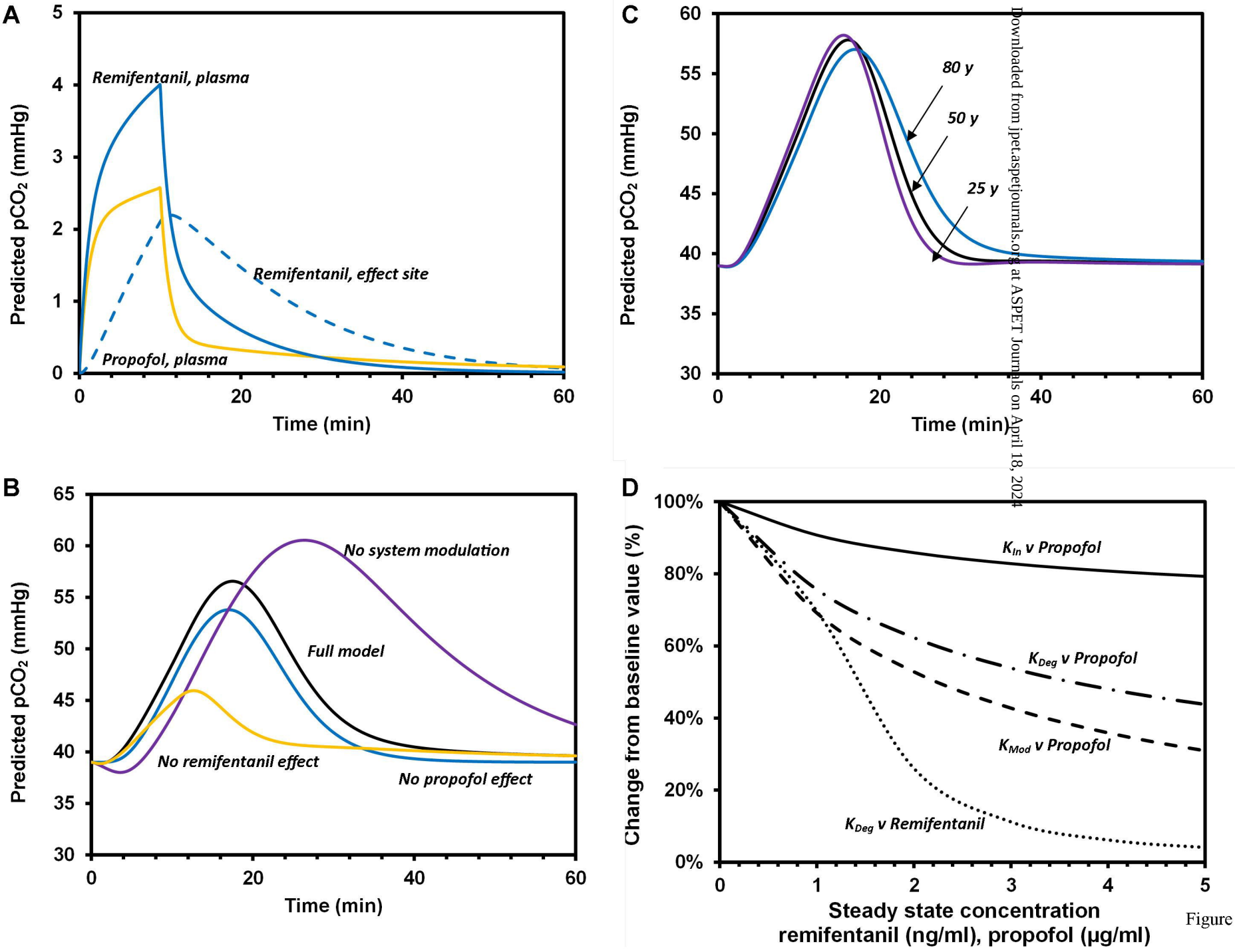

Figure 4

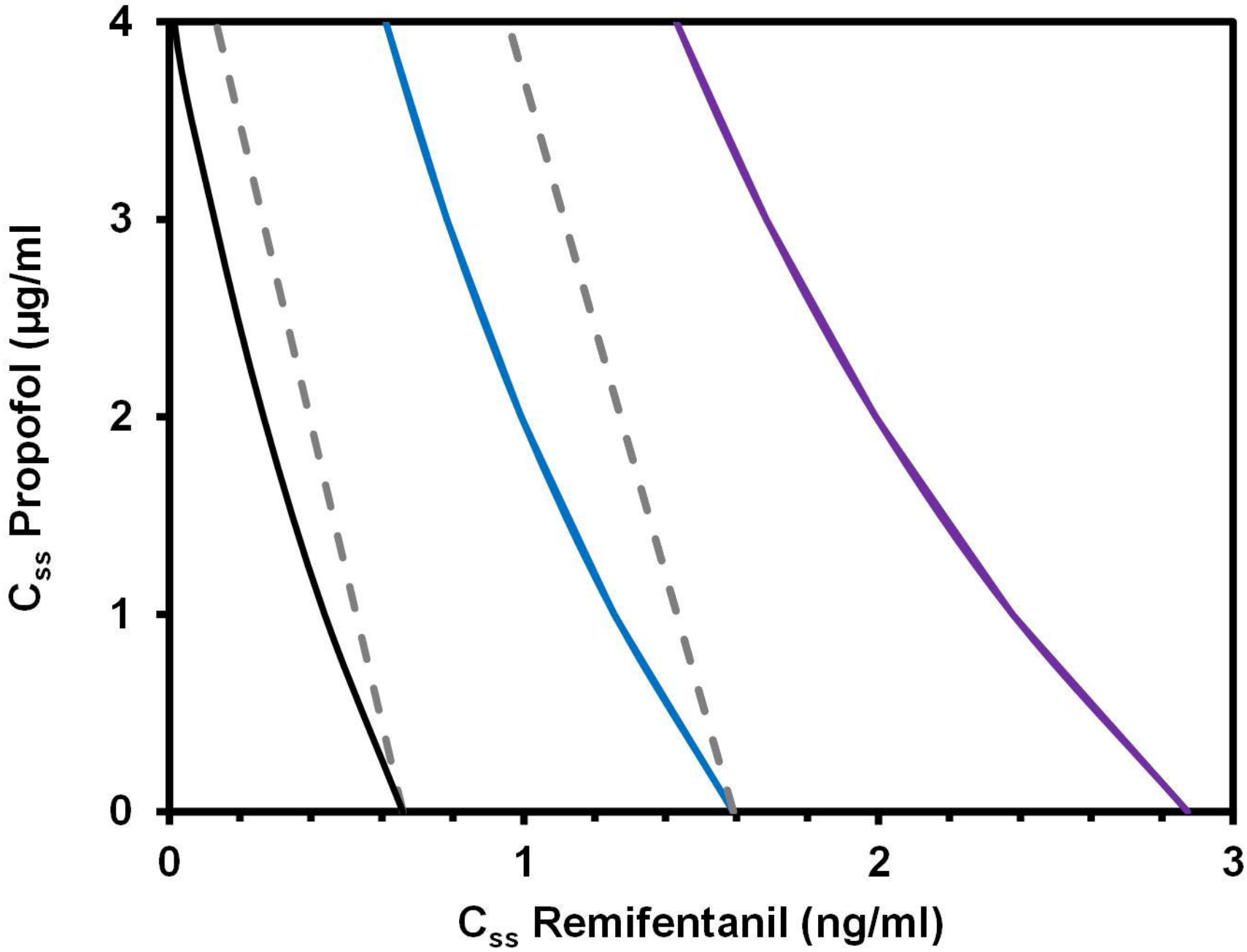

Figure 5

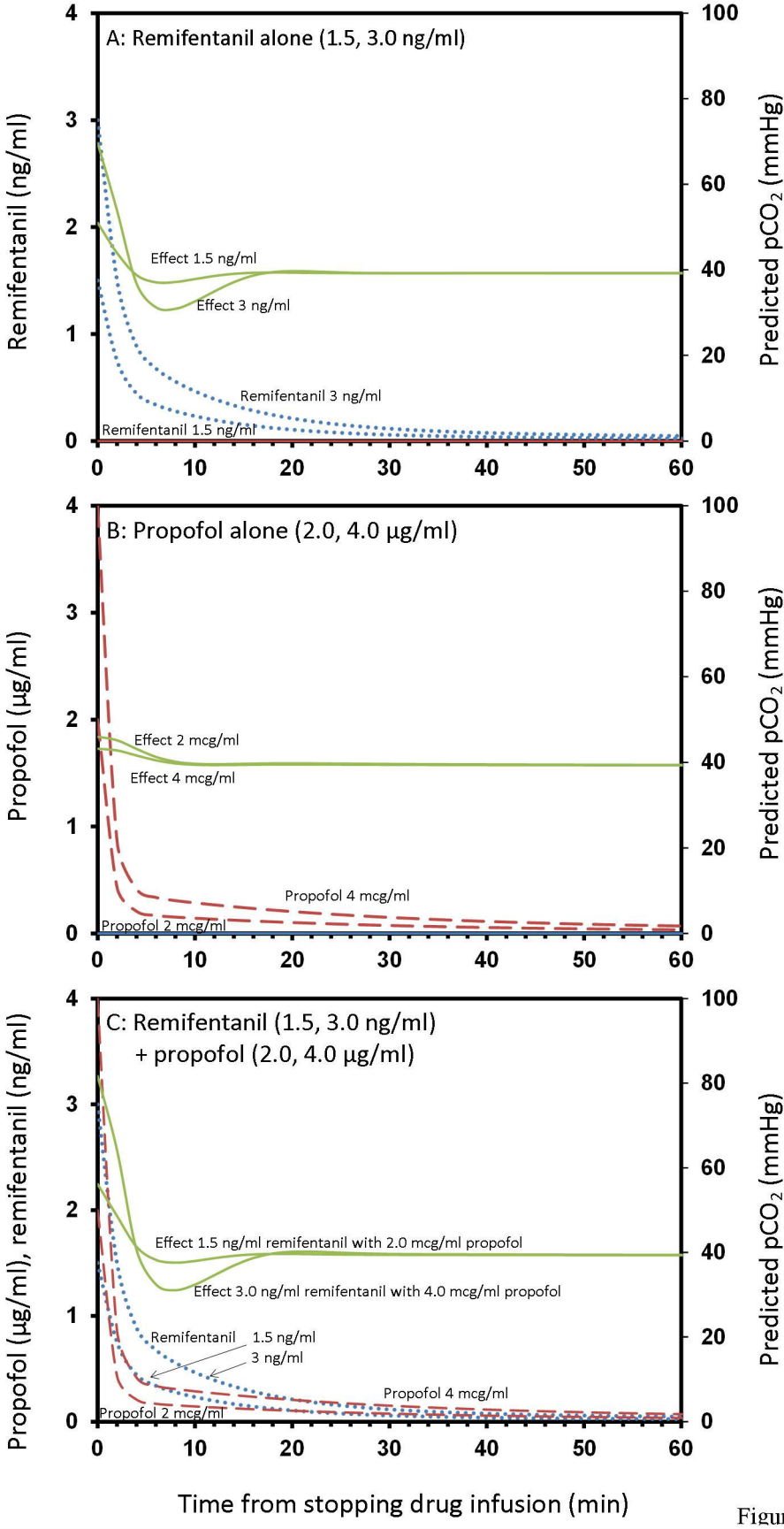
A: Remifentanil alone (1.5, 3.0 ng/ml)
Remifentanil (ng/ml)
Predicted pCO2 (mmHg)
Effect 1.5 ng/ml
Effect 3 ng/ml
Remifentanil 3 ng/ml
Remifentanil 1.5 ng/ml
B: Propofol alone (2.0, 4.0 µg/ml)
Propofol (µg/ml)
Predicted pCO2 (mmHg)
Effect 2 mcg/ml
Effect 4 mcg/ml
Propofol 4 mcg/ml
Propofol 2 mcg/ml
C: Remifentanil (1.5, 3.0 ng/ml)
+ propofol (2.0, 4.0 µg/ml)
Propofol (µg/ml), remifentanil (ng/ml)
Predicted pCO2 (mmHg)
Effect 1.5 ng/ml remifentanil with 2.0 mcg/ml propofol
Effect 3.0 ng/ml remifentanil with 4.0 mcg/ml propofol
Remifentanil 1.5 ng/ml
3 ng/ml
Propofol 4 mcg/ml
Propofol 2 mcg/ml
Time from stopping drug infusion (min)

Figure 6