Modeling Respiratory Depression Induced by Remifentanil and Propofol during Sedation and Analgesia Using a Continuous Noninvasive Measurement of pCO₂

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ABSTRACT

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. Data were available for 136 patients undergoing endoscopy with sedation. Participants randomly received infusions of propofol and remifentanil. Predicted plasma concentrations, outpuffed by infusion pumps, were available. Transcutaneous arterial pressure of carbon dioxide (pCO₂) 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 OPRM1 polymorphism. percent were recessive homozygous for OPRM1 polymorphism. An indirect-effect model with a “modulator” compartment best described pCO₂ data (P < 0.001) over a direct-effect model. Remifentanil inhibited pCO₂ removal with an IC₅₀ of 1.13 ng/ml and first-order rate constant (kₑ₀) of 0.28 minute⁻¹. Propofol affected the modulator compartment with an IC₅₀ of 4.97 µg/ml (no effect-site compartment). Propofol IC₅₀ and remifentanil kₑ₀ were reduced with increasing age. Noxious stimuli and genotype were not significant covariates. An indirect-effect model with a rebound mechanism can describe remifentanil- and propofol-induced changes in pCO₂ in patients undergoing noxious procedures. The model may be useful for identifying optimal dosing schedules for these drugs in a combination that provides adequate sedation but avoids 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 preprocedure 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:

- BIS, bispectral index; IV, interindividual variability; −2LL, −2 × log likelihood; NOX, noxious stimulation; OBJ, objective function; SNP, single nucleotide polymorphism; TCI, targeted controlled infusion; VPC, visual predictive check.

ABBREVIATIONS: BIS, bispectral index; IV, interindividual variability; −2LL, −2 × log likelihood; NOX, noxious stimulation; OBJ, objective function; SNP, single nucleotide polymorphism; TCI, targeted controlled infusion; VPC, visual predictive check.
oxygen saturation might show adequate levels during severe apnea; respiratory rate is difficult to measure objectively and clinically and, without an accurate evaluation of tidal volume, is hardly effective in assessing adequate ventilation; pCO₂ changes reflect respiratory function but must be measured by arterial blood sampling (invasive and noncontinuous) or through capnography, which may be susceptible to false negatives. Transcutaneous CO₂ monitors are based on arterIALIZATION of the capillary bed through the local application of heat. The use of Stow-Severinghaus electrodes provides information on the transcutaneous CO₂ tension continuously and noninvasively and with good correlation with arterial pCO₂. Transcutaneous measurement of arterial pCO₂ allows us to study respiratory depression by analyzing the time course of pCO₂ in individual patients undergoing sedation analgesia with propofol and remifentanil. Measuring and predicting pCO₂ levels is clinically relevant since pCO₂ reflects the level of respiratory depression. Very high levels of pCO₂ may be associated with severe consequences, such as 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, 2003, 2004a; Caruso et al., 2007). Few reports exist for models of combined effects of 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 from healthy volunteers (Nieuwenhuijs et al., 2003; Olofson et al., 2010). Respiratory control is determined by multiple processes, in which intrinsic feedback is provided by arterial pH levels and concentrations of O₂ and CO₂ (Lloyd et al., 1958; Dahan et al., 1990; 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, 2004a; Caruso et al., 2007; Olofson 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 was 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 pCO₂. A secondary aim was to test the influence of noxious stimulation on CO₂ 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, 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; the aim was 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 the 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 2.0 μg/ml propofol, 3.0 μg/ml remifentanil, or 2.0 ng/ml remifentanil. Infusions were given via a TCI system (Base Primera; Fresenius Kabi AG, Bad Homburg, Germany) set to target the desired concentration in the effect compartment. Parameter estimates as reported by Schneider et al. (1998, 1999) and 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 was 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 was 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 data from BIS (Bispectral Index A2000; Covidien, Boulder, CO) were recorded. pCO₂ was measured using a SenTec Digital Monitor (SenTec, Dübendorf, Switzerland). pCO₂ 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 CO₂ permeability. CO₂ 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 pCO₂ 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 5 minutes was observed before the monitor was ready to give accurate measures. Measurements were recorded online every second using specific software.

Data from pCO₂, drug infusion, predicted plasma concentrations, BIS, hemodynamics, noxious stimulation, and other relevant events were synchronized offline for further analysis, with a resolution of one datum 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 5-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 algorithm, followed by importance sampling, was used. Model selection was based on inspection of visual plots [including prediction-corrected visual predictive checks (VPcCs)] (Bergstrand et al., 2011) and the change in the minimum value of the objective function (OBJ) provided by
The minimum OBJ approximately equals the $-2 \times \log$ 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 $\chi^2$ distribution ($\alpha < 0.05$). Interindividual variability (IVV) was modeled exponentially, and residual error was determined using an additive error model. Subject-specific magnitude of residual error and the nondiagonal elements of the $\Omega$ variance-covariance 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 onset (Sheiner et al., 1979). Thus, the time course of the predicted concentrations in the effect site was described as:

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

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 (Minto et al., 1997; Schneider et al., 1999; Babenco et al., 2000; Bouillon et al., 2003, 2004a).

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 1) $CO_2$ production and removal rates (i.e., removal, from the lung alveolar via the process of respiration), as represented by the zero and first-order rate constants $K_{in}$ and $K_{deg}$, respectively, and 2) feedback mechanisms represented by the modulator $M$ (eqs. 2 and 3):

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

$$\frac{dM}{dt} = K_{mod} \times \left(\frac{pCO_2(t)}{pCO_2(0)}\right)^{\alpha} - K_{mod} \times M$$

where $K_{mod}$ is the turnover rate constant governing $M$ dynamics, and $\alpha$ scales the effect of the change in $pCO_2$ over time ($pCO_2(t)$) with respect to baseline ($pCO_2(0)$) on the production rate of $M$. In baseline conditions, the rate of $CO_2$ production is in equilibrium with its removal, then $dpCO_2/dt = 0$, $K_{in} = pCO_2(0) \times K_{deg}$, and $pCO_2(0)$ equals $pCO_2(0)$. 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 (Dershwitz et al., 1996; Babenco et al., 2000), and this mechanism of action was incorporated in the model as a reduction of the $K_{deg}$ parameter, as represented in eq. 4:

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

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

$$E_{REM} = 1 - \text{IMAX} \frac{C_{ER}^\gamma}{C_{ER}^\gamma + IC_{50ER}^\gamma}$$

where $IC_{50ER}$ is the concentration of remifentanil in the effect site ($C_{ER}$) that causes 50% of the maximal inhibition in $K_{deg}$, $\text{IMAX}$, and $\gamma$ is a slope parameter governing the slope of the $K_{deg}$ versus $C_{ER}$ relationship. $\text{IMAX}$ 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 by modifying the feedback mechanism affecting removal of $pCO_2$ (represented in eq. 6) following the observation that propofol alters the slope of the ventilation response to rising arterial $CO_2$ (Blouin et al., 1991). Specifically, we incorporated propofol effects through the modulator compartment as replacement of $K_{mod}$:

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

$E_{PROP}$ has a structure similar to $E_{REM}$ in eq. 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. (2004a) and Caruso et al. (2007, 2008) assuming an $\text{IMAX}$ of 0.3 for propofol effects on $K_{deg}$ (eq. 7):

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

The model described in eqs. 1–7 reflects 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 Fig. 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 $K_{e_0}$ of remifentanil, based on the results obtained from previous analyses performed by Minto et al. (1997) and 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 (Skaarke et al., 2003; Klepadlo et al., 2004; Borrat et al., 2013). The third covariate explored was that of noxious stimulation (NOX). We hypothesized that noxious stimulation, or pain, is likely to increase respiration rate; 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 was reduced by removing those that failed to contribute to model fit. In addition to investigating covariates as described earlier, 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 VPCs).

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 numbers of participants by group were $N = 36$ in the 2.0 $\mu$g/ml propofol group, $N = 29$ in the 3.0 $\mu$g/ml propofol group, $N = 29$ in the 1.0 $\mu$g/ml remifentanil group, and $N = 31$ in the 2.0 $\mu$g/ml remifentanil group. Demographic characteristics for the group are summarized in Table 1, whereas characteristics of the data are summarized in Table 2.

Model Building. Given the complexity of the mechanisms involved in the regulation of respiratory depression, as represented in previous published pharmacokinetic-pharmacodynamic models, and the observational characteristics of our data, we used the following techniques/approaches to during the model building process develop our selected model: 1) deterministic simulations with the aid software Berkeley-Madonna (Macey and Oster, 2010) to find proper initial estimates of the model parameters, and 2) sequential model building where data from each drug was analyzed 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 eqs. 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 Material).

Considering the presence of an effect-site compartment for remifentanil reduced the value of $-2LL$ by over 500 points ($P < 0.001$). In contrast, our data did not support the prediction of effect-site concentrations of propofol ($P > 0.05$); therefore, the effect of $E_{PROP}$ on $K_{mod}$ and $K_{in}$ (eqs. 6 and 7) is driven by predicted plasma concentrations of propofol. With respect to the pharmacodynamic relationships (i.e., eq. 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 Materials and 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.., 2008). Sigmoidicity was absent in the pharmacodynamic relationship of propofol ($\gamma$ parameter not significantly different from 1; $P > 0.05$); in the case of remifentanil, the estimate of $\gamma$ was 2.75.

The inclusion of a modulator compartment (represented by eqs. 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), but their parametrization worsened the fit in our case. In addition, we obtained an estimate of the $\alpha$ 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, such as 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 interpatient variability: pCO$_2(0)$, $K_{deg}$, and $IC_{50R}$. IIV was not supported by the data for the remaining parameters, despite individual testing. As stated in the Materials and Methods section, IIV was described with an exponential model. However, the distribution of the random effect for pCO$_2(0)$ was 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, such as 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 interpatient variability: pCO$_2(0)$, $K_{deg}$, and $IC_{50R}$. IIV was not supported by the data for the remaining parameters, despite individual testing. As stated in the Materials and Methods section, IIV was described with an exponential model. However, the distribution of the random effect for pCO$_2(0)$ 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 pCO$_2(0)$, $K_{deg}$, and $IC_{50R}$. We scaled pCO$_2(0)$ by weight, as this corrected a persistent misspecification in our VPCs.

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.

### Table 1

<table>
<thead>
<tr>
<th>Participants</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count of participants</td>
<td>136</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.0 (25.0–88.0)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.0 (147.0–190.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.0 (35.0–98.0)</td>
</tr>
<tr>
<td>Gender (count, male/female)</td>
<td>88 / 52</td>
</tr>
<tr>
<td>OPRM1* (count, %)</td>
<td>7 (5.4)</td>
</tr>
<tr>
<td>Propofol concentration ($\mu$g/ml)</td>
<td>2.72 (0, 13.0)</td>
</tr>
<tr>
<td>Remifentanil concentration (ng/ml)</td>
<td>1.50 (0, 9.8)</td>
</tr>
</tbody>
</table>

*Recessive homozygous (GG) for the SNP on the OPRM1 gene.
When introduced individually, significant covariate effects were identified for age on remifentanil IC50 and ke0, age on propofol IC50p, and NOX on Kdeg (see Supplemental Table S1). To identify the final model, all significant covariates included, and those that failed to estimate (indicating no effect) were removed. The final selected model included covariate effects for age on remifentanil ke0 (Age_ke0) and propofol IC50 (Age_IC50p).

Table 3 lists the model parameter estimates corresponding to the selected model for the interaction of propofol and remifentanil in respiratory depression. Some parameters (α, Age_ke0R, and Age_IC50p) showed a high standard error, indicating that they were not fully identifiable. The percentage of τ- and ε-shrinkage was lower than 5%.

Figure 2 shows the results of model performance. The panels corresponding to the prediction-corrected VPCs indicate 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., conditional weighted residuals = 0), indicating an absence of major model misspecifications. Conditional weighted residuals versus time data points are visible for propofol alone, remifentanil alone, and the combination (Fig. 2B).

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 pCO2 levels for six patients selected at random.

Through typical simulations, Fig. 4 demonstrates the contribution of the different elements of the selected model to the time course of respiratory depression. Drug pharmacokinetic profiles (Fig. 4A) are simulated using standard population models given in the literature (see Materials and Methods). The kinetic profiles in Fig. 4B show that the model elements with greater impact on pCO2 are EREM and the modulator. Age appears to have a marginal effect on respiratory response, as shown in Fig. 4C. The effect of remifentanil on Kdeg is more pronounced than the effect propofol exerts on Kmod and Kin.

Table 3
Final parameter estimates for the final model

IVI is expressed as CV(%) with 95% confidence intervals given in square brackets. pCO2(0) is baseline pCO2, estimated per kilogram. Kdeg is a rate constant describing the rate of pCO2 removal from the main system compartment, and α describes amplification of the feedback system in responding to changes in pCO2. IC50p and IC50R are the concentrations of propofol and remifentanil, respectively, that cause 50% the maximal drug effect. γR is a shape parameter describing the shape of the remifentanil concentration-response curve, and ke0 describes the transfer of remifentanil between the plasma and effect-site compartments. Minimal IVI terms were added and fixed to a low value for all parameters not already associated with IVI (indicated by “—”) to improve NONMEM efficiency during stochastic approximation expectation maximization estimation methods with MU referencing.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>[5th–95th]</th>
<th>Shrinkage</th>
<th>IVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCO2(0) (mm Hg/kg)</td>
<td>36.4 (0.52)</td>
<td>(0.49–0.56)</td>
<td>0</td>
<td>29.2 (27.6)</td>
</tr>
<tr>
<td>Kdeg (min⁻¹)</td>
<td>0.057 (39.1)</td>
<td>(0.01–0.10)</td>
<td>0.4</td>
<td>204.7 (32.7)</td>
</tr>
<tr>
<td>Kmod (min⁻¹)</td>
<td>0.45 (43.0)</td>
<td>[0.07–0.83]</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>α</td>
<td>3.82 (94.8)</td>
<td>[−3.28–10.92]</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Residual error (mm Hg)</td>
<td>1.98 (11.4)</td>
<td>[1.54–2.42]</td>
<td>1.9</td>
<td>52.82 (11.7)</td>
</tr>
<tr>
<td>Drug parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC50p (ng/ml)</td>
<td>1.13 (44.0)</td>
<td>[0.16–2.10]</td>
<td>4.0</td>
<td>80.0 (25.2)</td>
</tr>
<tr>
<td>γR</td>
<td>2.75 (18.3)</td>
<td>[1.77–3.73]</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ke0 (min⁻¹)</td>
<td>0.28 (37.3)</td>
<td>[0.07–0.48]</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age IC50p (μg/ml)</td>
<td>0.12 (73.4)</td>
<td>[−0.05–0.29]</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age IC50p (μg/ml)</td>
<td>4.97 (17.3)</td>
<td>[3.28–6.66]</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

CV, coefficient of variation.

1) IVI for pCO2(0) was best modeled using a Box-Cox transformation, and the Box-Cox parameter λ (CV%, 5th–95th) of −1.18 (11.4%–1.43 to 0.92).

2) Age covariate effects, introduced as θAge= θAge * (AGE/64) * θAge.
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 ≤ 3.0 ng/ml and propofol ≤ 4.0 µg/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 that, at time 0, the system is assumed to be at steady state. Predicted pCO$_2$ returns to near baseline levels within 30 minutes 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 pCO₂ induced by
propofol and remifentanil. OPRM1 genotype and noxious
stimuli were not significant covariates in our data set. A
combination of propofol 1.8 \( \mu \text{g/ml} \) propofol and remifentanil
1.5 ng/ml, which induces a sedation level where the patient is
not responsive to verbal command but is rousable, has an
expected pCO₂ response of 55.7 mm Hg (assuming steady-
state conditions, basal pCO₂ of 39 mm Hg in a 65-year-old,
70-kg male).

We found remifentanil potently inhibits pCO₂ 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 minute^{-1} (\( t_{1/2}k_{e0} \) of 2.48
minutes) that increased with age. Others suggest somewhat
faster onset (\( k_{e0} \) 0.34–1.3 minutes^{-1}, \( t_{1/2}k_{e0} \) 0.53–2.03 minutes)
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 years in
comparison with healthy volunteers aged <45 years). Slower
onset with increasing age has also been reported for remifenta-
nil electroencephalograph pharmacodynamics (Minto et al.,
1997). Propofol had an IC_{50} of 4.97 \( \mu \text{g/ml} \) in plasma. Older
individuals were more sensitive to propofol, with age-adjusted
IC_{50} estimates of 2.65 and 1.9 \( \mu \text{g/ml} \) in 50 and 65 year olds,
respectively. An IC_{50} for propofol in the effect site of 1.33 \( \mu \text{g/ml} \)

![Fig. 3. Plots of individual fits for six participants, selected at random. Predicted plasma concentrations are given for propofol (yellow line), and for predicted plasma and effect-site concentrations for remifentanil (blue solid and broken lines, respectively). Observed pCO₂ 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.](image-url)
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 IC50 in the effect site will be lower, as the drug is transferred more slowly and in smaller amounts to this compartment (dictated by the $k_{\text{e}}$ parameter). Propofol effects on tidal volume have a reported IC50 of 3.0 $\mu$g/ml in children undergoing sedation for endoscopy (Hahn et al., 2011). Remifentanil-propofol effects on ventilation response to stepped increases in pCO2 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 (IC50 of 1.0 $\mu$g/ml) and had a much smaller effect on reducing the set-point of that response. Our estimate of baseline pCO2 was less than that typically reported (36.4 mm Hg/70 kg vs. 40.9–42.4 mm Hg in other studies) (Bouillon et al., 2003, 2004a; Nieuwenhuijs et al., 2003; Caruso et al., 2007). Elevated ventilation rate in study participants as a result of preinduction anxiety sometimes occurs (Goodman et al., 1987) and may also be true of our patients, accounting for our lower baseline pCO2. We also scaled baseline pCO2 to weight; this was mandated by our data and a persistent misspecification in our checks of model performance. There are neither literature data nor a physiologic basis that we are aware of that supports the covariate effect of body weight on the baseline pCO2 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 from baseline, that could not be handled in another way.

Fig. 4. Contribution of different elements of the final model over time. Simulation shows the time course of drug concentrations for a 10-minute fixed infusion of 2.0 $\mu$g/ml propofol and 2.5 ng/ml remifentanil (based on literature population pharmacokinetic models; see Materials and Methods) (A), and the corresponding change in predicted pCO2 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 (B). (C) The contribution of age on pCO2 for the same infusion inputs. (D) The percentage change from baseline value for $K_{\text{deg}}$ and $K_{\text{mod}}$ parameters with increasing steady-state concentrations of either drug alone.

Fig. 5. Isoboles for steady-state concentrations of remifentanil and propofol that cause 10 and 20% increases in pCO2 from baseline. Broken lines indicate additive effects, whereas solid lines show model predictions and bow toward the plot origin, suggesting a synergistic relationship.
The remifentanil IC\textsubscript{50} estimate for bispectral index suppression in the same patients was much larger than that estimated for pCO\textsubscript{2} (19.6 ng/ml) (Borrat et al., 2013). The inability of remifentanil to substantively impact bispectral index leading to high IC\textsubscript{50} estimates is well documented (Nieuwenhuijs et al., 2003; Manyam et al., 2007) and is indicative of its low impact on sedation levels (Bouillon et al., 2004b). Conversely, we saw a smaller IC\textsubscript{50} estimate for propofol for bispectral index (3.86 \mu g/ml in the effect site) than that estimated for pCO\textsubscript{2}, 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\textsubscript{2} arterial and effect-site compartments (Bouillon et al., 2003, 2004a). Drug concentration indirectly affects CO\textsubscript{2} elimination from the arterial compartment (estimated at 0.08–0.11 minute\textsuperscript{-1} in volunteers, similar to our $K_{\text{deg}}$ parameter at 0.06 minute\textsuperscript{-1}) (Bouillon et al., 2003, 2004a). They also applied system feedback to CO\textsubscript{2} elimination (using an equivalent function to eq. 3), the delay of which was dependent on the parameter describing the CO\textsubscript{2} transfer rate between compartments ($k_{\text{CO}_2}$, 0.9 minute\textsuperscript{-1}) (Bouillon et al., 1999, 2003, 2004a). In our model, feedback delay is described by $K_{\text{mod}}$ (0.45 minute\textsuperscript{-1}). Our estimate of gain in the system response to increasing pCO\textsubscript{2} ($\alpha$), at 3.82, was close to reported values of 4.3–4.37 established in single-drug studies in volunteers (Bouillon et al., 2003, 2004a). The large confidence intervals surrounding this parameter estimate reflect the uncontrolled, non–steady-state conditions of our study.

Olofsen et al. (2010) also used two compartments (tissue and alveolar) to describe CO\textsubscript{2} pharmacokinetics, with remifentanil reducing inspired ventilation. Their model reflects the observation that opioids alter the baseline (or set-point) of the ventilatory response to rising pCO\textsubscript{2}, whereas 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\textsubscript{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\textsubscript{2}. Remifentanil effects were applied directly to the parameter describing pCO\textsubscript{2} removal, as done by others for opioids (usually minute ventilation, in our model $K_{\text{deg}}$) (Bouillon et al., 1999, 2003; Caruso et al., 2008; Olofsen et al., 2010). Thus, we include independent, concentration-based drug effects for both propofol and remifentanil on pCO\textsubscript{2}.

We modeled pCO\textsubscript{2} as an objective biomarker of respiratory depression. Previous work has established the correlation between pCO\textsubscript{2} and alveolar pCO\textsubscript{2} (Chhajed et al., 2010; Rollins et al., 2014). An absolute value above 75 mm Hg, 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 mm Hg have been associated with stupor and coma. Hypercapnia cannot easily be diagnosed clinically but is obvious with the aid of a quantitative CO\textsubscript{2} measurement system (Lumb, 2000). The trend of continuous measures of pCO\textsubscript{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 is 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 pCO₂. Arterial blood sampling, the gold standard for pCO₂, is not a continuous measure, nor is it practical in this setting for obvious reasons.

We could not detect altered pCO₂ response for A118G polymorphic patients. Similarly, Romberg et al. (2005) did not detect differences in respiratory effects despite an increase in analgesic requirements. Noxious stimulation is usually associated with increased respiratory rate, which should decrease pCO₂. 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 CO₂ 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 pCO₂ 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 pCO₂. Automatic control closed-loop systems have already been used for 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 pCO₂ as Bouillon et al. (2003) proposed for remifentanil and pCO₂ (Caruso et al., 2006).

Several limitations of our work should be acknowledged. Modulation of the respiratory system occurs via several physiologic processes (Lloyd et al., 1958; Dahan et al., 1990; 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 is 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 CO₂, 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 CO₂ production has been documented (Pavlín et al., 1996) and should be included to avoid biased parameter estimates (Bouillon et al., 2004a). We assumed only propofol inhibits CO₂ production, up to 30% of baseline (Bouillon et al., 2004a; Caruso et al., 2007, 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 earlier, 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 pCO₂, we developed a pharmacokinetic-pharmacodynamic 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 data set. Age significantly affected the propofol and remifentanil relationship with pCO₂, with older patients more prone to respiratory depression. Context-sensitive decrement times show that recovery from hypercapnia is fast, and within 15 minutes, pCO₂ nears baseline irrespective of the residual drug concentrations.

**Authorship Contributions**

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

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

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

Wrote or contributed to the writing of the manuscript: Hannam, Trocóniz, Gambús, Borrat.

**References**


Lumb AB, ed, ed (2000)


Supplemental Data.

Table S1: Summary of model development
Model development stages are ranked based on the absolute decrease in -2LL according to the model structure (i.e. system parameters, drug parameters, covariates).

<table>
<thead>
<tr>
<th>Description</th>
<th>+ n</th>
<th>ΔOBJ</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ IIV on $K_{mod}$</td>
<td>+1</td>
<td>-8917.55</td>
<td>***&lt; 0.001</td>
</tr>
<tr>
<td>+ modulator compartment (using $K_{mod}$)</td>
<td>+1</td>
<td>-635.10</td>
<td>***&lt; 0.001</td>
</tr>
<tr>
<td>+ unfix α parameter</td>
<td>+1</td>
<td>-336.489</td>
<td>***&lt; 0.001</td>
</tr>
<tr>
<td><strong>Remifentanil</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear remifentanil effect (3 parameters)</td>
<td></td>
<td>-2377.09</td>
<td>***&lt; 0.001</td>
</tr>
<tr>
<td>Fractional remifentanil effect (3 parameters)</td>
<td></td>
<td>-19255.5</td>
<td>***&lt; 0.001</td>
</tr>
<tr>
<td>+ IIV on IC$_{50R}$</td>
<td>+1</td>
<td>-1001.13</td>
<td>***&lt; 0.001</td>
</tr>
<tr>
<td>+ I$_{MAX,R}$*</td>
<td>+1</td>
<td>-531.56</td>
<td>***&lt; 0.001</td>
</tr>
<tr>
<td>+ effect compartment (using $k_{e0}$)</td>
<td>+1</td>
<td>-99.73</td>
<td>***&lt; 0.001</td>
</tr>
<tr>
<td>+ γ (slope parameter) remifentanil</td>
<td>+1</td>
<td>-2586.43</td>
<td>***&lt; 0.001</td>
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<td><strong>Propofol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ propofol effect on $K_{mod}$</td>
<td>+1</td>
<td>-19255.5</td>
<td>***&lt; 0.001</td>
</tr>
<tr>
<td>+ I$_{MAX,P}$ ‡</td>
<td>+1</td>
<td>-1069.24</td>
<td>***&lt; 0.001</td>
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<tr>
<td><strong>Covariates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Age cov effect on IC$_{50P}$ †</td>
<td>+1</td>
<td>-265.55</td>
<td>***&lt; 0.001</td>
</tr>
<tr>
<td>+ Age cov effect on $k_{e0R}$ †</td>
<td>+1</td>
<td>-201.01</td>
<td>***&lt; 0.001</td>
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<tr>
<td>+ Age cov effect on IC$_{50R}$</td>
<td>+1</td>
<td>-191.08</td>
<td>***&lt; 0.001</td>
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<tr>
<td>+ NOX cov effect on $K_{deg}$</td>
<td>+1</td>
<td>-117.14</td>
<td>***&lt; 0.001</td>
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<tr>
<td>+ OPRM cov effect on IC$_{50R}$</td>
<td>+1</td>
<td>+91.23</td>
<td>NS</td>
</tr>
</tbody>
</table>

+n indicates the number of additional parameters to be estimated from the comparison model. OBJ is NONMEM’s objective function value and roughly equates to the -2 x log likelihood. A reduction in OBJ ($\Delta$OBJ) greater than 3.84 between nested models is required for significance at $\alpha < 0.01$. *This parameter was later removed as the estimate approached 1 and removal did not result in a significant worsening of model fit. ‡The inclusion of a maximal inhibitory effect on propofol was statistically significant but estimated a 1.0 and so not included in the final model. Significant covariates were estimated together, and those that failed to contribute to model fit removed reach final model (retained parameters indicated in table by †)
Supplemental Data 2. Sensitivity analysis of parameters
The impact of changes in each individual parameter on the population pCO₂ profile is shown, for ten minute fixed infusions of 2.0 µg/ml propofol and 2.5 ng/ml remifentanil. Simulations show the average profile for the typical population value (θₜᵥ), and the 5% and 95% confidence interval values as calculated from the standard errors provided by NONMEM.