Propofol and remifentanil 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 opioid remifentanil). However, these have been developed in highly controlled conditions or in healthy volunteers. A model for propofol-remifentanil effects on respiratory depression in patients undergoing endoscopic 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 μ-opioid receptor) have reduced sensitivity to remifentanil. A secondary aim was to test the influence of the A118G SNP genotype on remifentanil-induced respiratory changes.

**Methods**

Data were available for 136 patients undergoing endoscopy with sedation using propofol and remifentanil. Participants were randomized to receive fixed, targeted controlled infusions (TCI) of propofol 2.0 µg/ml, propofol 3.0 µg/ml, remifentanil 1.0 ng/ml or remifentanil 2.0 ng/ml. TCI targets of the plasma drug concentrations were related to pCO₂ using an indirect model with rebound behavior. Remifentanil concentrations were not available, so predicted plasma concentrations were used. In baseline conditions, the rate of CO₂ production is in equilibrium with its removal, then propofol and remifentanil reduce respiratory production and removal (i.e., from the lungs via the process of respiration) rates, as represented by the rate constants Kmod and Kdeg, respectively, and (ii) feedback mechanisms represented by the modulator M (equations 1 and 2).

\[
dpCO2\mu = K_{\mu} - M = pCO2\mu
\]

\[
dpCO2\mu = K_{\mu} - K_{\mu} = pCO2\mu\rightarrow pCO2\mu = M
\]

where \(K_{\mu}\) is the turnover rate constant governing M dynamics, and \(m\) scales the effect of the change in \(pCO2\mu\) over time (\(pCO2\mu\) with respect to baseline \(pCO2_{0}\)) on the production rate of M. In baseline conditions, the rate of CO₂ production is in equilibrium with its removal, then propofol and remifentanil reduce respiratory production and removal (i.e., from the lungs via the process of respiration) rates, as represented by the rate constants \(K_{\mu}\) and \(K_{\mu}\), respectively, and (ii) feedback mechanisms represented by the modulator M (equations 1 and 2).

Data were analyzed using NONMEM 7.2. The stochastic approximation expectation maximization (SAEM) algorithm, followed by importance sampling (ISPs), was used. Covariate relationships were investigated for age, niosumul (endoscopy tube insertion) and A118G genotype for the μ-opioid receptor (DRMM).

**Discussion**

In this work, we developed an indirect-effect model with system feedback to describe changes in pCO₂ induced by propofol and remifentanil. DRMM genotype was not a significant covariate in our dataset. Effects appear to be synergistic, for a typical patient a combination of propofol 1.8 µg/ml and remifentanil 1.5 µg/ml that induces a level of sedation where the patient is not responsive to verbal command but rousable, the expected levels of pCO₂ would be 57.5 mmHg for a patient with a basal pCO₂ of 39 mmHg (assuming steady state conditions and a 65 kg, 70kg male).

Our model differs from those previously reported in that we include independent, concentration-based drug effects for both propofol and remifentanil on pCO₂, in a real patient population undergoing a nososalic procedure.

**Results**

All model features represented in equations 1-4 were supported by a significant reduction in AIC. An effect site compartment for remifentanil reduced the value of AIC by over 500 points (p(0.001), but this was not supported by our data for propofol (p(0.05)). Signficance was absent for propofol pharmacodynamics; in the case of remifentanil the pharmacodynamic slope estimate was 2.75. A118G SNP in the DRMM genotype caused a small increase in the remifentanil IC₅₀ from 1.12 µg/ml to 1.32 µg/ml (18%) in recessive homozygous individuals. However this effect was neither statistically nor clinically significant. The final model included covariate effects for age on remifentanil kₐ (Age_kₐ) and propofol IC₅₀ (Age_IC₅₀).

IV was described with an exponential model, except for pCO₂ 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 pCO₂ for concentration pairs in simulated steady state conditions suggest synergetic effects (Figure 3).

**References**