

# A MODEL FOR THE RESPIRATORY EFFECTS OF REMIFENTANIL AND PROPOFOL DURING SEDATION



Jacqueline A Hannam\*<sup>1</sup>, Iñaki F Trocóniz<sup>2</sup>, Xavier Borrat<sup>3</sup>, Pedro L Gambús<sup>3</sup>.

1 Department of Anaesthesiology, School of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand; 2 Pharmacometrics and Systems Pharmacology, School of Pharmacy, Universidad de Navarra, Pamplona, Spain;

\*Email: [j.hannam@auckland.ac.nz](mailto:j.hannam@auckland.ac.nz)

3 Systems Pharmacology Effect Control and Modeling Research Group, Department of Anesthesia, Hospital CLINIC de Barcelona, Barcelona, Spain.

## Introduction

Propofol and remifentanyl are commonly combined for sedation and may act synergistically on the respiratory system. Several models of respiratory effects have been reported for drugs commonly used during sedation (propofol, and the opioids remifentanyl and alfentanil),(1-5) but these have been developed in highly controlled conditions or in healthy volunteers. A model for propofol-remifentanyl effects on respiratory depression in patients undergoing noxious procedures has not been reported. We aimed to develop such a model for patients undergoing endoscopy.

Previous work has shown that carriers of the A118G single nucleotide polymorphism (SNP) of the OPRM1 genotype (which encodes the  $\mu$ -opioid receptor) have reduced sensitivity to remifentanyl.(6) A secondary aim was to test the influence of the A118G SNP genotype on remifentanyl induced respiratory changes.

## Methods

Data were available for 136 patients undergoing endoscopy with sedation using propofol and remifentanyl. Participants were randomised to receive fixed, targeted controlled infusions (TCI) of propofol 2.0  $\mu$ g/ml, propofol 3.0  $\mu$ g/ml, remifentanyl 1.0 ng/ml or remifentanyl 2.0 ng/ml. TCI targets of the second drug (remifentanyl or propofol) were determined using the Dixon up-down method.(7) Transcutaneous arterial pressure of carbon dioxide (pCO<sub>2</sub>) was measured using a SENTEC Digital Monitor (Therwil, BL, Switzerland). A single venous blood sample was drawn for A118G SNP genotyping.

Plasma drug concentrations were not available, so predicted plasma concentrations were related to pCO<sub>2</sub> using an indirect model with rebound mechanism.(8) pCO<sub>2</sub> levels are the result of (i) CO<sub>2</sub> production and removal (i.e. removal from the lung via the process of respiration) rates, as represented by the rate constants K<sub>in</sub> and K<sub>deg</sub>, respectively, and (ii) feedback mechanisms represented by the modulator M (equations 1 and 2).

$$d(pCO_2)/dt = K_{in} - K_{deg} \times M \times pCO_2 \quad \text{Equation 1}$$

$$d(M)/dt = K_{mod} \times (pCO_{2t} / pCO_{20})^\alpha - K_{mod} \times M \quad \text{Equation 2}$$

where K<sub>mod</sub> is the turnover rate constant governing M dynamics, and  $\alpha$  scales the effect of the change in pCO<sub>2</sub> over time (pCO<sub>2t</sub>) with respect to baseline (pCO<sub>20</sub>) on the production rate of M. In baseline conditions, the rate of CO<sub>2</sub> production is in equilibrium with its removal, then dpCO<sub>20</sub>/dt = 0, K<sub>in</sub> = pCO<sub>20</sub>  $\times$  K<sub>deg</sub>, and pCO<sub>2t</sub>=pCO<sub>20</sub>. Remifentanyl effects (E<sub>REM</sub>) were included as a reduction of the K<sub>deg</sub> parameter (equation 3). Propofol effects (E<sub>PROP</sub>) were included as inhibition of K<sub>mod</sub> (equation 4).

$$d(pCO_2)/dt = K_{in} - K_{deg} \times E_{REM} \times M \times pCO_2 \quad \text{Equation 3}$$

$$d(M)/dt = K_{mod} \times E_{PROP} \times (pCO_{2t} / pCO_{20})^\alpha - K_{mod} \times M \quad \text{Equation 4}$$

Data were analysed using NONMEM 7.2. The stochastic approximation maximisation (SAEM) algorithm, followed by importance sampling (IMP), was used. Covariate relationships were investigated for age, noxious stimuli (endoscopy tube insertion) and A118G genotype for the  $\mu$  opioid receptor (OPRM1).

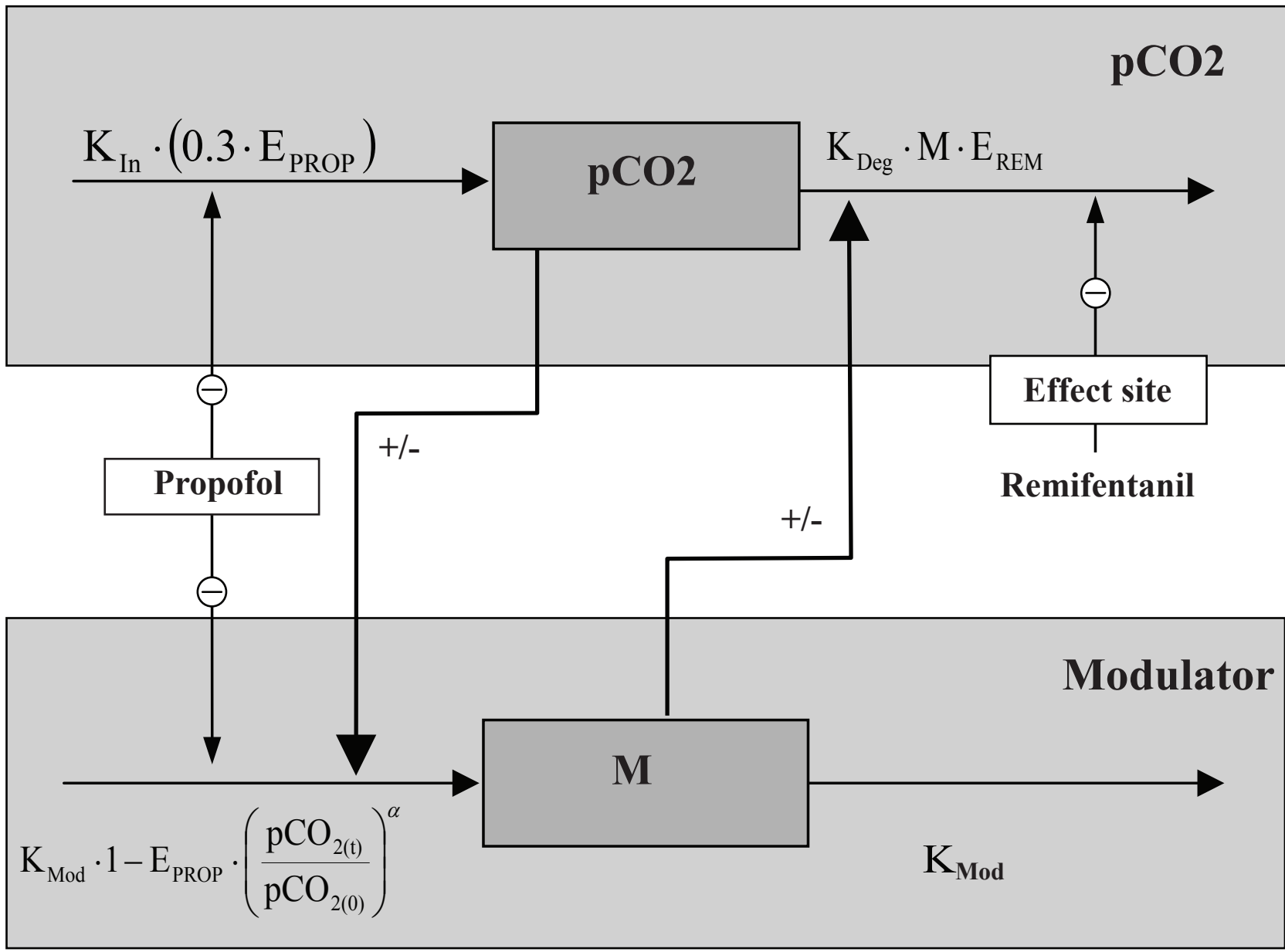


Figure 1. Model of propofol and remifentanyl effects on the pCO<sub>2</sub>. The model is based on two compartments: the main compartment describing changes in CO<sub>2</sub>, and a modulator compartment (M) representing feedback processes (such as control of ventilation rate) that work to maintain system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

| Parameter                                          | Estimate (CV%) | [5 <sup>th</sup> -95 <sup>th</sup> ] | Shrinkage (%) | IIV (%RSE)    |
|----------------------------------------------------|----------------|--------------------------------------|---------------|---------------|
| System parameters                                  |                |                                      |               |               |
| pCO <sub>20</sub> (mmHg/kg)                        | 0.52 (3.4%)    | [0.49-0.56]                          | 0%            | 29.2 (27.6%)  |
| <i>Standardized to 70 kg</i> <i>39.2 mmHg/70kg</i> |                |                                      |               |               |
| Box cox slope                                      | -1.18 (11.4%)  | [-1.43--0.92]                        | -             | -             |
| K <sub>deg</sub> (min <sup>-1</sup> )              | 0.057 (39.1%)  | [0.01-0.10]                          | 0.4%          | 204.7 (32.7%) |
| K <sub>mod</sub> (min <sup>-1</sup> )              | 0.45 (43.0%)   | [0.07-0.83]                          | -             | -             |
| $\alpha$                                           | 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 <sub>50R</sub> (ng/ml)                          | 1.13 (44.0%)   | [0.16-2.10]                          | 4.0%          | 80.0 (25.2%)  |
| $\gamma_R$                                         | 2.75 (18.3%)   | [1.77-3.73]                          | -             | -             |
| k <sub>e0R</sub> (min <sup>-1</sup> )              | 0.28 (37.3%)   | [0.07-0.48]                          | -             | -             |
| *Age <sub>ke0R</sub>                               | 0.12 (73.4%)   | [-0.05-0.29]                         | -             | -             |
| IC <sub>50P</sub> ( $\mu$ g/ml)                    | 4.97 (17.3%)   | [3.28-6.66]                          | -             | -             |
| *Age_IC <sub>50P</sub>                             | 2.73 (51.3%)   | [-0.01-5.47]                         | -             | -             |

Table 1. Inter-individual variability (IIV) is expressed as CV(%) with 95% confidence intervals given in square brackets. pCO<sub>20</sub> is baseline pCO<sub>2</sub>, estimated per kg. pCO<sub>2</sub> standardized to 70 kg is also provided. K<sub>deg</sub> is a rate constant describing the rate of pCO<sub>2</sub> removal from the main system compartment, K<sub>mod</sub> describes the rate of synthesis and degradation from the modulator compartment,  $\alpha$  describes amplification of the feedback system in responding to changes in pCO<sub>2</sub>. IC<sub>50P</sub> and IC<sub>50R</sub> are the concentrations of propofol and remifentanyl respectively that cause 50% the maximal drug effect.  $\gamma_R$  is a shape parameter describing the shape of the remifentanyl concentration-response curve and ke<sub>0R</sub> describes the transfer of remifentanyl 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.

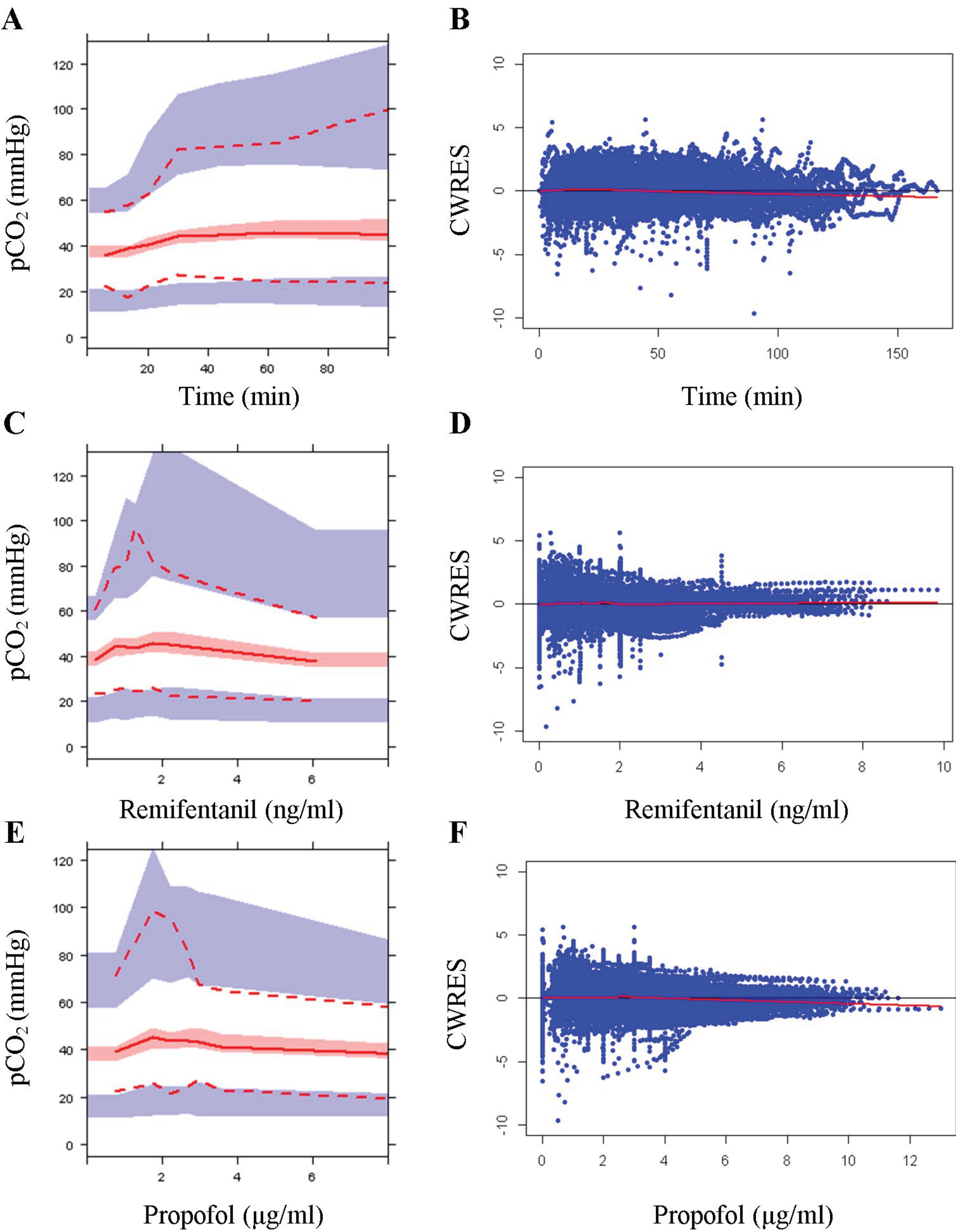


Figure 2. Goodness of fit plots. The left panel gives prediction-corrected visual predictive checks (pc VPCs), while the right panel gives conditional weighted residuals (CWRES). Goodness of fit is given for pCO<sub>2</sub> versus time (A and B), pump-predicted remifentanyl concentrations in the plasma (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 smooth line). VPCs were constructed using 1000 simulations.

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## Results

All model features represented in equations 1-4 were supported by a significant reduction in -2LL. An effect site compartment for remifentanyl reduced the value of -2LL by over 500 points (p<0.001), but this was not supported by our data for propofol (p>0.05). Sigmoidicity was absent for propofol pharmacodynamics; in the case of remifentanyl the pharmacodynamic slope estimate was 2.75.

A118G SNP in the OPRM1 genotype caused a small increase in the remifentanyl IC<sub>50</sub> from 1.12 ng/ml to 1.32 ng/ml (18%) in recessive homozygous individuals. However this effect was neither statistically, nor clinically, significant. The final model included covariate effects for age on remifentanyl ke<sub>0</sub> (Age<sub>ke0R</sub>) and propofol IC<sub>50</sub> (Age\_IC<sub>50P</sub>).

IIV was described with an exponential model, except for pCO<sub>20</sub> which was better described using a Box-Cox transformation. Final parameter estimates are given in Table 1, visual predictive checks and goodness of fit plots are given in Figure 2. Predicted pCO<sub>2</sub> for concentration pairs in simulated steady state conditions suggest synergistic effects (Figure 3).

## Discussion

In this work, we developed an indirect-effect model with system feedback to describe changes in pCO<sub>2</sub> induced by propofol and remifentanyl. OPRM1 genotype was not a significant covariate in our dataset. Effects appear to be synergistic. For a typical patient a combination of propofol 1.8  $\mu$ g/ml and remifentanyl 1.5 ng/ml that induces a level of sedation where the patient is not responsive to verbal command but rousable, the expected levels of pCO<sub>2</sub> would be 55.7 mmHg for a patient with a basal pCO<sub>2</sub> of 39 mmHg (assuming steady state conditions and a 65 y old, 70kg male). Our model differs from those previously reported in that we include independent, concentration-based drug effects for both propofol and remifentanyl on pCO<sub>2</sub>, in a real patient population undergoing a noxious procedure.

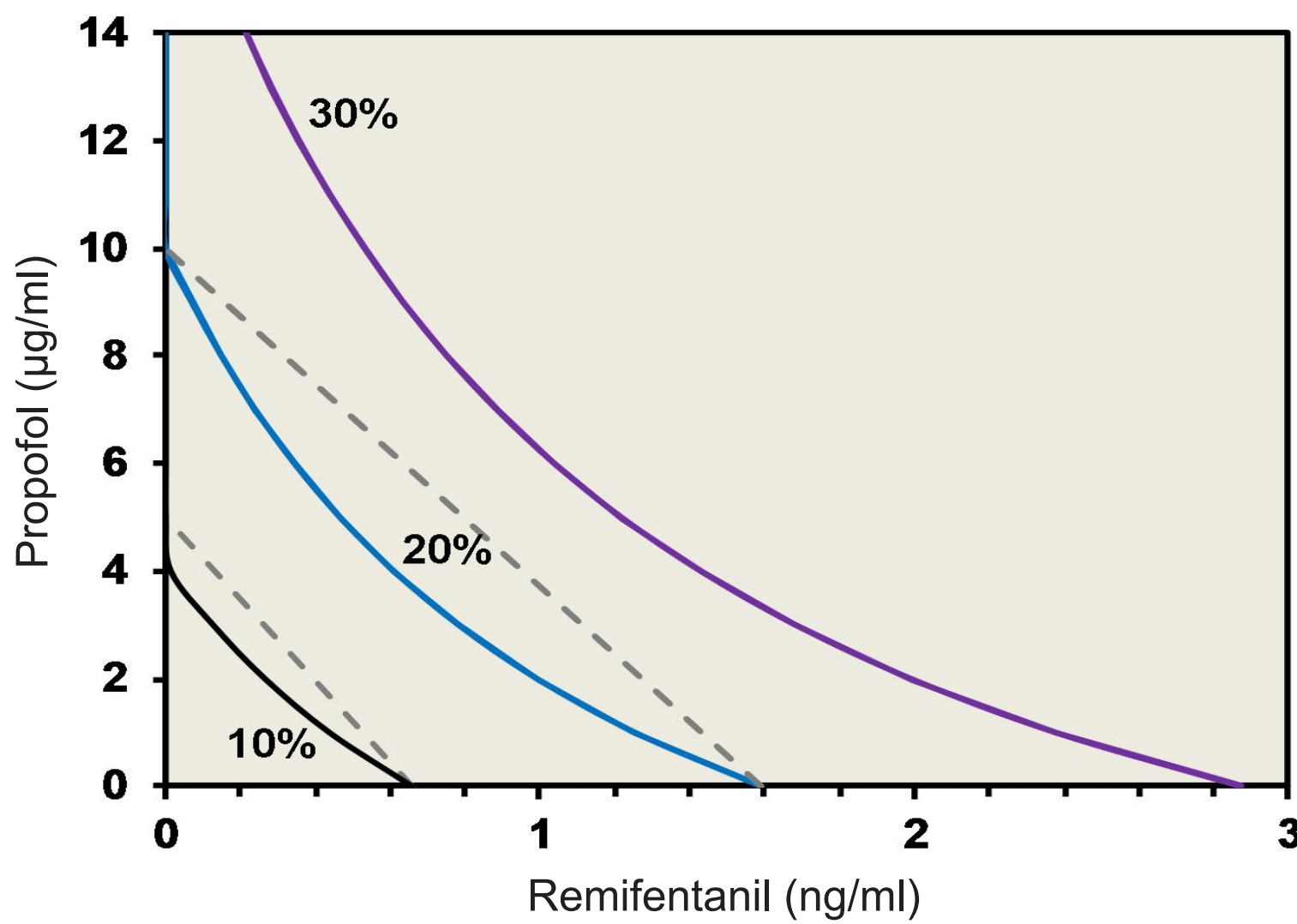


Figure 3. Isoboles for steady state concentrations of remifentanyl and propofol that cause 10% (black), 20% (blue) and 30% (purple) increases in pCO<sub>2</sub> from baseline. Broken lines indicate additive effects, while solid lines show model predictions and bow toward the plot origin suggesting a synergistic relationship.

## References

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