Pharmacodynamic Interaction between Propofol and Remifentanil Regarding Hypnosis, Tolerance of Laryngoscopy, Bispectral Index, and Electroencephalographic Approximate Entropy

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Background: The purpose of this investigation was to describe the pharmacodynamic interaction between propofol and remifentanil for probability of no response to shaking and shouting, probability of no response to laryngoscopy, Bispectral Index (BIS), and electroencephalographic approximate entropy (AE).

Methods: Twenty healthy volunteers received either propofol or remifentanil alone and then concurrently with a fixed concentration of remifentanil or propofol, respectively, via a target-controlled infusion. Responses to shaking and shouting and to laryngoscopy were assessed multiple times after allowing for plasma effect site equilibration. The raw electroencephalogram and BIS were recorded throughout the study, and AE was calculated off-line. Response surfaces were fit to the clinical response data using logistic regression models. Response surfaces were visualized using three-dimensional rotations. Model parameters were estimated with NONMEM.

Results: Remifentanil alone had an appreciable effect on response to shaking and shouting or response to laryngoscopy. Propofol could ablate both responses. Moderate remifentanil concentrations dramatically reduced the concentrations of propofol required to ablate both responses. The hierarchical response surface described the data better than empirical logistic regression. BIS and AE are more sensitive to propofol than to remifentanil.

Conclusions: Remifentanil alone is ineffective at abrating response to stimuli but demonstrates potent synergy with propofol. BIS and AE values corresponding to 95% probability of ablating response are influenced by the combination of propofol and remifentanil to achieve this endpoint, with higher propofol concentrations producing lower values for BIS and AE.

BOTH propofol and remifentanil pharmacodynamics, especially with regard to effects on the electroencephalogram,¹⁻⁴ have been extensively investigated. Several studies have also examined the interaction of propofol and remifentanil on electroencephalographic measures of drug effect.⁵⁻¹⁰ This investigation was intended to quantify the interaction between propofol and remifentanil with regard to clinically relevant endpoints, the probability of no response to shaking and shouting, and the probability of no response to laryngoscopy and to link that relation with the interaction on two electroencephalographic endpoints, Bispectral Index (BIS) and approximate entropy (AE).

Materials and Methods

Subjects

The study was approved by the Stanford University Institutional Review Board (Stanford, California). Written informed consent was obtained from each subject. Ten male and 10 female healthy volunteers (median age, 33.5 yr; range, 20–43 yr; median weight, 69.3 kg [range, 50–120 kg]) were studied. All volunteers received a physical examination, laboratory tests (complete blood cell count, blood chemistries), and an electrocardiogram.

Study Design

The study was performed as a randomized, prospective, open-label study. After arrival at the operating room, an electrocardiogram, a pulse oximeter, and a noninvasive blood pressure monitor were attached to the patient. Two intravenous cannulae for drug and fluid administration were placed in a forearm vein on each arm. A 20-gauge plastic cannula was inserted into the radial artery of the nondominant hand. Ventilation and mixed expired carbon dioxide pressure were measured and recorded continuously with an anesthesia monitor (Datex, A53, Helsinki, Finland). Drugs were administered via target-controlled infusion (TCI) with a Harvard infusion pump (Harvard Clinical Technology, Inc., South
Natick, MA) driven by STANPUMP™ running on a commercially available laptop computer. STANPUMP was programmed with the propofol pharmacokinetic parameters reported by Schnider et al.9 and the remifentanil pharmacokinetic parameters reported by Minto et al.4 Multiple arterial samples were drawn for analysis of the pharmacokinetic interaction of propofol and remifentanil. The timing of the samples and the pharmacokinetic analysis of the propofol and remifentanil infusions have been reported previously.10

Drug Administration

The study design was a modification of the “crisscross” design proposed by Short et al.11 The volunteers were studied in two phases, single drug and drug combination, the second phase immediately after the first. In the first phase, the volunteers received either propofol or remifentanil alone in a stepwise ascending fashion until their mixed expired carbon dioxide pressure exceeded 65 mmHg, apneic periods of more than 60 s occurred, or both. This phase was used to capture data on respiratory depression, which has been published,12,13 as well as to capture the electroencephalogram with single drug administration. After reaching apnea or a mixed expired carbon dioxide pressure greater than 65 mmHg, the propofol or remifentanil concentration was allowed to decrease to either 1 μg/ml or 1 ng/ml, respectively. That concentration was subsequently maintained with STANPUMP. After the target concentration had been maintained for at least 15 min according to the TCI predictions, clinical response to 1 μg/ml propofol or 1 ng/ml remifentanil was assessed, as described below.

After assessing the clinical response, the second phase commenced with the administration of the second drug. The second drug was administered with a TCI device at a target concentration that remained constant throughout the second phase of the study. The target concentration was 0–4 ng/ml if the second drug was remifentanil (table 1) and 0–4 μg/ml if the second drug was propofol (table 2). After starting the second drug, the concentration of the first drug was increased in a stepwise fashion, and the clinical response was assessed at each step, as described below, until the volunteer did not respond to laryngoscopy. The order of drug administration and the target concentration used for the second drug were allocated from a randomized list. Tables 1 and 2 display the peak concentrations of the titrated drug during the first and second phases of the study, as well as the target concentration for the second drug. Table 1 shows the study design for the subjects in whom the titrated (first) drug was propofol and the constant (second) drug was remifentanil. Table 2 shows the study design for the subjects in whom the titrated (first) drug was remifentanil and the constant (second) drug was propofol.

Assessment of Clinical Response

The clinical response was assessed after 15 min to allow for plasma effect site equilibration. At each time

![Table 1. Combinations of Propofol and Remifentanil, with Changing Propofol Concentrations and Constant Remifentanil Concentrations](https://example.com/table1.png)

<table>
<thead>
<tr>
<th>Individual</th>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Propofol Concentration, μg/ml</td>
<td>Peak Remifentanil Concentration, ng/ml</td>
<td>Propofol Concentration, mg/ml</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
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<td>4</td>
</tr>
<tr>
<td>18</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

With the exception of two patients (3 and 11; propofol only), every patient received a ramp up–down infusion of propofol, followed by a step up–down infusion of propofol in the presence of a constant concentration of remifentanil. The first concentration indicated refers to the highest concentration achieved during the respiratory depression phase (single drug administration), and the second concentration indicated refers to the highest concentration achieved during the central nervous system depression/interaction phase (changing concentrations of the first drug and constant concentrations of the respective second drug). The concentration ranges were determined by pharmacodynamic considerations (see Materials and Methods). The remifentanil target for one patient (15) was erroneously set to 2 ng/ml instead of 1 ng/ml.

![Table 2. Combinations of Propofol and Remifentanil, with Changing Remifentanil Concentrations and Constant Propofol Concentrations](https://example.com/table2.png)

<table>
<thead>
<tr>
<th>Individual</th>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Remifentanil Concentration, ng/ml</td>
<td>Peak Propofol Concentration, μg/ml</td>
<td>Propofol Concentration, mg/ml</td>
</tr>
<tr>
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<td>3</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
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<td>1</td>
</tr>
<tr>
<td>10</td>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>

With the exception of two patients (1 and 2; remifentanil only), every patient received a ramp up–down infusion of remifentanil, followed by a step up–down infusion of remifentanil in the presence of a constant concentration of propofol. The first concentration indicated refers to the highest concentration achieved during the respiratory depression phase (single drug administration), and the second concentration indicated refers to the highest concentration achieved during the central nervous system depression/interaction phase (changing concentrations of the first drug and constant concentrations of the respective second drug). The concentration ranges were determined by pharmacodynamic considerations (see text).
when the clinical response was assessed, the volunteer was exposed to a series of stimuli with increasing intensity:

1. calling his or her name in a low voice (positive responses were verbal acknowledgment, opening the eyes, or turning the head toward the speaker),
2. shouting his or her name (positive responses were verbal acknowledgment, opening the eyes, or turning the head toward the speaker),
3. shaking and shouting his or her name (positive responses were verbal acknowledgment, opening the eyes, turning the head in any direction, or withdrawing from the shaking),
4. insertion of a laryngeal mask airway, (positive responses were grimace, clenching the jaw, coughing, or bucking on the laryngeal mask airway), and
5. laryngoscopy (positive responses were clenching the jaw, coughing, or bucking).

All assessments of sedation were performed by one investigator (S. L. S.) to minimize interobserver variability. There was a delay of approximately 10 s between assessments 1, 2, and 3 and approximately 30 s between assessments 4 and 5. The assessment at each level was terminated as soon as a response (defined above) was observed or the volunteer tolerated laryngoscopy.

Electroencephalographic Monitoring

Electroencephalographic electrodes (ZipPrep; Aspect Medical Systems, Natick, MA) were placed on the scalp in the following configuration: bipolar frontomastoid montage (Fp1–A1 and Fp2–A2: international 10–20 system of electrode placement). The impedance of each electrode was less than 2 kOhm. The BIS (BIS® version 3.22) was recorded continuously using an Aspect A1000 electroencephalographic monitor (Aspect Medical Systems). Serial output files consisting of processed electroencephalographic parameters were collected on a personal computer. The raw electroencephalogram was digitized at 128 Hz, 12-bit resolution, and stored on a computer hard disk for subsequent processing.

The electroencephalographic AE was calculated offline from 1,024 data points (= 8-s epochs). The AE quantifies the predictability of subsequent amplitude values of the electroencephalogram, based on the knowledge of the previous amplitude values. The absolute value of the AE is influenced by three parameters: the length of the epoch (N), the number of previous values used for the prediction of the subsequent value (m), and a filtering level (r). In this study, N was fixed at 1,024; thus, one value of AE could be calculated for each 8-s electroencephalographic epoch. The noise filter r was defined as relative fraction of the SD of the 1,024 amplitude values. We used the parameter set m = 2 and r = 0.2 · SD, which gave the best performance for electroencephalographic AE in a previous study by Bruhn et al.14

The BIS and AE values were calculated by averaging the seven epochs (56 s) immediately before assessment. To minimize artifacts, patients were instructed not to open their eyes, talk, or move during the electroencephalogram recording before the sedation level was assessed.

Statistical Analysis

Independent variables available for analysis were TCI predicted drug concentrations of propofol and remifentanil as well as the Bayesian (individually predicted) concentrations. The Bayesian predictions are based on the concentrations calculated from each individual’s propofol and remifentanil post boc Bayesian pharmacokinetic parameters, as previously reported.10 Because TCI predictions are available in real-time to clinicians using TCI infusions (other than in North America, where the devices are still unavailable), we analyzed the interaction based on the propofol and remifentanil concentrations predicted by the TCI device. Because the post boc Bayesian predictions are the best representative of the “true” propofol and remifentanil concentrations, we also analyzed the interaction based on the post boc Bayesian pharmacokinetic parameters. Dependent variables available for analysis were the quantal responses (response vs. no response) to different stimuli, electroencephalographic BIS, and electroencephalographic AE. The influence of sex was examined as a covariate of the drug interaction.

Pharmacodynamic Analysis of the Quantal Responses

To maintain statistical power, we grouped our responses into a category that we believed showed profound depression of consciousness, no response to shouting and shaking, and a response that we believed combined profound depression of consciousness with lack of response to a noxious stimulation, no response to laryngoscopy. We modeled the probability of no response to shouting and shaking as Phypnosis, on the belief that it was primarily measuring hypnotic drug effect, and the probability of no response to laryngoscopy as Plaryngoscopy.

We used NONMEM to analyze the binary data using multiple graded binary responses, as described by Somma et al.15 Two response surface models were examined to characterize the interaction between remifentanil and propofol. The first model was the empirical response surface described by Minto et al.16 The model
for the probability of no response to shouting and shaking was:

\[
P_{\text{hypnosis}} = \frac{(U_{\text{hypnosis}} + U_{\text{hypnosis}})}{1 + (U_{\text{hypnosis}} + U_{\text{hypnosis}})}
\]

(1)

where \(P_{\text{hypnosis}}\) = probability of being unresponsive to shaking and shouting; \(U_{\text{hypnosis}}\) = remifentanil concentration/C50, remifentanil, hypnosis; C50, remifentanil, hypnosis = remifentanil concentration associated with 50% probability of no response to shaking and shouting; \(U_{\text{hypnosis}} = \text{propofol concentration/C50, propofol, hypnosis; C50, propofol, hypnosis = propofol concentration associated with 50% probability of no response to shaking and shouting; \(U_{\text{hypnosis}} + U_{\text{hypnosis}}\)}\).

\(\gamma_{\text{laryngoscopy}}\) = steepness of the relation between the drug combination and the probability of no response to laryngoscopy.

The second model was a novel hierarchical model for the interaction between opioids and hypnotics. The model is based on concepts proposed by Kissin17 and Glass18 that analgesia represents drug actions that act on ascending neuropathways to attenuate the response to noxious stimulation and that hypnotics is a cortical response that balances the ascending noxious stimulation against drug-induced cortical suppression. We expressed this hierarchy of opioid and hypnotic drug effect in the pharmacologic model shown in figure 1. Initially, the stimulus is processed at the level of the spinal cord, midbrain, and thalamus. At these levels, opioids attenuate the painful stimulus. Peripheral actions of opioids are lumped in at this level as well. The potency of the opioids in attenuating the stimulus is a function of the intensity of the stimulus (e.g., as demonstrated by Ausems et al.19). This yields the relation:

postopioid intensity = preopioid intensity

\[
(1 - \frac{\text{opioid}^\gamma}{\text{opioid}^\gamma + (\text{opioid}_{50} \cdot \text{preopioid intensity})^\gamma})
\]

(3)

where preopioid intensity is the intensity of the afferent noxious stimulus; postopioid intensity is the intensity of the noxious stimulus after attenuation of the stimulus by opioid action; opioid is the opioid concentration; opioid_{50} is the equilibrated opioid concentration associated with 50% attenuation of the postopioid intensity stimulus, at an intensity score of 1; and \(\gamma\) is the steepness of the opioid concentration-versus-response (attenuation) relation. Opioid_{50} is multiplied by preopioid intensity to reflect the decreasing potency of opioids in attenuating pain as the intensity of the pain increases, as shown in figure 1. Note that the intensity is unitless. The intensity value eventually relates to the probability of response, but at the level of opioid drug effect, the lower bound is 0, and (unlike probability) there is no intrinsic upper bound.

After opioid-mediated attenuation of the noxious stimulus, the postopioid intensity stimulus is projected to the cortex, where the central nervous system arousing characteristics of intense stimulation are suppressed by the
central nervous system depressant effects of hypnotics. The pharmacologic expression of this would be:

\[
\text{Probability of Nonresponsiveness} = 1 - \frac{\text{hypnotic}^\theta}{\text{hypnotic}^\theta + \left(\text{hypnotic}_{50} \cdot \text{postopioid intensity}\right)^\theta}
\]

where the probability of nonresponsiveness is \(P_{\text{hypnosis}}\) or \(P_{\text{laryngoscopy}}\); hypnotic is the concentration of the sedative; hypnotic\(_{50}\) is the hypnotic concentration associated with 50% probability of nonresponsiveness when the postopioid intensity equals 1; and \(\phi\) is the steepness of the hypnotic concentration-versus-probability of nonresponsiveness relation. Note that the output of equation 1 is probability, on a 0–1 scale. Also, note that postopioid intensity is necessarily greater than 0, so that in this pharmacologic view of the anesthetic state, merely being alive (e.g., nonstimulated baseline) is associated with some postopioid stimulation that is countered by hypnotic drug action.

In the hierarchical model, the only difference between the model for the probability of no response to shouting and shaking, \(P_{\text{hypnosis}}\), and the model for the probability of no response to laryngoscopy, \(P_{\text{laryngoscopy}}\), is the estimate of the preopioid intensity of the stimulus.

The parameters of the Minto empirical model and the proposed hierarchical model were analyzed separately. Separate analyses of each model were performed based on the concentrations predicted by TCI and the concentrations predicted from the post boc Bayesian pharmacokinetics in each individual. However, within each model, \(P_{\text{hypnosis}}\) and \(P_{\text{laryngoscopy}}\) were analyzed concurrently, based on the observed response at each time point as follows:

1. response to shaking and shouting (response to laryngoscopy assumed): \(P = (1 - P_{\text{hypnosis}}) \cdot P_{\text{laryngoscopy}}\);
2. no response to shaking and shouting, response to laryngoscopy: \(P = P_{\text{hypnosis}} \cdot (1 - P_{\text{laryngoscopy}})\);
3. no response to shaking and shouting, no response to laryngoscopy: \(P = P_{\text{hypnosis}} \cdot P_{\text{laryngoscopy}}\);
4. response to shaking and shouting, no response to laryngoscopy: \(P = (1 - P_{\text{hypnosis}}) \cdot P_{\text{laryngoscopy}}\). Note that this state could not be observed because, for ethical reasons, laryngoscopy was not attempted on patients who responded to shaking and shouting. However, it is included in this list to demonstrate that the sum of all probabilities equals 1.

Pharmacodynamic Analysis of the Continuous, Electroencephalographic-derived Responses

In contrast to the quantal responses, both BIS and AE were available during monoadministration and coadministration of propofol and remifentanil. However, the electroencephalographic recordings during monoadministration of remifentanil in concentrations low enough to maintain spontaneous breathing were extremely noisy (eye and occasional limb movements in the awake volunteers) and could not be included in the pharmacodynamic modeling process. Because propofol induced unconsciousness, including cessation of eye and limb movements, with maintained spontaneous respiration, the electroencephalographic recordings were almost artifact free and could be used to determine the influence of propofol alone on BIS and AE.

The electroencephalographic response was modeled using a fractional sigmoid Emax model:

\[
\text{EEG Response} = \text{Baseline} \left(1 - \frac{U_R + U_P}{U_{50}(\theta)}\right)\left(1 + \frac{U_R + U_P}{U_{50}(\theta)}\right)^\gamma,
\]

where EEG Response = electroencephalographic response (BIS or AE); \(U_R\) = remifentanil concentration normalized to the \(C_{50, \text{remifentanil}}\); \(C_{50, \text{remifentanil}}\) = remifentanil concentration associated with 50% maximal remifentanil-induced electroencephalographic suppression; \(U_P\) = propofol concentration normalized to the \(C_{50, \text{propofol}}\); \(C_{50, \text{propofol}}\) = propofol concentration associated with 50% maximal propofol induced electroencephalographic suppression; \(\theta = U_P(U_R + U_P)\); \(U_{50}(\theta)\) = number of units associated with 50% probability at the respective \(\theta\); and \(\gamma\) = steepness of the concentration-versus-response relation factor.

The electroencephalographic recordings during monoadministration of propofol were combined with those obtained during coadministration of remifentanil and analyzed with a response surface population model based on a fractional sigmoid Emax model. The interaction on potency of the drugs was modeled with a quadratic polynomial; no interaction on slope was included. The approach has been published in detail by Minto et al.

Parameter Estimation

Model parameters were estimated using NONMEM version V (Globomax LLC, Hanover, MD). For all parameters, interindividual variability was modeled using a log-normal distribution, \(\theta_i = \theta_{\text{TV}} e^\eta\), where \(\theta_i\) refers to the individual value of the respective pharmacokinetic parameter, \(\theta_{\text{TV}}\) is the typical value of the parameter, and \(\eta\) is a normally distributed random variable with mean zero and variance of \(\omega^2\). \(\omega\) was only estimated on those parameters for which NONMEM could estimate a parameter significantly different from 0. Residual variability was described with an additive error model, \(D_V = D_V \text{exp} + \epsilon\), where \(D_V\) refers to the observed dependent variable, and \(D_V \text{exp}\) refers to the predicted depen-
dent variable. $\epsilon$ is normally distributed with mean zero and variance $\sigma^2$.

The objective function for the analysis was $-2 \log$ likelihood. Separate parameters were combined into single parameters (e.g., $\gamma_{\text{hypnosis}}$ and $\gamma_{\text{laryngoscopy}}$) if the model was not significantly worse (e.g., change in $-2 \log$ likelihood $< 3.84$; $P < 0.05$, chi-square test) with the reduced model. Similarly, the interaction parameters were tested for significance by comparing $-2 \log$ likelihood when $\beta = 0$ (additive interaction) with the $-2 \log$ likelihood when $\beta$ was not fixed equal to 0. If the difference of the objective function was more than 3.84 using both the TCI predictions and Bayesian concentrations, then a synergistic interaction was concluded. SEs were also estimated using NONMEM.

The data files, the NONMEM control files, and the NONMEM output files are available on the Anesthesiology Web site at http://www.anesthesiology.org.

Representations of Response Surfaces

Visual representation of response surfaces was performed with Mathematica 4.1 (Wolfram Research, Champaign, IL). We explored the use of three-dimensional rotations for representing the response surface data. Mathematica was used to create the response surfaces and then generate individual frames showing progressive rotations of the model in space. The individual frames, saved as .jpg files, were assembled into an Audio Video Interleaved video using JPGVideo.†† The video was converted into .wmv and .mov formats using Procoder 1.50 (Canopus Corporation, San Jose, CA). Two video codecs were used: windows media format, .wmv, using Microsoft Windows Media Encoder 9 (Microsoft Corporation, Redmond, WA), and Quicktime media format, .mov, using Sorenson Video 3 (Sorenson Corporation, Salt Lake City, UT). The movie files and the Mathematica programs used to create them are available on the Anesthesiology Web site.

Simulations

Based on the calculated parameters, propofol–remifentanil combinations for a 95% probability of no response to shaking and shouting and no response to laryngoscopy were calculated based on the hierarchical model. BIS and AE values were calculated for each simulated concentration pair to examine the relation between these electroencephalographic measures and the clinical endpoints of loss of response to shaking and shouting and loss of response to laryngoscopy. In a subsequent simulation, propofol–remifentanil concentrations associated with 5%, 10%, . . . , 95% probability of no response to shaking and shouting and no response to laryngoscopy were calculated based on the hierarchical model.

The BIS values were calculated for each simulated concentration, and interactions for responses ranging from 5% to 95% probability of no response were projected onto the BIS-versus-propofol-remifentanil response surface.

Results

All volunteers completed the study. The results of the pharmacokinetic analysis yielded an average overprediction of the propofol concentrations by 30% by the TCI pump, leading to correspondingly lower propofol $C_{50}$ values when Bayesian concentration were used compared with TCI predictions.

Subject responsiveness was assessed 100 times, for an average of 5 assessments of responsiveness per volunteer. Each assessment measured the response to series of stimuli, as described in the Materials and Methods. The assessments comprised a total of 430 stimuli–response pairs, for an average of 21.5 stimulus–response pairs per subject. Of the stimulus–response pairs, 49 first responded to talking, 7 first responded to shouting, 10 first responded to shaking, 12 first responded to laryngeal mask airway insertion, 4 first responded to laryngoscopy, and 18 had no response to laryngoscopy. The two patients who never lost response to laryngoscopy were subjects 1 and 17, who responded to laryngoscopy at a remifentanil target concentration of 24 ng/ml, and in both cases, we elected not to continue advancing the remifentanil concentration. One data point was censored from the analysis. Subject 2 lost response to laryngoscopy at a remifentanil target concentration of 40 ng/ml remifentanil. Inclusion of this data point led to numerical errors with NONMEM, and so it was removed from the data set.

Clinical Assessment of Propofol–Remifentanil Interaction: Model Results

Figure 2 displays the observed responses to shaking and shouting and to laryngoscopy at different combinations of propofol and remifentanil. Open circles show responses to shaking and shouting. Filled circles indicate no response to shaking and shouting but response to laryngoscopy. Filled triangles indicate no response to laryngoscopy. The top panel shows the TCI predicted concentrations, and the lower data shows the post hoc Bayesian predicted concentrations. The grid evident in the top panel is an expected result of giving both drugs using target controlled infusions, where concentrations necessarily line up on preselected values along the grid specified in the study design. Both figures clearly show the inability of remifentanil to suppress responsiveness at clinically relevant concentrations when given alone, the high concentrations of propofol required to ablate...
response in the absence of an opioid, and the profound effect of low concentrations of remifentanil when combined with propofol.

Table 3 summarizes the estimated pharmacodynamic parameters for the Minto empirical model of the probability of response to shaking and shouting and to laryngoscopy. A synergistic model was chosen over an additive model with $P < 0.001$ for the TCI predictions and $P < 0.05$ for the Bayesian predictions. In addition, NONMEM was unable to distinguish separate $C_{50}$ values for remifentanil in its ability to blunt the response to shaking (hypnosis) or laryngoscopy. The high $C_{50}$ for remifentanil results from the inability of remifentanil to suppress response to shouting and shaking in the absence of a hypnotic. Sex was not a significant covariate of any model parameter. The fit to the TCI concentrations improved significantly when the same interindividual variability parameter was applied to $C_{50\text{, propofol, hypnosis}}$ and $C_{50\text{, propofol, laryngoscopy}}$, indicating that a patient’s sensitivity to the hypnotic effects of propofol almost perfectly predict that patient’s sensitivity to propofol at stronger levels of stimulation. The model was not significantly improved by estimating separate steepness parameters for propofol and remifentanil or separate parameters for no response to shouting and shaking and no response to laryngoscopy, and so only a single steepness parameter was estimated in each fit. For each model, the interaction parameter for loss of response to shouting and

**Fig. 2.** Elicited responses (○ = arousable by shaking and shouting; ● = not arousable by shaking and shouting, but does not tolerate laryngoscopy; ▲ = tolerates laryngoscopy) at different combinations of propofol and remifentanil. *(Top)* Target-controlled infusion (TCI) predictions of propofol and remifentanil concentrations. *(Bottom)* Bayesian predictions of propofol and remifentanil.
shaking differed significantly from the interaction parameter for loss of response to laryngoscopy.

Table 4 summarizes the corresponding variables for the proposed hierarchical model of the probability of response to shaking and shouting (hypnosis) and to laryngoscopy. First note the substantial decrease in objective function compared with the Minto empirical model. This cannot be directly compared using the likelihood ratio test because one model is not a reduced form of the other. It is nevertheless the case that an improvement in the NONMEM objective function of approximately 13 represents a hugely better fit to the data. Considering that each model has six structural parameters, the hierarchical model must be considered the better of the two models. Patient sex was not a significant covariate for any model parameter.

Clinical Assessment of Propofol–Remifentanil Interaction: Graphical Results

Figure 3 shows the response surfaces for the probability of no response to shaking and shouting (hypnosis) and to laryngoscopy. The surfaces predicted by the Minto empirical models are shown in the top two graphs, and the surfaces predicted by the proposed hierarchical models are shown in the bottom two graphs. The left graph of each pair is the interaction based on the TCI concentrations, and the right graph of each pair is the interaction based on the post hoc Bayesian prediction of concentration. Although the overall shapes of the interaction surfaces are similar, examination of the response surfaces for the Minto empirical model shows an odd inward bowing at low propofol concentrations that is not seen with the hierarchical model. In addition, the hierarchical model does not predict that remifentanil alone can ablate response, whereas the Minto model necessarily predicts that remifentanil alone can ablate response, albeit at very high concentrations.

Figure 4 shows the response surfaces for the probability of no response to laryngoscopy. The surfaces predicted by the Minto empirical models are shown in the top two graphs, and the surfaces predicted by the proposed hierarchical models are shown in the bottom two graphs. The left graph of each pair is the interaction based on the TCI concentrations, and the right graph of each pair is the interaction based on the post hoc Bayesian prediction of concentration. All four graphs show that high concentrations of propofol are required to ablate response to laryngoscopy in the absence of remifentanil and that the concentrations are dramatically reduced in the presence of modest concentrations of remifentanil. However, even very high concentrations of

Table 3. Response Surface Parameters for the Interaction of Propofol and Remifentanil with Regard to Hypnosis (Tolerance of Shaking and Shouting) and Tolerance to Laryngoscopy Based on the Empiric Model Described by Minto

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TCI Predicted Drug Concentration</th>
<th>Bayesian Predicted Drug Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Typical Value (%SE) CV, %</td>
<td>Typical Value (%SE) CV, %</td>
</tr>
<tr>
<td>C50, remifentanil, hypnosis / C50, remifentanil, laryngoscopy ng/ml</td>
<td>19.0 (9) (37)</td>
<td>19.3 (&lt;1) 52</td>
</tr>
<tr>
<td>C50, propofol, hypnosis / C50, propofol, laryngoscopy µg/ml</td>
<td>2.16 (19) 37</td>
<td>1.6 (&lt;1) 45</td>
</tr>
<tr>
<td>C50, hypnosis, laryngoscopy / C50, laryngoscopy µg/ml</td>
<td>5.63 (22) 37</td>
<td>3.19 (&lt;1) (–)</td>
</tr>
<tr>
<td>Steepness</td>
<td>7.94 (33) (–)</td>
<td>5.25 (&lt;1) (–)</td>
</tr>
<tr>
<td>Interaction, hypnosis</td>
<td>2.13 (16) (–)</td>
<td>2.55 (&lt;1) 2</td>
</tr>
<tr>
<td>Interaction, laryngoscopy</td>
<td>2.13 (16) (–)</td>
<td>1.22 (&lt;1) 4</td>
</tr>
<tr>
<td>Objective function</td>
<td>82.7</td>
<td>83.8</td>
</tr>
</tbody>
</table>

%SE is the standard error expressed as a percent of the estimated parameter. CV is the SD in the log domain, which is approximately the coefficient of variation (CV) in the standard domain.

(–) = interindividual variability was indistinguishable from 0 in the NONMEM analysis; TCI = target-controlled infusion.

Table 4. Response Surface Parameters for the Interaction of Propofol and Remifentanil with Regard to Hypnosis (Tolerance of Shaking and Shouting) and Tolerance to Laryngoscopy Based on the Proposed Hierarchical Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TCI Predicted Drug Concentration</th>
<th>Bayesian Predicted Drug Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Typical Value (%SE) CV, %</td>
<td>Typical Value (%SE) CV, %</td>
</tr>
<tr>
<td>C50, remifentanil, ng/ml</td>
<td>1.07 (&lt;1) 26</td>
<td>1.01 (&lt;1) 10</td>
</tr>
<tr>
<td>C50, propofol, µg/ml</td>
<td>8.04 (&lt;1) (–)</td>
<td>6.68 (&lt;1) (–)</td>
</tr>
<tr>
<td>Steepness, remifentanil</td>
<td>0.97 (&lt;1) 23</td>
<td>0.72 (&lt;1) 19</td>
</tr>
<tr>
<td>Steepness, propofol</td>
<td>5.1 (&lt;1) 90</td>
<td>6.9 (&lt;1) 106</td>
</tr>
<tr>
<td>Preopioid intensity, hypnosis</td>
<td>0.60 (&lt;1) (–)</td>
<td>0.48 (&lt;1) (–)</td>
</tr>
<tr>
<td>Preopioid intensity, laryngoscopy</td>
<td>1.05 (&lt;1) (–)</td>
<td>0.83 (&lt;1) (–)</td>
</tr>
<tr>
<td>Objective function</td>
<td>69</td>
<td>70</td>
</tr>
</tbody>
</table>

%SE is the standard error expressed as a percent of the estimated parameter. CV is the SD in the log domain, which is approximately the coefficient of variation (CV) in the standard domain.

(–) = interindividual variability was indistinguishable from 0 in the NONMEM analysis; TCI = target-controlled infusion.
remifentanil are not able to totally ablate the response to laryngoscopy in the absence of propofol.

Figure 5 shows the isoboles for the 50% probability of no response to shaking and shouting (top) and 50% probability of no response laryngoscopy (bottom) based on TCI concentrations (left) or post hoc Bayesian predictions (right) for the Minto empirical model and the proposed hierarchical model. For the most part, the isoboles estimated with each model follow each other closely. The biggest separation is at low propofol concentrations, where the curves for the hierarchical model predict the need for higher propofol concentrations.

Figure 6 shows the sigmoid curves of the hierarchical model (as shown in fig. 1) fit to the observed data for hypnosis (left figures) and laryngoscopy (right figures), based on the TCI concentrations (solid lines) or the post hoc Bayesian concentrations (dashed lines). The top graphs show the attenuation of noxious stimulation by opioids, based on the modeled stimulus intensity (table 4). The bottom graphs show propofol concentration versus probability of no response in the absence of opioid (e.g., graphs C and D in figs. 3 and 4 for remifentanil = 0).

The three-dimensional rotations cannot be printed on a page and so must be download from the Anesthesiology Web site. The rotations start with a view of the interaction surface from the top, which shows the 50% isobole between propofol and remifentanil. The surface is then
rotated into a three-dimensional view, showing how the 50% isobole relates to the overall response surface. The surface is then rotated twice about the vertical axis, revealing the steepness of the joint concentration-versus-response slopes, the bowing of the surface caused by the interaction, and the relative steepness of the propofol concentration versus response (left edge) versus the remifentanil concentration versus response (right edge).

Comparing the rotations of the Minto versus the hierarchical model approaches shows the somewhat odd appearance of the Minto empirical model at low concentrations of propofol, where a slight bowing is seen, particularly for the hypnosis model based on the Bayesian concentrations (also noted in Fig. 5). This bowing results from the use of a quadratic relation in the denominator, which gives an exaggerated interaction as the interaction term approaches 4, at which point the relation is undefined. By contrast, the behavior of the model is closer to the expected quadratic shape for all four hierarchical models, despite the lack of an explicit quadratic relation in the hierarchical model.

Electroencephalographic Assessment of Propofol–Remifentanil Interaction

Table 5 shows the parameters of the fractional sigmoid Emax model relating propofol to AE, based on the electroencephalographic approximate entropy.

![Fig. 5. Isoboles showing the 50% probability of nonresponse for hypnosis (top panels) and laryngoscopy (bottom panels) based on concentrations predicted by the target-controlled infusion (TCI) (left panels) or post hoc Bayesian predictions (right panels). In general, the empirical Minto model and the proposed hierarchical model yield similar predictions, although the proposed hierarchical model uniformly predicts higher propofol concentrations in the absence of opioid.](image)

![Fig. 6. The sigmoid curves of the hierarchical model (as shown in Fig. 1) fit to the observed data for hypnosis (left panels) and laryngoscopy (right panels), based on the target-controlled infusion (TCI) concentrations (solid lines) or the post hoc Bayesian concentrations (dashed lines). The top panels show the attenuation of noxious stimulation by opioids, based on the modeled stimulus intensity (table 4). The propofol concentration-versus-response relations shown in the bottom panels depend on the level of transmitted stimulus. The figures shown are the propofol concentration-versus-probability of no response curves in the absence of opioid (e.g., graphs C and D in Figs. 3 and 4 for remifentanil = 0).](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TCI Predicted Drug Concentration</th>
<th>Bayesian Predicted Drug Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Typical Value (%SE)</td>
<td>CV, %</td>
</tr>
<tr>
<td>Baseline</td>
<td>1.61 (0.8)</td>
<td>(−)</td>
</tr>
<tr>
<td>C50, µg/ml</td>
<td>4.34 (6.1)</td>
<td>14.1</td>
</tr>
<tr>
<td>Steepness</td>
<td>1.79 (10.7)</td>
<td>29.8</td>
</tr>
</tbody>
</table>

%SE is the standard error expressed as a percent of the estimated parameter. CV is the SD in the log domain, which is approximately the coefficient of variation (CV) in the standard domain.

TCI = target-controlled infusion.
troencephalographic data gathered during propofol mono-administration in phase 1 of each study. Table 6 shows the parameters relating propofol to BIS. AE and BIS yielded nearly identical parameters for the $C_{50}$ of propofol. Figures 7 and 8 display the concentration–effect relation of propofol-induced depression of AE and BIS, respectively, as well as plots of measured versus predicted electroencephalographic response.

Table 7 shows the parameters of the interaction model relating propofol and remifentanil to AE, based on the electroencephalographic data gathered during combined propofol–remifentanil administration in phase 2 of each study. Table 8 shows the parameters of the interaction model relating propofol and remifentanil to BIS. The interaction of propofol and remifentanil on both electroencephalographic measures of drug effect was additive. The SEs for the estimates of $C_{50}$ for propofol were well below 10%, indicating that this parameter was determined with confidence during the model estimation. The $C_{50}$ values for propofol for both BIS and AE were similar both in the interaction models (tables 7 and 8) and in the mono-administration models (tables 5 and 6), and the presence of remifentanil did not significantly alter the estimates of the $C_{50}$ of propofol. The $C_{50}$ of remifentanil was much higher, nearing the top of the concentration range explored, and was determined with less accuracy, showing an SE of approximately 40% for the $C_{50}$ for the BIS response. This reflects that modest effect of remifentanil alone on electroencephalographic measures of drug effect. The $C_{50}$ for remifentanil effect on AE was significantly smaller than the $C_{50}$ of remifentanil on the BIS, suggesting that AE is more sensitive to opioid drug effect.

Figure 9 displays the AE response surface and a plot of the measured versus predicted AE values for the combination of propofol and remifentanil (TCI predictions). Figure 10 is identical but based on Bayesian predictions of propofol and remifentanil concentrations. Figure 11 displays the BIS response surface and a plot of the measured versus predicted BIS values for the combination of propofol and remifentanil (TCI predictions). Figure 12 is identical but based on Bayesian predictions of propofol and remifentanil concentrations.

### Table 6. Pharmacodynamic Parameters for Propofol-induced Changes of the Electroencephalographic Bispectral Index

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TCI Predicted Drug Concentration</th>
<th>Bayesian Predicted Drug Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>97.3 (0.3) (CV: 0%)</td>
<td>97.4 (0.3) (CV: 0%)</td>
</tr>
<tr>
<td>$C_{50}$, $\mu$g/ml</td>
<td>4.47 (4.4) (CV: 9.0%)</td>
<td>3.2 (4.7) (CV: 9.4%)</td>
</tr>
<tr>
<td>Steepness</td>
<td>1.29 (10.4) (CV: 25.2%)</td>
<td>1.31 (10.3) (CV: 25.6%)</td>
</tr>
</tbody>
</table>

%SE is the standard error expressed as a percent of the estimated parameter. CV is the SD in the log domain, which is approximately the coefficient of variation (CV) in the standard domain.

TCI = target-controlled infusion.

Fig. 7. Concentration–effect curve relation of propofol for decreasing electroencephalographic approximate entropy (● = individual measurements; solid lines = population predictions). (Top) Target-controlled infusion (TCI) predictions of propofol concentrations. (Bottom) Bayesian predictions of propofol concentrations.

**Simulations Integrating Clinical and Electroencephalographic Measures**

Figure 13 displays the relation between equipotent combinations of propofol and remifentanil for 95% probability of no response to shaking and shouting (hypnosis) and 95% probability of no response to laryngoscopy, based on the hierarchical interaction model (Table 4), and the AE (upper graph) and BIS (lower graph) values calculated using the parameters in tables 7 and 8. Models based on concentrations predicted by TCI were chosen for the simulation because these predictions are, at least in theory, available to anesthesiologists in the operating room. In the clinically relevant concentration range (propofol $\geq$1 $\mu$g/ml), AE and BIS values associated with 95% probability of no response to shouting and shaking...
range from 0.35 to 1.2 and from 27 to 72, respectively, depending on the combination of propofol and remifentanil selected to ablate the response. For propofol concentrations greater than 1 \( \mu \text{g/ml} \), the AE and BIS values associated with 95% probability of no response to laryngoscopy vary from 0.14 to 0.80 and from 15 to 54, respectively.

Figure 14 shows the same simulations as in figure 13 but superimposes a series of probability of no response curves, ranging from 5% to 95%, on the additive interaction surface for the effect of propofol and remifentanil on BIS. The top graph shows the probability of no response to shouting and shaking, and the bottom graph shows the probability of no response to laryngoscopy, in both cases based on the hierarchical interaction model. The graph shows that some propofol is required even to have only a 5% chance of nonresponse. It also shows that modest doses of remifentanil greatly decrease the propofol requirement and concurrently increase the BIS for a given probability of response to each stimulus.

**Discussion**

This investigation was intended to quantify interaction between propofol and remifentanil on abating response to a primarily hypnotic endpoint, loss of response to shaking and shouting, and a hypnotic–analgesic endpoint, the loss of response to laryngoscopy, while concurrently quantifying the interaction of propofol and remifentanil on two electroencephalographic measures of drug effect, BIS and AE. The major results are as follows:

1. The interaction between propofol and remifentanil is synergistic for loss of response to shaking and shouting and for loss of response to laryngoscopy.
2. Remifentanil is not hypnotic in clinically relevant concentrations.
3. Remifentanil concentrations of 4 ng/ml reduce the propofol concentration associated with loss of response to shaking and shouting and to laryngoscopy by approximately two thirds. Further increases in remifentanil only modestly reduce the propofol concentration required to ablate the response to either stimulus.

### Table 7. Pharmacodynamic Parameters for Propofol- and Remifentanil-induced Changes of the Electroencephalographic Approximate Entropy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TCI Predicted Drug Concentration</th>
<th>Bayesian Predicted Drug Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.61 (0.7) CV, %</td>
<td>1.62 (0.6) CV, %</td>
</tr>
<tr>
<td>( C_{50} ) remifentanil, ng/ml</td>
<td>13.1 (21.4) CV, %</td>
<td>14.5 (24.1) CV, %</td>
</tr>
<tr>
<td>( C_{50} ) propofol, ( \mu \text{g/ml} )</td>
<td>4.53 (6.5) CV, %</td>
<td>3.07 (5.4) CV, %</td>
</tr>
<tr>
<td>Steepness</td>
<td>1.98 (11.6) CV, %</td>
<td>1.91 (10.3) CV, %</td>
</tr>
</tbody>
</table>

%SE is the standard error expressed as a percent of the estimated parameter. CV is the SD in the log domain, which is approximately the coefficient of variation (CV) in the standard domain. Because the interaction was additive, no interaction parameters are included (default to 0).

TCI = target-controlled infusion.
4. Propofol was equipotent in its effect on BIS and AE, with or without remifentanil.

5. The interaction between propofol and remifentanil on BIS and AE was additive, but in the clinical range (< 8 ng/ml), remifentanil had little effect on either electroencephalographic measure of drug effect.

6. The combination of propofol and remifentanil chosen to ablate response has a large effect on the concurrent electroencephalographic measure of drug effect.

7. The new hierarchical model provides a better prediction of the likelihood of response than the empirical model described by Minto.16

**Clinical Assessment of Propofol-Remifentanil Interaction**

The synergy between opioids and propofol is well established.20-26 In this light, our findings of a synergistic interaction on loss of response to shaking and shouting and loss of response to laryngoscopy are hardly surprising. Only two other studies specifically investigating the interaction between propofol and remifentanil...
with regard to clinical endpoints are available for comparison. Roepcke et al.\textsuperscript{7} investigated the interaction of propofol and remifentanil to maintain a BIS between 45 and 55 during orthopedic surgical procedures. Propofol was administered with a TCI device at predetermined concentrations between 1.5 and 6 g/ml and supplemented with the corresponding remifentanil concentration via TCI to maintain the target BIS. The data were analyzed with an isobolographic analysis, and a synergistic interaction was found similar to that reported here.

Mertens et al.\textsuperscript{26} investigated the interaction of propofol and remifentanil on tolerance of laryngoscopy, intubation, adequate anesthesia, and awakening. They concluded that the interaction is synergistic, but additive in the clinical range. Their results for loss of response to laryngoscopy are similar to ours. In their study, the $C_{50}$ of propofol for tolerance to laryngoscopy decreased was 6 g/ml in absence of remifentanil, which decreased to 2 g/ml when the remifentanil concentration was 3.4 ng/ml. Our corresponding results are 6.62 g/ml.
propofol (TCI predictions) in the absence of remifentanil and 2 μg/ml propofol at a remifentanil target concentration of 3.5 ng/ml. As judged from figure 5, the interaction between remifentanil and propofol, although synergistic over the entire range of propofol concentrations, may seem additive for propofol concentrations between 2 and 6 μg/ml propofol, and thus, the findings reported by Mertens et al. are consistent with our results.

Our estimates of the C50 of propofol alone for attenuation of response to noxious stimulation are less than some previously reported estimates. For example, Kazama et al. estimated that the C50 to blunt response to laryngoscopy was 9.8 μg/ml, which was confirmed as being 10.9 μg/ml in a subsequent study by the same authors. As reported by Kazama et al. and by Zbinden et al., the C50 for laryngoscopy is similar for that to incision. Therefore, it is also relevant that Smith et al. reported that the C50 of propofol for skin incision in the absence of opioids was 15.2 μg/ml. In contrast, our values for the C50 of propofol to ablate response to

Fig. 11. (Top) Response surface describing the interaction of propofol and remifentanil (target-controlled infusion [TCI] concentrations) on electroencephalographic Bispectral Index (● = individual Bispectral Index values above the surface; ○ = individual Bispectral Index values below the surface). (Bottom) Population predictions (○) and Bayesian predictions (●) plotted against individually determined Bispectral Index values.
laryngoscopy range from a low of 3.2 μg/ml (table 3) to a high of 8.44 μg/ml (table 4, C₅₀ propofol × preopiod stimulus for the model using TCI concentrations). We do not have a ready explanation for this discrepancy. It could relate to laryngoscopic technique, but we were able to visualize vocal cords in every laryngoscopy, so in our view, the technique was adequately vigorous. Nevertheless, the data suggest that our laryngoscopy technique was less stimulating than that of other investigators, resulting in a lower estimate of the C₅₀ of propofol.

The hypnotic properties of remifentanil and other opioids have been investigated. Jhaveri et al. concluded that the median effective concentration of remifentanil for loss of consciousness equals 54 ng/ml, and therefore, remifentanil is not suitable as a sole induction agent. We calculated the C₅₀ of remifentanil at approximately 19 ng/ml, much lower, but still clearly outside the clinically used range. This agrees with the findings of Vuyk et al. as well, who concluded that alfentanil was not suitable as a sole induction agent.

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Although remifentanil is not a hypnotic in the clinically relevant concentration range, it profoundly decreases the propofol concentration for loss of response to shaking and shouting. Without remifentanil, 8.6 µg/ml propofol is needed to ablate response to shaking and shouting in 95% of patients (hierarchical model, TCI concentrations, calculated from table 4). This is reduced to only 0.88 µg/ml in presence of 6 ng/ml remifentanil, a concentration of remifentanil that does not cause unconsciousness during monoadministration. A similar relation exists with regard to laryngoscopy. In the absence of remifentanil, 15 µg/ml propofol is needed to ensure a 95% probability of no response to laryngoscopy. In presence of 6 ng/ml remifentanil, the propofol concentration associated with 95% probability of no response decreases to 2.5 µg/ml. These data is similar to data from interaction studies between propofol and fentanyl\textsuperscript{21} (corrected for relative potency of the fentanyl), as well as isoflurane and remifentanil.\textsuperscript{29}

The SEs of the parameter estimates for the Minto empirical model with TCI concentrations were modest (table 3), suggesting that there was enough data relative to the numbers of parameters in the model to estimate the parameters accurately. However, we found that our data set was very sensitive to initial estimates. Some initial estimates produced reasonable estimates of SEs but had objective functions approximately 10 points higher than those in tables 3 and 4. When we used starting estimates that produced the best fits, as determined from the objective function, the estimates of SEs became exceedingly small. Our guess is that the small SEs are NONMEM’s representation of the same dependence on starting estimates, in that very small changes in the estimates produce significantly worse fits, thus leading to very small SEs.

We also note that the coefficient variations on most of the parameters in tables 3 and 4 are reasonable. This means that although the subjects differ from each other, the response of the typical patient (e.g., figs. 3 and 4) is a useful starting point for titration. We also note the high coefficient variation values (about 100%) for the estimates of the steepness of the propofol concentration–versus–probability of no response relation with the hierarchical model. When the slopes become quite steep (e.g., 5 and 7 for the TCI and Bayesian models, respectively), they can vary considerably without being clinically distinguishable.

### Choice of Models for Clinical Assessment

The parameters for the hierarchical model are interesting in comparison with those of the Minto empirical model. First, the $C_{50}$ of remifentanil has been reduced from approximately 19 in the empirical model (table 3) to approximately 1 ng/ml in the hierarchical model (table 4). This is because the model estimates something that remifentanil can do: attenuate the intensity of noxious stimulation, rather than something remifentanil cannot do: prevent response to noxious stimulation. The model thus directly reports the “take home” message: Only a modest amount of remifentanil is required to blunt response to noxious stimulation. Our estimate that 1 ng/ml remifentanil reduces the propofol dose by 50% is similar to the estimate of Lang \textit{et al.}\textsuperscript{29} that the minimum alveolar concentration (MAC) of isoflurane is 50% reduced by a remifentanil concentration of 1.37 ng/ml.

The model also estimates a steepness parameter for remifentanil slightly less than 1. This indicates that increasing the opioid beyond the $C_{50}$ does continue to...
produce increased opioid drug effect but that the incremental benefit relative to the increase in concentration is modest. This is exactly the message from careful analysis of the empirical model as well, but it does not emerge from simple analysis of the parameters of the empirical model (table 3).

The $C_{50}$ values for propofol in the hierarchical model are higher than those estimated with the Minto model. For the hierarchical model, the propofol $C_{50}$s are, by definition, the hypnotic concentration associated with 50% probability of no response when the preopioid stimulus intensity equals 1 and no opioid is present. This is approximately the level of intensity of stimulation associated with laryngoscopy. The propofol $C_{50}$ for hypnosis in the absence of opioids is the $C_{50}$ value times the prestimulus intensity of shaking and shouting, which is approximately 0.5. This can be seen in the bottom two graphs of figure 6, which are the propofol concentration-versus-probability of no response curves for hypnosis (left) and laryngoscopy (right) in the absence of opioid.

It is interesting that the “preopioid stimulus,” the only

Fig. 14. The additive interaction surface for the effect of propofol and remifentanil on Bispectral Index (BIS), with the propofol effect being considerably more profound than BIS. The trajectory lines are simulations of BIS for equipotent combinations of propofol and remifentanil for 5–95% probabilities of no response to shouting and shaking ranging (A), and 5–95% probabilities of no response to laryngoscopy (B), based on the hierarchical model, showing that some propofol is required even to have only a 5% chance of nonresponse, and that modest doses of remifentanil greatly decrease the propofol requirement and concurrently increase the BIS, for the same probability of response to each stimulus. TCI = target-controlled infusion.
parameter that differs between the model for no response to shouting and shaking, and the model for no response to laryngoscopy suggest that the level of arousal associated with shaking and shouting is 0.5, whereas the level associated with laryngoscopy is 1.0. We speculated that perhaps this parameter could be set arbitrarily to 1.0 for the first model and could thus be interpreted as "stimulation level relative to shaking and shouting." However, this significantly reduced the NONMEM objective function, indicating that this parameter cannot arbitrarily be set to one for a particular stimulus-response pair. We have two possible explanations for why the preopioid stimulus for shaking and shouting is half of that for laryngoscopy, rather than, say, a tenth. One possibility is that the baseline stimulus of simply being alive is only slightly less than 0.5, and thus, shaking and shouting is adding only slightly to the baseline stimulus level (e.g., baseline = 0.4, shaking and shouting = +0.1), while laryngoscopy adds several-fold more input (e.g., +0.5). Alternatively, shouting and shaking as practiced by the assessor (S. L. S.) may have been quite noxious and thus benefited from the analgesic properties of remifentanil. This is the first introduction of the hierarchical model. We expect that as experience with this model grows, it will become clearer how to interpret the preopioid stimulus estimated by the model. The model could be expanded by adding another input for strictly hypnotic drug effect to equation 4:

\[
\text{Probability of Nonresponsiveness} = 1 - \frac{\text{hypnotic}^6}{\text{hypnotic}^6 + (\text{hypnotic}_{50} \cdot \text{postopioid} \cdot \text{intensity} + \text{hypnotic stimulus})^6}.
\]

We did not test this model because our data were well described without this additional complexity, but there may be circumstances in which explicit separation of portion of the stimulus ablated by analgesics from the portion of the stimulus ablated solely by the hypnotic component would be useful.

**Electroencephalographic Assessment of Propofol–Remifentanil Interaction**

The C50 of propofol for reduction of the BIS was almost identical to that for AE with both monoadministration and the propofol–remifentanil interaction model, indicating that both measurements are nearly interchangeable measures of propofol drug effect. The C50 values for both propofol and remifentanil are in good agreement with those published previously.1,3,4 Initial studies of the BIS showed that it worked well when propofol was the primary anesthetic agent40 but did not work well for anesthetics that combined nitrous oxide with high-dose opioids.31 For this reason, we integrated the synergistic response surface of the hierarchical model with the additive response surface of the electroencephalographic model to explore the influence of the anesthetic combination on the electroencephalographic measure of drug effect. The results (figs. 13 and 14) show that electroencephalographic measures alone are not adequate to predict the probability of response but must be interpreted in light of the drug concentration used to achieve the electroencephalographic response. For example, at 16 ng/ml remifentanil and 0.11 μg/ml propofol, the probability of response to shouting and shaking is 95%, but the calculated BIS is 54 (fig. 14, top graph). However, at a remifentanil concentration of 4 ng/ml and a propofol concentration of 1.25 μg/ml, the probability of no response to shouting and shaking is 95%, and the calculated BIS is 72. Similarly, at a propofol concentration of 4.7 μg/ml, in the absence of remifentanil, there is a 95% chance of response to laryngoscopy (fig. 14, bottom graph), even though the calculated BIS is 46. However, at a propofol concentration of 2.5 μg/ml and a remifentanil concentration of 6 ng/ml, there is a 95% chance of no response, and the calculated BIS is 54. This analysis emphasizes that BIS (and, presumably, most other electroencephalographic measures used to assess anesthetic depth) are measures of hypnotic drug effect, and the brain’s response to both the drugs and the surgical stimulus and are not measures of the brain’s likelihood of response to noxious stimulation. Because electroencephalographic response does not measure an intrinsic state of the brain, interpretation of electroencephalographic measures requires consideration of the drugs used.

In summary, response surface methodology has demonstrated that propofol and remifentanil are synergistic for the clinical endpoints of no response to shouting and shaking and no response to laryngoscopy and have additive effects on two electroencephalographic measures of drug effect, the BIS and AE. This should caution the reader against using BIS or other measurements of anesthetic depth without considering the relative contributions of a hypnotic and an opioid to the anesthetic state. These models may have applicability in designing anesthetic regimens and closed-loop control of anesthesia administering both an opioid and a hypnotic using electroencephalographic measures of drug effect.

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