Modeling the Influence of the A118G Polymorphism in the OPRM1 Gene and of Noxious Stimulation on the Synergistic Relation between Propofol and Remifentanil

Sedation and Analgesia in Endoscopic Procedures


ABSTRACT

Background: The presence of the A118G single nucleotide polymorphism in the OPRM1 gene as well as noxious stimulation might affect the requirements of remifentanil for patients undergoing ultrasonographic endoscopy under sedation-analgesia with propofol and remifentanil. Bispectral index (BIS) was used as a surrogate measure of effect.

Methods: A total of 207 patients were screened for A118G and randomly received different combinations of propofol and remifentanil, changed depending on the nausea response to endoscopy tube introduction. Nonlinear mixed effects modelling was used to establish the relation between propofol and remifentanil with respect to BIS and to investigate the influence of A118G or noxious stimulation. The value of $k_{e0}$ for propofol and remifentanil was estimated to avoid the hysteresis between predicted effect site concentration (Ce) and BIS.

Results: Data from 176 patients were analysed. Eleven were recessive homozygous for A118G (OPRM = 1). A total of 165 patients were either dominant homozygous or heterozygous and considered normal (OPRM = 0). The estimated values of $k_{e0}$ for propofol and remifentanil were 0.122 and 0.148 min⁻¹. Propofol and remifentanil were synergistic with respect to the BIS ($\alpha = 1.85$). EC₅₀ estimate for propofol was 3.86 µg/ml and for remifentanil 19.6 ng/ml in normal patients and 326 ng/ml in OPRM = 1 patients. BIS increases around 4% for the same effect site concentrations with noxious stimulation.

Conclusions: Predicted effect site concentration of remifentanil ranging 1–5 ng/ml synergistically potentiates the effects

What We Already Know about This Topic

- The common A118G polymorphism (single nucleotide polymorphism) in the $\mu$1 opioid receptor gene is associated with reduced opioid sensitivity, and could thus contribute to variability in drug responsiveness.
- Propofol and remifentanil infusions interact synergistically in producing sedation.

What This Article Tells Us That Is New

- Subjects with A118G single nucleotide polymorphism showed no synergy between propofol and remifentanil under sedation for upper endoscopy using bispectral index as a measure of effect.
- Genetic polymorphisms can affect sensitivity to opioids, which has implications for drug dosing or selection.
of propofol on the BIS but has no effect in A118G patients. Noxious stimulation increases BIS values by 4% at the same concentrations of propofol and remifentanil.

**D**iagnostic and therapeutic procedures under sedation–analgesia are becoming an important part of the daily work in anesthesia. In our hospital during 2010, more than 5,000 patients underwent diagnostic and/or therapeutic procedures outside the operating room under sedation–analgesia. In the gastrointestinal endoscopy area, more than 20 patients a day require sedation–analgesia.

Propofol and remifentanil are commonly used for such purpose and are optimally administered by using target-controlled infusion (TCI) systems. The initial target intervals of propofol and remifentanil concentrations to be used in a TCI system for sedation–analgesia in ultrasonographic endoscopic (USE) procedures of the gastrointestinal tract were previously defined.1

The hierarchical model of the interaction of hypnotic and analgesic effects proposes that opioids could act at different levels in the nervous system attenuating how the noxious stimuli get to the cortex.2,3 Depending on the intensity reaching cortical levels, an arousal response could be detected on measures of hypnotic effect, as the bispectral index (BIS), observing an increase in BIS value.

Anesthesia is one of the medical specialties where personalized approaches are more widely used. The anesthesiologist administers a drug, observes an effect in a highly dynamic fashion, and adjusts further dosing according to the response of the patient. Several factors have been demonstrated to affect the pharmacokinetics–pharmacodynamics (PK–PD) of propofol and remifentanil.4,5 It is also likely that differences in genetic factors might affect the disposition or the sensitivity of the patients to either propofol or remifentanil. But the influence of genetic variability in drug dosing of anesthetic drugs has not been widely studied.6

The **OPRM1** gene encodes the μ-opioid receptor, which is a member of the G protein–coupled receptor family.7 Genetic variations in exon 1 of the **OPRM1** gene, located at chromosome 6, have been associated with changes in the spatial conformation of the μ-opioid receptor as a result of amino acid changes in the receptor protein and thereby altering its function. The A118G single nucleotide polymorphism (SNP) change (rs1799971) results in an amino acid substitution from asparagine to aspartate at chromosome 6, have been associated with changes in the **OPRM1** gene, located at chromosome 6, have been associated with changes in the disposition or the sensitivity of the patients to either propofol or remifentanil.8

Noxious stimulation increases BIS values by 4% at the same concentrations of propofol and remifentanil. It might have clinical relevance since a significant number of patients undergoing procedures under sedation might be homozygous for this genetic variant. Up to date, no predictive modeling analysis on anesthetic drugs has been conducted with a SNP factor as a potential significant indicator of dosage adjustments.

We hypothesized that patients homozygous for the A118G SNP in the **OPRM1** gene undergoing sedation–analgesia for USE with propofol and remifentanil will have increased requirements of remifentanil to induce BIS changes. This increase would be quantifiable using a population modeling approach. The model generated would allow investigating whether the presence of noxious stimulation increases drug requirements to achieve the same degree of effect on the BIS.

**Methods and Materials**

The prevalence of A118G in the **OPRM1** gene has been studied by other authors and estimated to be approximately 10–19% in general population.15 Based on this observation, we studied 207 patients with the aim to include between 20 and 40 patients who could have the A118G SNP. All patients were enrolled under Institutional Review Board of the Hospital CLINIC de Barcelona, Barcelona, Spain, approval of the study protocol and they signed an informed consent.

The patients were randomized to four groups depending on the fixed target effect site concentration of either propofol or remifentanil administered: remifentanil 1 ng/ml, remifentanil 2 ng/ml, propofol 2 μg/ml, or propofol 3 μg/ml. The groups were named REMI 1, REMI 2, PROP 2, and PROP 3, respectively.

**Genetic Determination of A118G SNP**

Before starting the procedure and while monitoring systems were set up, a venous blood sample was drawn from every patient for posterior genetic analysis to detect A118G SNP. Genomic DNA was isolated from blood using the QiaAmp® DNA Mini kit (Qiagen, Courtaboeuf, France) according to the manufacturer’s instructions. Genotyping for A118G SNP was performed by TaqMan® (Invitrogen, Life Technologies Ltd., Paisley, United Kingdom) allelic discrimination using a predesigned SNP Genotyping Assay in the 7300 Real-Time PCR System (Applied Biosystems, Foster City, CA) following the manufacturer’s instructions. Genotyping was scored manually and blindly by two independent operators to avoid errors.

**Patient Monitoring**

Patients were noninvasively monitored with continuous electrocardiogram, arterial blood pressure, pulse oximetry, respiratory rate analysis based on thoracic bioimpedance, and transcutaneous continuous carbon dioxide measurement using a SENTEC Digital Monitor (Sentec AG; Therwil,

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Drug Administration

Propofol and remifentanil were administered by means of a TCI system (Base Primea, Fresenius Kabi, Chemin de Fer, France) running PK-PD models for propofol\(^4,16\) and for remifentanil.\(^5\) Target concentrations were selected to be achieved in the effect site.

For the REMI 1 and REMI 2 subjects, the initial target effect site concentration of propofol was 2.5 \(\mu\)g/ml. For the PROP 2 and PROP 3 subjects, the initial target effect site concentration of remifentanil was 1.5 ng/ml. With the aim of having different drug concentrations for each one of the four random groups, the target concentration of the other drug was changed individually based on the nausea response reflex (GAG) of the previous patient to the introduction of the USE probe according to the Dixon up–down method\(^17,18\) as follows:

If GAG (+), in the groups PROP 2 or PROP 3, the target concentration of remifentanil in the next patient of the group will be increased by 0.5 ng/ml and decreased by the same concentration if GAG (−).

If GAG (+), in the groups REMI 1 or REMI 2, the target concentration of propofol in the next patient of the group will be increased by 0.5 \(\mu\)g/ml and decreased by the same concentration if GAG (−).

After observation of GAG response, which was evaluated by the endoscopist, the drug target was adjusted according to the anesthesiologist judgment and clinical requirements for the rest of the procedure. Both the initial target concentrations and the magnitude of the target changes were based on previous work from our group.\(^1\)

Data Collection

The flux of data coming from the different monitoring and drug infusion systems were collected online (Rugloop, Demed, Belgium) at 1-s intervals on a computer and stored for posterior data analysis. Rugloop allows entering events manually at exact times, for instance, the Ramsay Sedation Scores, the exact moments of introduction and extraction of the USE probe, the GAG response, and any other event that was considered potentially relevant to the study objectives by the attending anesthesiologist. Hyperterminal\(^7\) (Windows, Microsoft, Redmond, WA) was used to record data coming from the Sentec Digital Monitor. Internal clocks of all the devices were synchronized.

Data Analysis: Modeling Approach

The time course of BIS data was described based on the population approach using the software NONMEM VII\(^19\) (Icon Development Solutions, Ellicott City, MA) with the first-order conditional estimation method and the INTERACTION option. Intersubject variability was modeled exponentially as follows:

\[
P_i = \theta_{\text{pop}} \cdot e^{\eta_i}
\]  

where \(P_i\) and \(\theta_{\text{pop}}\) represent the individual and the population mean estimates of the \(P\) parameter, respectively; \(\eta_i\) quantifies the discrepancy between \(P_i\) and \(\theta_{\text{pop}}\). It is generally assumed that the set of \(\eta_i\) is symmetrically distributed around the value of zero and has a variance of \(\omega^2\), which represents the magnitude of the interpatient variability associated to the \(P\) parameter. The exponential model prevents \(P_i\) to be nonpositive. Residual variability was described with the use of an additive error model of the form

\[
BIS_{\text{obs},i} = BIS_{\text{pred},i} + \epsilon_i
\]  

where \(BIS_{\text{obs},i}\) and \(BIS_{\text{pred},i}\) represent the observed and model predicted BIS in the \(i^{th}\) subject at the \(j^{th}\) time, and \(\epsilon_i\) is the difference between the measured and predicted BIS. The set of \(\epsilon_i\) is assumed in general to be subject independent, symmetrically distributed around 0 with variance equal to \(\sigma^2\).

Model Selection Criteria

Different models were fit to the data. Selection of the most appropriate model was based on the following:

1. The goodness-of-fit plots including \(BIS_{\text{obs}}\) versus typical population model predictions, \(BIS_{\text{obs}}\) versus individual model predictions, and conditional weighted residuals versus time.\(^20\)

2. The minimum value of the objective function given by NONMEM and approximately equal to \(-2\text{Log(Likelihood)} [-2\text{LL}].\) Generally speaking, a lower value of the objective function indicates a better performance of the new model, although it requires statistical comparison as follows: the difference \(-2\text{LL}\) between two hierarchical models was compared with a \(\chi^2\) distribution in which a difference of 3.84, 6.63, and 10.83 points is considered significant at \(P = 0.05, 0.01,\) and 0.001 for one extra parameter in the model. For the case of nonnested models, the Akaike information criteria were used instead.\(^21\) It was calculated according to the following expression:

\[
AIC = -2\text{LL} + 2 \cdot N_p
\]  

where AIC stands for Akaike information criteria and \(N_p\) is the number of parameters in the model.
(3) Precision of parameter estimates was expressed as 95% CI calculated using the standard error provided by NONMEM. In case of model parameters for which the CI included the zero value, the log-likelihood profiling method with Perl-speaks-NONMEM was used to compute CIs.

**Model Development**

Plasma concentrations of propofol and remifentanil were not measured in any of the patients during the course of the study. Predicted plasma and effects site concentrations for both drugs were obtained from the TCI system based on population PK-PD models for propofol24-26 and remifentanil.

Figure 1 shows an example where it can be observed that there is a time lag between predicted effect site concentration of propofol and the effect, as reflected in the BIS in the sense that BIS keeps decreasing, whereas effects site concentrations are already stable. Based on these observations, it was decided to use predicted plasma concentrations (C_p) for both drugs to estimate a value of k_0, the first-order rate constant governing the disappearance of the drugs from the effect site. This newly estimated k_0 would allow a calculation of the predicted effect site concentration (C_e) with respect to measured BIS effect. Equation (1) represents the expression used to generate the C_e versus time profiles:

\[
\frac{dC_e}{dt} = k_0 \times (C_p - C_e)
\]

For each drug, a corresponding k_0 will be estimated (k_0,Prop and k_0,Remi).

**Pharmacodynamic Models for Single Drug Effects**

Linear and nonlinear models were fit to the data. Equation (5) shows the mathematical representation of the pharmacodynamic model used to describe the single drug effect:

\[
BIS = BIS_0 \times \left(1 - I_{MAX} \times \frac{C_e}{C_{50} + IC_{50}^e}\right)
\]

BIS_0 represents the BIS response at baseline, I_{MAX} is the maximum response that both drugs could elicit and it was fixed to 1 during all analyses, indicating that at enough high predicted effect site concentrations, BIS response can be completely blocked. EC_{50} is the effect site concentration eliciting a BIS response equal to half of BIS_0 and γ is the parameter governing the steepness of the BIS versus C_e curve.

**Pharmacodynamic Models for Drug Interaction**

The interaction between propofol and remifentanil was characterized using the empirical model for drug interaction proposed by Greco et al.25 as applied in Kern et al.26 It was modified to allow the estimation of different γ parameters for propofol and remifentanil as represented in Equation (6):

\[
\text{BIS} = \text{BIS}_0 \times \left[1 - I_{MAX} \times \frac{C_{\text{Prop}}}{EC_{50,\text{Prop}} + C_{\text{Prop}}} + \frac{C_{\text{Remi}}}{EC_{50,\text{Remi}}} \alpha \times \frac{C_{\text{Prop}}}{EC_{50,\text{Remi}}} \times \frac{C_{\text{Remi}}}{EC_{50,\text{Remi}}} \right]^{\text{Prop,Remi}}
\]

Subscripts Prop and Remi refer to parameters corresponding to propofol and remifentanil, respectively. The interaction parameter, α, might have a value equal, greater, or lower than 0, indicating the absence of interaction (additivity), synergistic, or antagonistic interaction, respectively.

\[
\gamma_{\text{Prop,Remi}} = SLP \cdot L \cdot \gamma_{\text{Prop}} + (1 - SLP) \cdot \gamma_{\text{Remi}}
\]

Here, SLP is defined as follows.
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SLP is a variable that is a function of the concentrations of propofol and remifentanil normalized by their corresponding potency ($EC_{50}$). It is constrained between 0 and 1.

In the absence of propofol or remifentanil, $\gamma_{\text{Prop,Remi}}$ is equal to $\gamma_{\text{Remi}}$ or $\gamma_{\text{Prop}}$, respectively, and Equation (6) reduces to Equation (5).

During model development, an additional model representing among others allosteric modulation and response surface models was also fit to the data.

**Covariate Model Selection**

The following demographic covariates were explored for significant effects on all the parameters in the model, regardless if they were associated to intersubject variability or not: age, weight (continuous), and gender.

The presence of the endoscopy probe inside the upper digestive tract of the patient was explored as an indicator of noxious stimulation (NOX) and incorporated in the model as a categorical covariate: NOX = 1 when no probe was inside the patient and NOX = $\theta_{\text{NOX}}$ when the endoscopy probe was inside the patient.

The possible role of the genetic variant A118G in the $OPRM1$ gene was also tested as a noncontinuous, binary covariate factor. This covariate factor ($OPRM$) was incorporated in the model to evaluate whether its presence could increase the requirements of remifentanil to achieve the same effects on the BIS.

First, each covariate was tested individually. Then, those covariates that showed statistical significance ($P < 0.05$) were further tested following the forward inclusion and backward elimination approaches using significance levels of 5 and 1%, respectively.

**Results**

From all 207 patients enrolled in the study, only 176 were included in the final analysis. Reasons for excluding some individuals were poor quality of BIS data defined as quality of BIS less than 50% for over 80% of the time ($n = 20$), technical problems such as interruption of data collection flow due to software or hardware malfunction ($n = 6$), or intravenous line disconnection during the study ($n = 3$). One patient exceeded the weight and height limitations accepted by the TCI software after blood sample was already drawn and was not included in the study. In one case, the study was interrupted because of severe desaturation requiring stop drug infusion, and with assisted ventilation the patient recovered uneventfully and the USE was finished. No other patient required assisted ventilation or administration of vasopressors or atropine or any other recovery measure.

Table 1 shows the demographic characteristics of the individuals included in each of the four groups. Of the 207 patients screened for the SNP on the $OPRM1$ gene, only 12 were recessive homozygous (GG), which represents 6%
of the total number of patients screened, whereas the number of heterozygous (AG) was 78, representing 38% of those screened. The remaining 56% were dominant homozygous (AA). The allelic frequency for G was 21.93% and that for A was 78.07%. From the 176 patients included in the data analysis, 11 were GG (OPRM = 1) and 165 were AA or AG (OPRM = 0). Group OPRM = 0 is considered normal. For every study group, table 2 shows the duration of the sedation-analgesia administration, number of data per individual, and the time under noxious stimulation and time without stimulation.

**Modeling Results**

**Single Drug Effects.** Single drug effects were best described with the model represented by Equation (5). For both drugs, propofol and remifentanil, the sigmoidicity parameter resulted significant ($P < 0.01$) and the use of the TCI-based predicted $C_p$ or $C_e$ resulted in worse fits, indicating the need of incorporating the $k_{e0}$ parameters in the models. Data did not allow identifying an estimate of the $I_{MAX}$ parameter different from 1.

**Drug Combination.** The BIS versus time data were analyzed first using the empirical interaction model presented in Equation (6). In that first model, intersubject variability was included on BIS$_0$, $EC_{50,Prop}$, $k_{e0,Prop}$, $\alpha$, and $\gamma$, did not improve the fit significantly ($P > 0.05$). The estimates of BIS$_0$, $EC_{50}$, $k_{e0}$, and $\gamma$ parameters and the magnitude of the interpatient and residual variability obtained from the analysis of all data available resulted very similar to those estimated using data in the presence of a single drug only.

During model development, it was found that the parameter $\alpha$ was statistically different from 0, and it was always estimated as a positive number indicating synergism ($P < 0.001$). A decrease in −2LL of 94 points ($P < 0.001$), meaning a significantly better fit of the model, was found when two different $\gamma$s were incorporated in the model as represented by Equations (7) and (8). The use of the surface modeling approach, as it was initially proposed, resulted in 18 points increase in the objective function of NONMEM, meaning that the fit was not better.

The typical estimate of $EC_{50,Remi}$ was very high (≈20 ng/ml) compared with the predicted concentration range achieved in the current study (median of ≈2 ng/ml). The possibility that under our study design conditions, remifentanil was acting as a modulator of the effect elicited by propofol was also considered. However, a model corresponding to an allosteric modulation worsened the fit resulting in a 273 points increase of −2LL.

Last, the two compartments effect site model applied to BIS effects of propofol, recently proposed by Bjornsson et al., was also fit to the current data, but no improvements were found.

Based on the observation of the time delay between predicted $C_{e,Prop}$ and BIS, a value for $k_{e0}$ was estimated for propofol and remifentanil. As can be seen in figure 2, the time course of BIS can be better predicted by $C_{e,Prop}$ with the estimated value of $k_{e0}$ than using the $k_{e0}$ values included in the PK-PD models used by the TCI system. Also in both patients, the individual predictions of BIS closely follow the observed BIS values.

**Covariate Selection.** NOX and OPRM were the only two covariates that improved the fit with statistical significance ($P < 0.01$). The presence of the USE probe inside the gastrointestinal tract of the patients, a noxious stimulation, was incorporated in the model as the following equation, and a decrease in 3,209 points in −2LL ($P < 0.001$) was observed.
When a different EC50,Remi was estimated for the patients who were homozygous (GG) to the A118G polymorphism, the value of the objective function decreased in an additional 101 points (P < 0.001). Such a decrease indicates a significant influence of the genetic variant on the BIS versus Cc,Remi relationship.

Table 3 lists the population pharmacodynamics parameters of propofol and remifentanil administered in combination together with their corresponding uncertainty. EC50,Remi shows an estimated value of 19.6 ng/ml for normal patients, which increases almost 20-fold for OPRM = 1 patients (EC50,Remi,OPRM). The CI reported in table 3 for the parameters α and EC50,Remi,OPRM was calculated by log-likelihood profiling.

**Model Diagnosis**

Figures 3 shows different goodness-of-fit plots: observations versus population predictions (3A), observations versus individual predictions (3B), and the absolute value of weighted residuals versus individual predictions (3C). Figure 4 shows the time course of conditional weighted residuals (4A) as well as conditional weighted residuals versus Ce,Remi (4B) and Ce,Prop (4C), respectively. Both figures confirm that the model has good performance.

Figure 5 represents the behavior of the selected model in detail for a noncarrier or heterozygous carrier of A118G SNP patient (OPRM = 0). Figure 5A shows the time course of Cp and Cc, as for both propofol and remifentanil, where the delay between the two compartments is evident. Figure 5B shows the time course of predicted and measured BIS, taking into account the effect of noxious stimulation for the same individual. NOX effect, although highly significant with regard to the decrease in −2LL, has little impact on the response curve, approximately 4%, as can be seen in table 3.

Figure 6 shows the predictions of the model for the relation between effect site concentrations and BIS effect for all patients with the normal genetic trait. For the case of patients with the A118G homozygous (GG) polymorphism, remifentanil has virtually no effect and the relation between remifentanil effect site concentration and BIS in the normal patient is therefore identical. Figure 7 shows the relation between remifentanil effect site concentration and BIS in the normal patient compared with the relation in the patient with the A118G polymorphism.

Figure 8 allows the evaluation of the synergistic interaction between propofol and remifentanil by comparing the response surface corresponding with the selected model (8A), with the response surface from the final model in which the interaction parameter α was fixed to 0 (8B), i.e., as if it was an additive

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>CI</th>
<th>Shrinkage, %</th>
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<tr>
<td>BIS0, %</td>
<td>95.6</td>
<td>(95–96.2)</td>
<td>—</td>
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<tr>
<td>IC50,Prop*</td>
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<td>(3.34–4.38)</td>
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<tr>
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<td>19.6</td>
<td>(4.9–34.1)</td>
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</tr>
<tr>
<td>IC50,Remi,OPRM*</td>
<td>326</td>
<td>(95–600)*</td>
<td>—</td>
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<tr>
<td>k0,Prop min⁻¹</td>
<td>0.122</td>
<td>(0.10–1.14)</td>
<td>—</td>
</tr>
<tr>
<td>k0,Remi min⁻¹</td>
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<td>(0.09–0.21)</td>
<td>—</td>
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<td>(2.2–2.9)</td>
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<tr>
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<td>—</td>
</tr>
<tr>
<td>α</td>
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<td>(1.25–3.1)*</td>
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<td>IPV kep0%</td>
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<tr>
<td>Residual error, BIS, %</td>
<td>6.6</td>
<td>(6.3–6.9)</td>
<td>—</td>
</tr>
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</table>

CI, 95th CIs; BIS0, BIS (bispectral index) response at baseline; IC50,Prop and IC50,Remi, effect site concentration eliciting a BIS response equal to half of BIS0 for propofol and remifentanil, respectively; IC50,Remi,OPRM, remifentanil effect site concentration eliciting a BIS response equal to half of BIS0 for OPRM = 1 patients; k0,Prop and k0,Remi, the first-order rate constant governing the disappearance of the drugs from the effect site for propofol and remifentanil, respectively; γProp and γRemi, parameter governing the steepness of the BIS vs. Cc curve for propofol and remifentanil, respectively; α, interaction parameter indicating the absence of interaction (α = 0), synergistic (α > 0), or antagonistic interaction (α < 0); θNOX parameter indicating the influence of noxious stimulation; IPV_BIS0, IPV_IC50,Prop*, IPV kep0, and IPV_SLP* interpatient variability for BIS0, IC50,Prop*, IPV kep0, and IPV_SLP* respectively.

* Calculated by log-likelihood profiling. Parameters are defined in the text.
Fig. 3. Goodness-of-fit plots. Time course of the observations versus population or individual predictions on (A) and (B), respectively. The absolute values of the individual weighted residuals (IWRES) are also displayed in (C). Each panel shows the identity (gray) and smooth (red) lines.

Interaction. Figure 8C shows the result of subtracting the predicted response surface (synergism) from the additive response as a graphical representation of the degree of synergy.

To evaluate the performance of the model, a visual predictive check method was used. Based on the population model, 100 studies of the same design and similar patient characteristics were simulated and new model predictions computed. The predictions of the model, the 50th percentile, and the 5th and 95th percentiles are shown in figure 9.

Discussion
This study demonstrates that a genetic trait such as the A118G SNP in the OPRM1 gene can affect the requirements of remifentanil in patients undergoing procedures under sedation-analgesia. To the best of our knowledge, it is the first use of specific genetic characteristics, a SNP, as a covariate factor in the modeling process to optimize dosing of an anesthetic drug. It can be considered as a first step to a “pharmacogenetic-based” personalized drug administration in anesthesia. It has been previously shown that the A118G SNP affects the requirements of opioids to control postoperative pain and chronic cancer pain, but it has not been studied for the combined administration of propofol and remifentanil under clinical conditions as the ones studied in the current project.

These results demonstrate that patients who are homozygous (GG) for the A118G variant do not show any change in the BIS response curve in the presence of remifentanil, whereas the OPRM = 0 patients exhibit a more intense response. Our approach has intentionally been restrictive in considering only as OPRM = 1 those patients who were homozygous (GG) for the A118G SNP. Other authors have shown that opioid requirements were not increased in heterozygous carriers or noncarriers of the variant.

The population modeling approach, using nonlinear mixed effects models, extracts maximal benefits when all the factors that could affect the relation between drug concentrations and observed effects are integrated in the same steps of data analysis. In our case, to extract the maximal information possible, all BIS data from all patients at any level of propofol and remifentanil concentration, including single-drug administration, with or without the A118G variant or presence and absence of noxious stimulation must be analyzed together. Such a complex model, integrating the interaction between both drugs, has allowed estimating their relative potency based on their EC50 values, the changes attributed to genetic variants, and the influence of noxious stimulation. It has also allowed to refine the values of k0, reflecting the delay in transferring propofol and remifentanil from plasma to the biophase, based on the effect site model approach.
Fig. 4. Goodness-of-fit plots. A shows the time course of conditional weighted residuals (CWRES). B and C show the CWRES with respect to remifentanil and propofol concentrations, respectively. Each panel shows the perfect fit CWRES = 0 (gray) and smooth (red) lines.

Fig. 5. Predictions of propofol and remifentanil concentrations and of bispectral index (BIS) response. Predicted plasma (solid lines) and effect site (dashed lines) concentrations versus time profiles for propofol (blue) and remifentanil (red) are showed in A. Propofol concentrations are μg/ml and remifentanil are ng/ml. (B) Observed (points) and model predicted (solid line) BIS response versus time profile as well as duration of noxious stimulation.
BIS is a mathematically constructed index based on the dynamic integration of several subparameters extracted from the processed electroencephalographic signal. The raw electroencephalogram is collected and processed, and in a simultaneous way, subparameters are calculated and dynamically integrated into the BIS index which is finally displayed in the screen and used to guide anesthesiologists in optimally controlling the hypnotic component of anesthesia. The whole process represents a time lag between signal collection and BIS display that might vary depending on smoothing and processing of artifact-free signal.29

The value of \( k_{e0} \) estimated by Schnider and used in the TCI system is based on the analysis of electroencephalographic signal undergoing semilinear canonical correlation, a different mathematical approach than the one used in BIS. The approach used had no signal smoothing or other factors delaying its calculation as it is present in BIS calculation.4 This difference in hypnotic measures might explain the hysteresis observed between effect site propofol and BIS also reported by other authors.30

The \( k_{e0} \) value estimated from our data, 0.122 min\(^{-1}\), is smaller than the one reported originally in Schnider et al., 0.456 min\(^{-1}\). Other authors, using the BIS, have reported values like 0.16 min\(^{-1}\) for young adults31 or 0.3 min\(^{-1}\) on average for different age groups.32 Different study designs or surrogate measures of hypnotic effect make comparisons difficult.

The speed of infusion of propofol might also have influenced the performance of PK-PD models, especially when propofol is administered at high speed on infusion as in a bolus injection. This has been shown using the cerebral state index, a parameter calculated from the electroencephalogram or the BIS. The lack of accuracy in the prediction of BIS effect during fast infusion was attributed to a misspecification of the pharmacokinetic model in the first minutes after a bolus injection. The current study uses a TCI system targeting the effect site as drug administration technique. This approach consists in the initial injection of a very fast bolus, combined with an infusion, adjusted to the specific characteristics of the patient, to achieve the target effect site concentration as soon as physiologically possible. This could be another factor influencing the observed delay between BIS and \( C_{e,prop} \).
The reestimation of pharmacodynamic parameters for propofol tries to calculate the prediction of $C_e$ under specific conditions: first, using the BIS as measure of effect; second, in patients undergoing procedures requiring sedation-analgesia and as a consequence under low levels of drug concentrations; and third, in the presence of an opioid, remifentanil, that might exert some influence on the pharmacodynamic properties of propofol with respect to the BIS. It must be noted also that the effect site model approach has some limitations and it cannot describe adequately every step in the cascade between the arrival of the drug to the target organ, tissue, or cell; the molecular mechanisms underlying; and the anesthetic effect.

Our work might be of help in improving the administration of sedation and analgesia using a TCI system and the BIS as a monitor of sedation. The use of $C_p$ concentrations to estimate pharmacodynamic parameters, although questioned by some authors, has allowed adapting the PK-PD models to produce a prediction of $C_e$ that closely reflects the changes in the BIS.

The estimation of EC$_{50,\text{prop}}$ in the current study can also be compared with the values published by other authors being the most recently reported 2.5 µg/ml with respect to the BIS. Values ranging from 4.5 to 1.3 µg/ml have also been reported in other studies performed without coadministration of opioids. However, the interaction between

Fig. 8. Propofol and remifentanil synergism with respect to the bispectral index. Surface response plots corresponding to the selected model of synergism (A), the additivity response in which the $\alpha$ parameter in Equation (3) was fixed to 0 (B), and result of the difference between panels B and A (C), showing the magnitude of the synergism.

Fig. 9. Results of the Visual Predictive Check obtained from 100 model-based simulated studies. Points represent raw bispectral index data. Lines correspond to the 5th, 95th (dashed), and 50th (solid) percentiles. The simulated studies have the same design characteristics as the original dataset.
propofol and remifentanil toward different measures of effect has also been studied and reported by other authors as synergistic in most of the cases. Under low concentrations of propofol and remifentanil, Nieuwenhuis and et al. reported an absolute lack of effect of remifentanil on the BIS even when combined with propofol or sevoflurane. Bruhn et al. used the BIS and other electroencephalogram-derived parameters as measures of effect and a response surface model for data analysis. The concentrations studied ranged from 0 to 12 μg/ml for propofol and 0 to 40 ng/ml for remifentanil. Their estimation of C_{50,Prop} was 2.3 μg/ml and 25.7 ng/ml for C_{50,Remi} and the interaction was highly synergistic. Using a similar data analysis method as the one in the current paper reported a value of α, the interaction parameter, of 5.1 for the sedation responses indicating a significant synergism, with EC_{20} values of 1.8 μg/ml and 12.5 ng/ml for propofol and remifentanil, respectively. The values are in good agreement with the ones estimated in the current study. Unlike in our work, all the previous studies were conducted in volunteers and under well-controlled conditions.

Previous work from our group using a different data analysis approach, although under similar clinical conditions, estimated the influence of noxious stimulation by around 20%, but when the effect is measured using the AAL/2, a parameter derived from the auditory-evoked potentials. Our current analysis quantifies the difference in only a 4% using the BIS, which is a value similar to that estimated for BIS in our previous work. From a clinical standpoint, this project shows that genetic factors, specifically A118G, must be taken into account when dosing anesthetic drugs. In this particular case, as there is no objective way to quantify the response to noxious stimulation, we have used the BIS. Based on the findings reported, when an expected decrease in BIS value is not observed after adequate dosing of analgesics, one of the factors to be considered might be the presence of the A118G variant in OPRM gene in chromosome 6. Another relevant aspect is the possibility that these effects of the variant could be observed at any concentration of analgesic drugs under anesthesia; so further studies should be conducted under general anesthesia conditions. In the setting of sedation-analgesia, it would also be interesting to know how the A118G variant might change the sensitivity of patients to other effects of opioid drugs such as respiratory depression. Olofsen et al. have studied the influence of A118G in a group of subjects who previously exhibited resistance to the analgesic effects of morphine 6 glucuronide. They have demonstrated that their A118G subjects had the same pattern of respiratory depression as normal subjects. In their study, there was no patient homozygous for the variant, all were heterozygous. It would be interesting to know the respiratory effects of opioids in a group of homozygous A118G patients.

To conclude, while C_{50} of remifentanil ranging 1–5 ng/ml synergistically potentiates the effects of propofol on the BIS, they exhibit no effect in those patients with the A118G SNP. Noxious stimulation in this setting increases BIS values by 4% at the same concentrations of propofol and remifentanil. These results warrant the need for further studies to establish the respiratory effects as well as the requirements of opioids under general anesthesia conditions in homozygous patients with the A118G SNP.

References

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