

Opioid–Hypnotic Synergy

A Response Surface Analysis of Propofol–Remifentanyl Pharmacodynamic Interaction in Volunteers

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Background: Characterizing drug interactions using a response surface allows for the determination of the interaction over a complete range of clinically relevant concentrations. Gathering the data necessary to create this surface is difficult to do in a clinical setting and requires the use of volunteer experiments with surrogate noxious stimuli to adequately control the process for data collection. The pharmacodynamic synergy of opioids and hypnotics was investigated using a volunteer study paradigm.

Methods: Twenty-four volunteer subjects (12 male, 12 female) were studied using computer-controlled infusions of propofol and remifentanyl to create an increasing staircase drug concentration profile in each subject. Three different drug delivery profiles were administered to subjects, one with a single agent and two with combinations of propofol and remifentanyl. At each plateau of the staircase profile, drug effect was assessed using four surrogate measures: Observer Assessment of Alertness/Sedation score, tibial pressure algometry, electrical tetany, and response to laryngoscopy. Response surfaces were developed that mapped the interaction of propofol and remifentanyl to these surrogate effect measures in all subjects. An interaction parameter was used to assess whether these two drugs behave synergistically to blunt response to noxious stimuli.

Results: The response surfaces showed considerable synergy between remifentanyl and propofol for blunting response to the noxious stimuli. The interaction index, a measure of synergy, was 8.2 and 14.7 for response to algometry and tetany, respectively ($P < 0.001$), and 5.1 and 33.2 for sedation and laryngoscopy, respectively ($P < 0.001$), using the Greco interaction model. The surrogate stimuli mapped to clinically relevant concentrations for these agents in combination.

Conclusions: The response surface models reveal the tremendous synergy between remifentanyl and propofol. The surface morphologic features give some indication of the relative contribution of sedation and analgesia to blunting subject response. Further, the results of this investigation validate the volunteer study paradigm and use of surrogate effect measures for its clinical relevance.

DURING drug development, particularly in the early stages when fundamental pharmacokinetic and pharmacodynamic parameters are estimated, anesthetic agents

are typically characterized in isolation. For practical purposes, however, anesthesia in the modern age is at least a two-drug process consisting of an opioid and a sedative hypnotic (e.g., fentanyl and isoflurane in combination, among others). Therefore, it is important to understand the interaction pharmacodynamics of these agents as they are used clinically.

A good method for visualizing the pharmacodynamic interaction behavior of drug combinations is through response surface models.¹ Unlike traditional isobolograms that represent the concentrations of two agents that combine to produce a single degree of drug effect (e.g., a C_{50} level—the concentration producing 50% of maximal drug effect), response surface models characterize the complete spectrum of interaction between two or more agents for all possible levels of concentration and effect. The surface morphologic features can also identify whether the interaction is additive, synergistic, or antagonistic, and the degree of this interaction can be quantitatively expressed. In addition, the response surface can also be integrated with other information (e.g., pharmacokinetic, pharmacoeconomic) to identify target concentration pairs of the two drugs that optimize some outcome of interest. For example, Vuyk *et al.*² have combined knowledge of the response surface interaction between propofol and alfentanil with pharmacokinetic models to identify target concentrations of the two drugs that result in adequate anesthesia with the most rapid awakening at the end of the anesthetic.

To identify target concentration pairs that optimize some outcome of interest (e.g., recovery time, drug acquisition costs, analgesic state on emergence, among others), it is critical that the entire response surface be defined. A shortcoming of the existing drug interaction literature is that, because the studies were primarily performed in patients, it was not practically or ethically possible to study the entire concentration–effect relation for the opioid and the hypnotic (*i.e.*, low to high concentrations for both drugs). The aim of this study was to address this gap in the drug interaction literature by characterizing the complete spectrum of interaction between opioids and hypnotics using remifentanyl and propofol as drug class prototypes in a volunteer study paradigm in which target-controlled drug delivery technology and surrogate drug effect measures for analgesia and hypnosis were used. We hypothesized that propofol and remifentanyl would exhibit profound pharmacody-

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dynamic synergy for both analgesic and hypnotic effect measures as described by response surface models. A secondary aim of the study was to confirm that surrogate analgesic and hypnotic effect measures can reliably characterize the drug interaction so that surrogate effect measures can be mapped to clinical measures in a meaningful way.

Materials and Methods

Volunteer Recruitment and Instrumentation

After approval by the Human Institutional Review Board at the University of Utah Health Sciences Center (Salt Lake City, Utah), informed written consent was obtained from 24 healthy adult male and female volunteers. Eligible subjects had an American Society of Anesthesiologists physical status of I, were nonsmokers, were aged 18–45 yr, and deviated in weight by no more than 15% from ideal body weight. All volunteers had no significant medical illness or medication requirement and no history of drug or ethanol abuse.

The study used an open-label, randomized, parallel group study design. The subjects were randomized to two groups of 12. Group 1 received propofol as the primary agent first by itself and then in subsequent combinations with two randomly chosen levels of remifentanyl as a background infusion. Group 2 received remifentanyl as the primary agent with two randomly chosen levels of propofol as a background infusion. Each subject had venous catheters placed for fluid and drug administration and a radial artery catheter for pharmacokinetic sampling. Ventilation with 100% oxygen was assisted with bag and mask as needed. Safety monitoring including electrocardiography, pulse oximetry, invasive blood pressure, capnography, and arterial blood gas measurement. Before remifentanyl administration, each subject was pretreated with 0.2 mg glycopyrrolate and 1 mg pancuronium to minimize bradycardia and muscle rigidity.

Drug Administration and Effect Measurement

The study used a crisscross design for assessing drug interactions, a paradigm that Short *et al.*³ showed to be the most efficient for assessing drug interactions. Volunteers were randomized to receive an initial computer-controlled infusion of either propofol or remifentanyl as a single agent to target concentrations from low to very high (group 1: 0.5–12 $\mu\text{g/ml}$ propofol, or group 2: 0.5–80 ng/ml remifentanyl) in a “staircase” fashion. Computer-controlled infusion was implemented using STANPUMP software.^{||} For remifentanyl delivery, the pharmacokinetic parameters of Minto *et al.*⁴ were used. For propofol delivery, the pharmacokinetic parameters of Tackley *et al.*⁵ were used. For

subjects receiving remifentanyl as their primary agent, the stepped concentration target began at 0.5 ng/ml and increased at 1- to 10-ng/ml intervals until the subject no longer responded to laryngoscopy or the development of side effects from the opioid prevented further concentration increases. For subjects receiving propofol as their primary agent, the stepped concentration target began at 0.5 $\mu\text{g/ml}$ and was increased by 1–4 $\mu\text{g/ml}$ again until the subject no longer responded to laryngoscopy. The steps were chosen based to span the full concentration response range for the particular stimulus and the particular drug.

At each drug concentration plateau level, the clinical surrogate effect measurements were applied beginning with the least noxious stimuli and progressing to the greatest at 1 min after the concentration in the effect site was predicted to be at the target level. Sedation response was determined by the Observer Assessment of Alertness/Sedation (OAA/S) scale, with the subjects considered sedated if they exhibited an OAA/S score of 1, 2, or 3 and not sedated if the OAA/S score was 4 or 5.⁶ The analgesia response was measured next using pressure algometry applied to the subject's tibia.⁷ The algometer was designed in our laboratory using industrial control components and applies a 1-cm-diameter piston to the anterior surface of the tibia. The pressure driving this piston is manually increased at a steady rate from 0 lb-in⁻² until the pressure produced a level of pain that the subject considered intolerable, up to a maximum pressure of 60 lb-in⁻². After pressure algometry, tetanic electrical stimulation of the posterior tibial nerve was applied using a Digistim II nerve stimulator (Neurotechnologies, Inc., Houston, TX).⁸ The tetanic stimulation current was increased until the volunteer considered the stimulus to be intolerable or the maximal stimulus current (90 mA) was reached. When the concentration plateau reached a level where consciousness was lost, tetanic stimulation was followed by assessment of the subject's response to laryngoscopy. At this point, response to the noxious stimuli was based on whether the volunteer exhibited withdrawal movement, painful verbalization, or an increase in heart rate of 20% over the prestimulus level. With the exception of laryngoscopy, baseline measurements of the subject response to each surrogate effect was made before drug administration. Each concentration step lasted approximately 5 min after the estimated desired effect site level had been achieved.

After achieving the maximum level of effect or the maximal targeted concentration, the infusion was terminated, and the patient was allowed to recover spontaneously to baseline. After recovery from the first staircase profile of the primary drug, a constant computer-controlled infusion of the secondary agent was started and allowed to stabilize at the desired effect site concentration level before the stepwise infusion of the primary drug was repeated. Before beginning this second profile,

^{||} Available from Steven L. Shafer, M.D., at: <http://anesthesia.stanford.edu/pkpd/>. Posted April 29, 1998. Accessed June 6, 2003.

baseline measurements were again made of the surrogate effect measures except response to laryngoscopy. During this second staircase profile, pharmacodynamic measurements and arterial blood sampling were repeated as in the first infusion. After the maximal stimulus response was blunted, the secondary agent infusion was terminated at the same time as the primary agent infusion, and the volunteer again recovered to baseline. Baseline surrogate effect measures were made again, and the process was repeated a third time (third staircase profile) at a different secondary agent infusion target concentration. The target concentrations for the secondary drug infusion were randomly chosen for each subject. Subjects whose primary agent was remifentanyl received an infusion of propofol randomized between 0.25 and 4 $\mu\text{g}/\text{ml}$. A subject whose primary agent was propofol received an infusion of remifentanyl randomized between 1 and 5 ng/ml . This allowed for some overlap in the crisscross design such that for each desired pair of concentrations studied, there were four subjects who were assessed at that given level.

Blood Sample Processing and Concentration Assay

Arterial blood samples of 3 ml were obtained at each targeted concentration for remifentanyl or propofol assay in the first staircase profile. In the second and third staircase profiles, arterial blood samples of 6 ml were obtained at each targeted concentration for remifentanyl and propofol assay. Because of the metabolic pathway of remifentanyl, special processing was necessary to prevent continued metabolism of remifentanyl after sample collection. The details of sample processing and concentration assay technique have been described previously.^{9,10} The analysis of propofol was performed on samples of plasma (stored at -20°C), using a sensitive high-pressure liquid chromatography electrochemical detection analytical method as described by Dowrie *et al.*¹¹

Pharmacodynamic Analysis

The data from algometry, tetanic stimulus, OAA/S, and laryngoscopy were analyzed using response surface methodology. For continuous response data, the individual response was normalized from 0 to 1 for the maximum stimulus response level. Response to laryngoscopy was assigned a value of 1 if the patient did not respond to laryngoscopy and 0 if the patient did respond. The sedative response was assigned a value of 1 if the subject's OAA/S score was 1, 2, or 3 and 0 if the OAA/S score was 4 or 5. These transformations were made so that for each response surface, an increasing surface level indicated increasing level of anesthesia as indicated by the lack of response to the noxious stimuli. The data from the first staircase profile with single drug administration were fitted to a sigmoid Emax model for both propofol and remifentanyl by a two-stage approach using WinNonLin (Pharsight Corp., Palo Alto, CA). Because this was a

data-rich experiment, the data from all three staircase profiles given with both drugs alone and in combination were used to fit the three-dimensional response surface using a naive pooled technique.¹² This approach was chosen because we were primarily interested in mapping the generalized interaction surface for the different surrogate effects, rather than determining best individual estimates of the surfaces.

Modeling of the anesthetic effect measured by algometry and tetanic stimulus from all three staircase profiles was performed using S-Plus (version 5; MathSoft, Inc., Seattle, WA). For the response data that were continuous variables (algometry pressure, tetanic stimulation), the interaction model of Greco *et al.*¹³ was used to describe the relation between the normalized surrogate effect and plasma propofol and remifentanyl concentration. This general interaction model is represented by the following relation:

$$E = \frac{\text{Emax} \times \left(\frac{C'_A}{C_{50A}} + \frac{C'_B}{C_{50B}} + \alpha \times \frac{C'_A}{C_{50A}} \times \frac{C'_B}{C_{50B}} \right)^n}{\left(\frac{C'_A}{C_{50A}} + \frac{C'_B}{C_{50B}} + \alpha \times \frac{C'_A}{C_{50A}} \times \frac{C'_B}{C_{50B}} \right)^n + 1}$$

where Emax is the maximal effect of drug A and drug B, C_{50A} and C_{50B} are the individual drug concentrations that produce 50% of the maximal effect, n is the slope of the pharmacodynamic response curve, and α is a unique parameter that characterizes the nature and extent of interaction between two drugs for a particular effect measure. If $\alpha = 0$, the drug interaction is additive. If $\alpha < 0$, the drug interaction is antagonistic. If $\alpha > 0$, the drug interaction is synergistic. The uniqueness of α allows for a quantitative comparison of the nature and extent of interaction across different drug combinations. Nonlinear regression was used to estimate the model parameters. The probability of the interaction term coefficient α being different from zero was used to assess whether the interaction was additive. This was determined in the nonlinear regression analysis. A P value less than 0.01 was considered significant to indicate that the response was not additive. Modeling of the noncontinuous indicators of anesthetic effect measured by laryngoscopy and OAA/S from all three staircase profiles was also performed with S-Plus using the Greco model.

Assessment of Response Surface Goodness of Fit

The goodness of fit for the response surfaces were assessed visually by plotting the distribution of residual errors for each surface and quantitatively using regression metrics. For the nonlinear regression of the continuous surrogate effect measures, the surface coefficient of determination (r^2) was evaluated to assess how well the regression model described the experimental data.¹⁴

Table 1. Demographics of the Study Volunteers

	Group 1 (n = 12)	Group 2 (n = 12)
Age, yr	29.0 ± 3.8	31.0 ± 6.0
Weight, kg	69.0 ± 11.8	73.0 ± 10.9
Height, cm	169.5 ± 8.9	175.8 ± 12.8
Sex, M/F	5/7	7/5

Values are presented as mean ± SD. Group 1: propofol as primary agent; group 2: remifentanyl as primary agent.

Clinical Assessment of Interaction Responses

In addition to the three-dimensional response surfaces that were modeled, standard pharmacodynamic curves for remifentanyl combined with different fixed levels of propofol and for propofol combined with different fixed levels of remifentanyl were modeled. These curves in essence represent different vertical “slices” taken from the response surface and serve as a visual way to assess the interaction predictions in terms of clinically relevant combinations of these two agents. Although not indicating the specific degree of synergy that occurs from the combination, this representation presents the results in a manner in which clinicians can make a direct comparison with their clinical practice.

Results

All 24 volunteers completed the study. The mean volunteer age was 30 yr (24–45 yr), and the mean weight was 71 kg (55–92 kg). The height ranged from 152 to 195 cm. The ages, heights, weights, and sexes of both groups are shown in table 1. There were no significant differences between the two groups with respect to these demographic parameters.

The mean pharmacodynamic parameters for each drug and each surrogate effect when the drug was administered alone in the first study ramp are given in table 2. Because the surrogate effect measures have been normalized to their maximum value, the Emax value is always 1 for both the continuous and the binary response data. The pharmacodynamic curves for each sur-

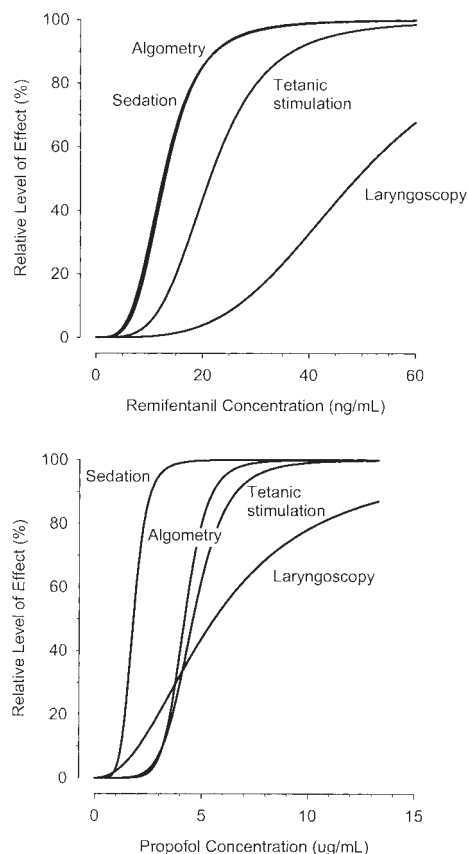


Fig. 1. Pharmacodynamic model predictions for remifentanyl and propofol administered alone for each of the surrogate effects. The model for remifentanyl is shown in the top panel; the model for propofol is shown in the bottom panel.

rogate effect when subjects received propofol alone or remifentanyl alone are shown in figure 1.

Nonlinear regression analysis of the concentration-response data showed that the interaction model was able to fit the response data of algometry and tetanic stimulus with r^2 values of 0.72 and 0.71, respectively. The regression coefficients of the interaction term (α) for algometry and tetanic stimulus were positive with the values of 8.2 ($P < 0.001$) and 14.7 ($P < 0.001$), respectively, which indicates a strong degree of synergistic interaction between propofol and remifentanyl.

Table 2. Mean Pharmacodynamic Parameters for the Individual Drugs

	Propofol		Remifentanyl	
	EC ₅₀ , µg/ml	Slope	EC ₅₀ , µg/ml	Slope
Algometry	4.16 (0.65)	8.3 (0.64)	8.84 (1.48)	4.3 (1.11)
Tetanic stimulus	4.56 (0.52)	6.0 (0.88)	21.3 (3.55)	2.1 (0.53)
Laryngoscopy	5.6 (0.42)	2.2 (0.37)	48.9 (2.3)	3.6 (0.72)
OAA/S	1.8 (0.06)	5.8 (1.05)	12.5 (0.53)	3.8 (0.54)

SEs are given in parentheses.

OAA/S = Observer Assessment of Alertness/Sedation score.

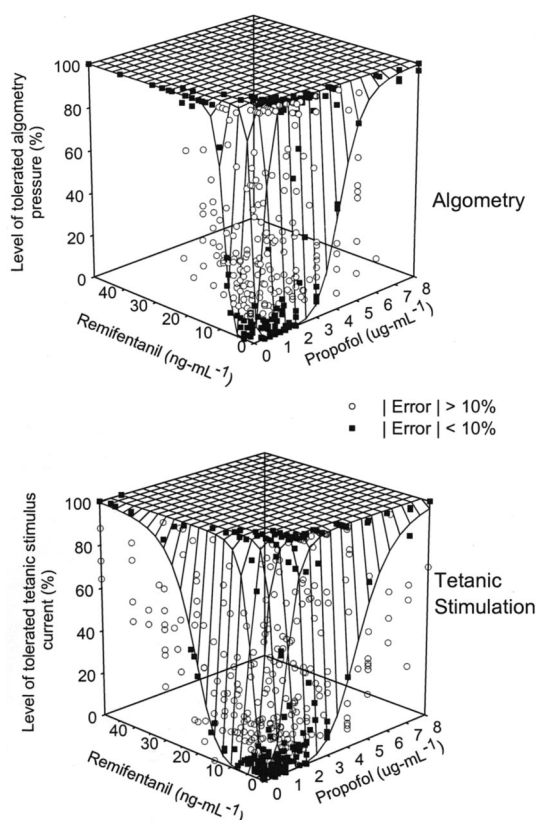


Fig. 2. Response surface model prediction for blunting the response to algometry (top) or tetany (bottom). The symbols show actual measured values from the volunteers and are shaded by the degree of prediction error.

The models for response data of algometry and tetanic stimulation are as follows:

Effect_{Algometry}

$$= \frac{\left(\frac{C'_P}{4.16} + \frac{C'_R}{8.84} + 8.2 \times \frac{C'_P}{4.16} \times \frac{C'_R}{8.84} \right)^{8.34}}{\left(\frac{C'_P}{4.16} + \frac{C'_R}{8.84} + 8.2 \times \frac{C'_P}{4.16} \times \frac{C'_R}{8.84} \right)^{8.34} + 1}$$

Effect_{Tetanicstimulus}

$$= \frac{\left(\frac{C'_P}{4.57} + \frac{C'_R}{21.3} + 14.7 \times \frac{C'_P}{4.57} \times \frac{C'_R}{21.3} \right)^{6.0}}{\left(\frac{C'_P}{4.57} + \frac{C'_R}{21.3} + 14.7 \times \frac{C'_P}{4.57} \times \frac{C'_R}{21.3} \right)^{6.0} + 1}$$

The response surface plot for these two surrogate effects is shown in figure 2 along with a graph of the residual model errors. The strong synergism between these two agents on blocking subject response to these noxious stimuli is apparent from the outward bowing of the response surfaces. The residual error of the surface prediction of patient response compared with the actual subject response was small, with a mean and SD of 0.04 ± 0.268 and 0.02 ± 0.343 for algometry and tetanic

stimulus, respectively. These error values indicate that for the algometry surface, the response prediction had an average error of 4%, whereas the absolute error for the surfaces is 26.8%. The tetanic surface average error was 2%, and the absolute error in response prediction was 34%.

We fit a model to our binary data of OAA/S and laryngoscopy, which is similar to the Greco model but adjusted for categorical data.¹⁵ The regression coefficients of the interaction term (α) for sedation indicated by an OAA/S score less than 3 and response to laryngoscopy were also positive with the values of 5.1 ($P < 0.001$) and 33.2 ($P < 0.001$), respectively. The r^2 values for the response surface fits were 0.73 and 0.59 for sedation and laryngoscopy, respectively. The models for the response surface are as follows:

Effect_{Sedation}

$$= \frac{\left(\frac{C'_P}{1.8} + \frac{C'_R}{12.5} + 5.1 \times \frac{C'_P}{1.8} \times \frac{C'_R}{12.5} \right)^{3.76}}{\left(\frac{C'_P}{1.8} + \frac{C'_R}{12.5} + 5.1 \times \frac{C'_P}{1.8} \times \frac{C'_R}{12.5} \right)^{3.76} + 1}$$

Effect_{Laryngoscopy}

$$= \frac{\left(\frac{C'_P}{5.6} + \frac{C'_R}{48.9} + 33.2 \times \frac{C'_P}{5.6} \times \frac{C'_R}{48.9} \right)^{2.2}}{\left(\frac{C'_P}{5.6} + \frac{C'_R}{48.9} + 33.2 \times \frac{C'_P}{5.6} \times \frac{C'_R}{48.9} \right)^{2.2} + 1}$$

The response surface plot for these two surrogate effects is shown in figure 3, along with a graph of the residual model errors. As with the previous stimuli, the synergism between these two agents on the subject response to these stimuli is apparent from the outward bowing of the response surfaces. The residual error of the surface prediction of patient response compared with the actual subject response was small, with a mean and SD of 0.007 ± 0.25 and 0.11 ± 0.29 for sedation and laryngoscopy response, respectively. These error values indicate that for the sedation surface, the response prediction had an average error of 0%, whereas the absolute error for the surfaces is 25%. The laryngoscopy response surface average error was 11%, and the absolute error in response prediction was 29%.

Assessment of Model Predictions

For any response surface model, it is critical to evaluate the model predictions at characteristic points to assure that the model predictions are reasonable. The values of the four response surface models were evaluated at multiple concentration pairs of remifentanil and propofol and are listed in table 3. The models show that spanning clinically relevant effect site concentration levels of these drugs, the models predict a range of drug effect from no effect to maximal effect. The chosen combinations give an indication for the relative relation between

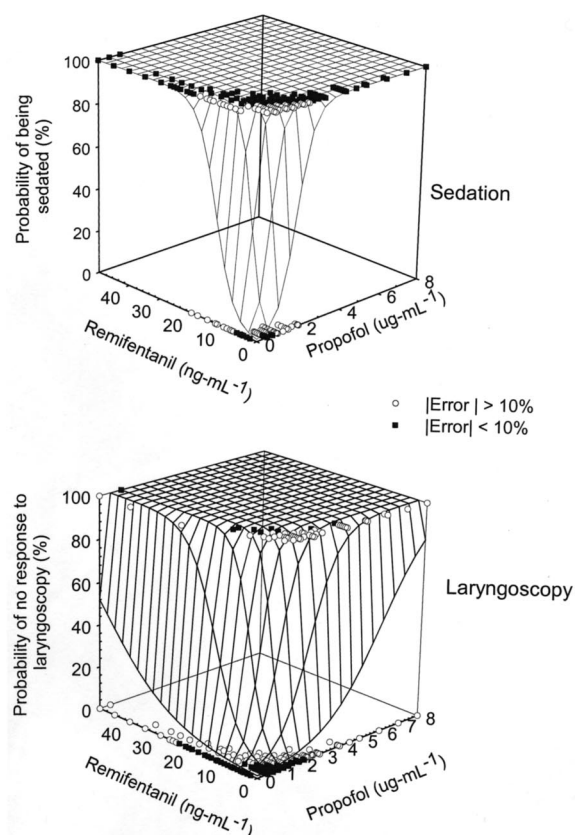


Fig. 3. Response surface model prediction for sedation (*top*) or blunting the response to laryngoscopy (*bottom*). Sedation is indicated by an Observer Assessment of Alertness/Sedation score of 0–3. The symbols show actual measured responses from the study subjects.

the surrogate measure of drug effect and corresponding clinical stimuli to which they map. The concentration–response relation for the sedation and laryngoscopy model approximates the concentrations needed clinically for loss of consciousness and intubation, and the models for algometry and tetanic stimulation approximate concentrations needed clinically for skin closure and surgical incision, respectively. When there is no drug present, all the models predict no drug effect.

With respect to the pharmacodynamic response plots, which represent vertical slices from the response sur-

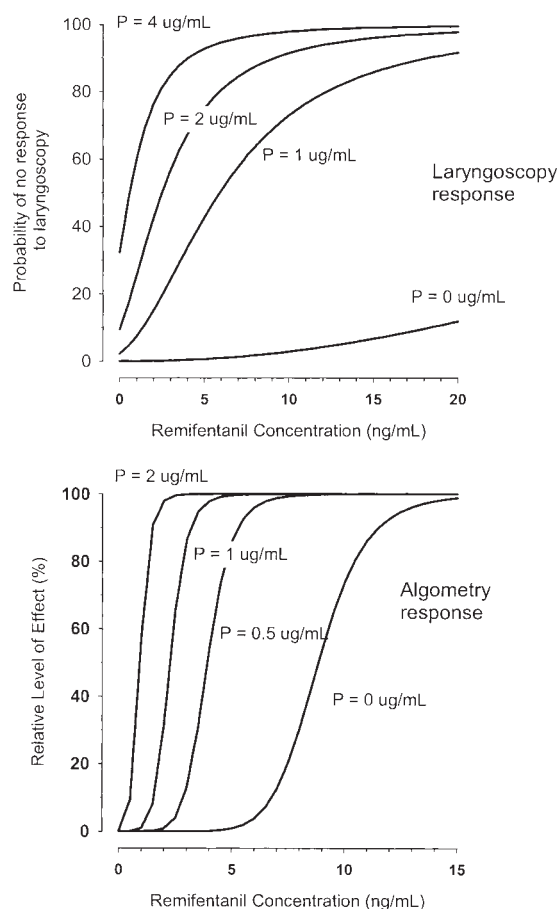


Fig. 4. Pharmacodynamic curves from the models showing the effect of different combinations of remifentanyl and propofol on blunting response to two different surrogate stimuli, laryngoscopy (*top*) and algometry (*bottom*). Each curve represents the concentration–response curve for remifentanyl in combination with a fixed concentration of propofol. These curves represent the significant synergism, indicated by the leftward shift of the concentration–response curves, when the two agents are combined.

faces (fig. 4), the results showed that combinations of propofol and remifentanyl commonly used for light anesthesia were adequate to suppress the response to algometry, and concentrations typical of those used on induction were necessary to prevent response to laryngoscopy. In this sense, the models showed that the

Table 3. Response Surface Model Predictions for Different Combinations of Remifentanyl and Propofol

Remifentanyl Concentration	Propofol Concentration	Sedation Prediction, %	Algometry Prediction, %	Tetany Prediction, %	Laryngoscopy Prediction, %
0	0	0	0	0	0
2	0	0	0	0	0
5	0	3	1	0	1
10	0	30	74	1	3
0	1	10	0	0	2
0	2	60	0	1	9
0	4	95	42	31	32
2	2	95	98	68	43
5	2	99	100	99	75
10	2	100	100	100	91

surrogate effect measures provided a level of stimulus intensity that mapped to clinically relevant combinations of these two agents and represent the level of anesthesia needed clinically at the beginning and end of a surgical procedure.

Discussion

The hypothesis that remifentanyl and propofol would exhibit profound pharmacodynamic synergy for both analgesic and hypnotic endpoints as described by response surface methodology was confirmed. When combined, substantially less remifentanyl and propofol are required to achieve a given fraction of maximal effect than when the agents are used alone. As is typical of hypnotic-opioid pharmacodynamic interactions, this synergy is most apparent at the lower range of concentrations when the drugs in isolation are producing nowhere near maximal drug effect.

Inspection of the two-dimensional representation of synergy is perhaps the most intuitively comprehensible way of appreciating the extent of the pharmacodynamic synergy. As shown in figures 1 and 4, when remifentanyl and propofol are used alone, the concentrations required to produce unresponsiveness to experimental pain measures are very high and are for practical purposes off the scale of what is commonly used clinically. In contrast, when the drugs are used in combination with a second agent, there is a substantial left shift in the concentrations of the primary agent required to produce unresponsiveness to the experimental pain measures. This translates clinically into a substantial dosage reduction when these agents are used together.

The representation of the opioid-hypnotic synergy in the response surfaces further enhances our understanding of the essential findings of the study from a clinical perspective. For example, it is clear that there is a large plateau area at the top of the surfaces within which further increases in either drug concentration do not result in more drug effect. Therefore, there is no advantage in achieving those concentrations clinically. Furthermore, it is clear that the opioid and the hypnotic are different in terms of the maximal effects they can produce. The response surface to laryngoscopy illustrates that it is difficult to achieve no response to laryngoscopy in the complete absence of a hypnotic. Perhaps most importantly, it is interesting to note that achieving unresponsiveness to the experimental pain stimuli with either the hypnotic or the opioid alone requires concentrations that are out of the reasonable clinical range.

Because the experiment used surrogate measures, relating these surrogates to clinical endpoints is critical to understanding the clinical implications of the study. Although model interpretation will be the entire focus of a future article, a few general points are worth noting.

First, two of the drug effect measures, the OAA/S and laryngoscopy, are, strictly speaking, not surrogate measures. The OAA/S, although admittedly not well suited for clinical practice because it is a somewhat laborious assessment, is an intuitively comprehensible scale representing the continuum of responsiveness under the influence of sedatives. Similarly, laryngoscopy is a common clinical stimulus applied during many general anesthetics (we endeavored to standardize the degree of noxiousness during laryngoscopy by attempting to produce the same laryngoscopic view—a grade I view as described by Cormack and Lehane¹⁶ for 5 s). Although laryngoscopy alone is clearly not clinically equivalent to laryngoscopy followed by tracheal intubation, it does represent at least part of a stimulus applied during most cases that anesthesiologists intuitively understand in terms of the degree of noxiousness. Our study and others show that laryngoscopy and tracheal intubation can be viewed as a supramaximal stimulus requiring high levels of drug concentrations to prevent responses.^{17,18}

Electrical tetany and pressure algometry, as true surrogate measures, are more difficult to interpret clinically. Our data suggest that pressure algometry produces a stimulus that is obviously less noxious than that produced by electrical tetany. In some subjects, the drug levels required to produce nonresponsiveness to electrical tetany approached those necessary to prevent responses to laryngoscopy. There are data to suggest that electrical tetany is a surrogate stimulus somewhat akin to the clinical stimulus of surgical skin incision.⁸ In future work, it should be possible to relate these surrogate measures to clinical measures in a more sophisticated, quantitative way.

The morphologic features of the surfaces reveal some interesting associations between the surrogate effect measures and the drug combinations needed to ablate subject response as shown in figure 5. In particular, laryngoscopy and algometry surfaces were skewed toward the axis for the analgesic and the sedative-hypnotic, respectively. This indicates that it takes proportionally greater concentrations of these agents to block the respective effect than the alternative agent studied (*i.e.*, the amount of remifentanyl by itself necessary to block response to laryngoscopy relative to normal clinical values is much greater than that necessary for propofol when it is given alone). This would indicate that the surrogate effect measure, response to laryngoscopy in this case, has a greater component that is related to hypnosis or cognition than analgesia. A similar pattern exists for the OAA/S assessment, although the range of concentrations needed to completely ablate the response is much less for this stimulus. In contrast, algometry, which is primarily a painful stimulus, is skewed toward the hypnotic surface, indicating that the surrogate has a greater component that is related to analgesia than hypnosis. Interestingly, response to tetany was

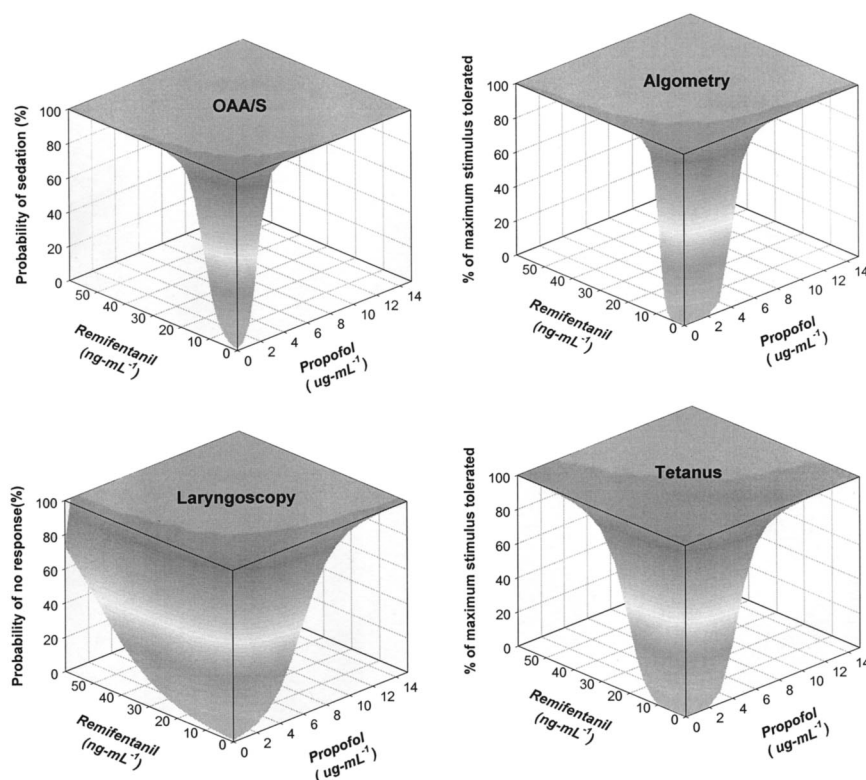


Fig. 5. Response surface model plots to compare the surface morphologic features for the different surrogate effect measures. The surface shapes reveal important clinical subtleties about the interactions (see text for details).

equally distributed toward both the analgesia and hypnosis axes, indicating that this stimulus may represent a more balanced surrogate for both hypnosis-sedation and analgesia.

A few issues related to study design deserve emphasis. Although the volunteer study design relies on surrogate measures that must be mapped to the clinical domain, there are several fundamental advantages to the volunteer study paradigm *versus* studies in patients. Chief among these is the ability to produce deliberately periods of inadequate anesthesia. Because the experimental pain measures are noninvasive and the degree of noxiousness is under the volunteer's control, it is ethically acceptable to target concentrations that are subtherapeutic by design. In doing so, the investigator can gather data that will define the boundaries between adequate and inadequate anesthesia on the interaction surface. Perhaps not surprisingly, defining this boundary between adequate and inadequate anesthesia is difficult to do in patient studies. Because one cannot deliberately produce inadequate anesthesia in patients, often there are not enough responders to noxious stimuli in patient studies to accumulate the raw data necessary to perform the analysis. Drover and Lemmens,¹⁹ for example, encountered this problem studying the interaction between nitrous oxide and remifentanyl in patients; the paucity of responders to noxious stimuli made it impossible to generate the responder *versus* nonresponder curves.

A second advantage of the volunteer study paradigm is

the opportunity to study the entire surface of the drug interaction, from low to high concentrations for both drugs. In patient studies, the drug doses and resulting concentrations are obviously constrained by what is clinically prudent and consistent with the product labeling. In volunteers, however, it is possible to study the extremes of the drug concentration spectrum even though these very low or high concentrations on the dosage spectrum would not typically be targeted clinically. For example, we were able to study volunteer responses to noxious stimuli under the influence of remifentanyl alone from very low to very high concentrations, including concentrations that are more than an order of magnitude greater than those produced during routine clinical use. This is important because it is difficult to characterize the interaction surfaces unless each drug is studied to the point of near maximal effect in isolation. Traditional drug interaction studies that seek to describe a single isobologram (*i.e.*, a single slice through the interaction surface), such as studies of the reduction of minimum alveolar concentration by opioids, do not describe the entire surface of the interaction. To use information from drug interaction studies to optimize clinical outcomes (*e.g.*, speed of recovery, drug acquisition costs, among others), more than a single slice of the interaction surface is necessary. For example, to identify target concentrations that optimize the speed of recovery, information about both the targets necessary to maintain adequate anesthesia and the targets that permit return of responsiveness is required. Studies that identify a single

isobologram (a single slice through the surface) cannot provide this information. Volunteer studies that characterize the entire surface do.

From a modeling perspective, there are also limitations to our approach that should be addressed. First, the use of the model by Greco *et al.* rather than a previously published approach advocated by Minto *et al.* has limitations because it requires the exponent of the response surface to be fixed. This necessarily makes the fit for a drug by itself suboptimal. However, unlike the Minto model, the model we used estimates a specific interaction parameter that can give a comparative indication of the degree of synergism that exists between the two drugs for differing degrees of stimulus. Because our primary aim of this investigation was determining the degree of interaction, the model we used provided the most suitable means for its determination. There are also potential issues in our processing of the continuous surrogate effects indicated by algometry and tetanic stimulation response. We limit the maximum stimulus that can be applied due to the instrumentation used to create the stimulus. Therefore, our maximum limit can be considered a censored measurement from a statistical point of view. This has the potential to artificially compress the pharmacodynamic curves when the maximum response is censored, which would result in a lower estimate of potency than the true value. Approaches for handling this type of censoring have been proposed by Sarton *et al.*²⁰; however, we do not have the ability in our data set to make the necessary assumptions that are inherent in using this approach. Therefore, the surrogate response curves can only be considered to represent the stimulus over the range that they are administered. Extension of these responses beyond those used in this study would need further validation. Because we advocate the use of these surrogates only for comparison with clinical stimuli over the same range of drug concentrations, this limitation is not significant.

In summary, the results of this study indicate that intravenous hypnotic-sedative agents and analgesics, represented by propofol and remifentanyl, exhibit profound degrees of synergism that can be quantified using a volunteer study paradigm. The surfaces produced predict reasonable concentration combinations to blunt response to the surrogate stimuli used in this study and can

be used to optimize delivery of these agents in combination based on a number of minimization criteria. The clinical application of this optimization will be the basis of further investigation with the models.

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