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Opioid–Volatile Anesthetic Synergy

A Response Surface Model with Remifentanil and Sevoflurane as Prototypes

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Background: **Combining a hypnotic and an analgesic to produce sedation, analgesia, and surgical immobility required for clinical anesthesia is more common than administration of a volatile anesthetic alone. The aim of this study was to apply response surface methods to characterize the interactions between remifentanil and sevoflurane.**

Methods: **Sixteen adult volunteers received a target-controlled infusion of remifentanil (0–15 ng/ml) and inhaled sevoflurane (0–6 vol%) at various target concentration pairs. After reaching pseudo–steady state drug levels, the Observer's Assessment of Alertness/Sedation score and response to a series of randomly applied experimental pain stimuli (pressure algometry, electrical tetany, and thermal stimulation) were observed for each target concentration pair. Response surface pharmacodynamic interaction models were built using the pooled data for sedation and analgesic endpoints. Using computer simulation, the pharmacodynamic interaction models were combined with previously reported pharmacokinetic models to identify the combination of remifentanil and sevoflurane that yielded the fastest recovery (Observer's Assessment of Alertness/Sedation score ≥ 4) for anesthetics lasting 30–900 min.**

Results: **Remifentanil synergistically decreased the amount of sevoflurane necessary to produce sedation and analgesia. Simulations revealed that as the duration of the procedure increased, faster recovery was produced by concentration target pairs containing higher amounts of remifentanil. This trend plateaued at a combination of 0.75 vol% sevoflurane and 6.2 ng/ml remifentanil.**

Conclusion: **Response surface analyses demonstrate a synergistic interaction between remifentanil and sevoflurane for sedation and all analgesic endpoints.**

IN the modern era, anesthesia is at least a two-drug process consisting of an opioid and a sedative. The sedative component is typically provided by a volatile anesthetic or the intravenous sedative propofol. The opioid component is most commonly provided by fentanyl or one of its congeners. Although it is possible to achieve anesthesia with high doses of the sedative alone (*i.e.*, a volatile anesthetic or propofol), this approach is often associated with excessive hemodynamic depression[1] and other adverse effects such as prolonged time to awakening from anesthesia.[2] Therefore, for practical purposes, the current state of the art is to produce anesthesia with an opioid and a sedative in combination.

Opioid-hypnotic drug interaction studies have traditionally evaluated the effects of adding one or two fixed doses or concentrations of a drug to several defined concentrations of the second drug.[3–7] Analyses of these interaction data are most commonly performed using an isobologram or demonstrating the shift of parallel dose–response curves. Studies designed to characterize the interaction between sedatives and opioids using these traditional methods confirm the synergistic nature of the pharmacodynamic interactions.[8–10] A significant drawback of the isobologram technique is that it describes the interaction at a single level of drug effect (*e.g.*, the minimum alveolar concentration [MAC]—the end-tidal concentration of volatile anesthetic where there is a 50% probability of moving to a skin incision—among others). Recently, response surface methodology has been applied to the study of anesthetic drug interactions.[11–14] Response surface models allow the complete characterization of pharmacodynamic interactions over the entire spectrum of possible concentration pairs.[12,15] Isobolograms represent just a single "slice" through the response surface, whereas the response surface approach provides information over the entire spectrum of drug effect.

Response surface pharmacodynamic interaction methods provide a framework to define and explore opioid–hypnotic interactions. Information about whether the interaction between two drugs is supra-additive (synergistic), additive, or antagonistic is easily determined by the morphology of the surface. Furthermore, through computer simulation, it is possible to combine these response surface pharmacodynamic models with pharmacokinetic models to identify combinations of drugs that produce the same probability of producing a therapeutic effect while optimizing some other desirable outcome, such as the speed of awakening from anesthesia.[8]

Previous work in our laboratory created response surface pharmacodynamic models for remifentanil and propofol in combination.[13] The current study is intended to extend this work to the interaction between volatile anesthetics and opioids using sevoflurane and remifentanil as prototypes of their respective drug

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classes. The principle aim of this study was to characterize the pharmacodynamic interactions of remifentanil and sevoflurane in producing sedation and analgesia using response surface models. We hypothesized that sevoflurane and remifentanil would demonstrate synergistic interactions for all the analgesic and sedative endpoints. By quantitatively describing these interactions and using previously described pharmacokinetic models, we hypothesized that we could determine, through simulation, those combinations of sevoflurane and remifentanil that would provide clinically adequate anesthesia and result in the most rapid emergence from anesthetics of varying durations.

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 16 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 by no more than 25% from their ideal body weight. Volunteers who had a history of significant alcohol or drug abuse, a history of allergy to opioids, a family history of malignant hyperthermia, or a history of chronic drug use or medical illness that is known to alter the pharmacokinetics or pharmacodynamics of opioids or inhalation anesthetics were not eligible.

After a period of overnight fasting, volunteers had an intravenous catheter placed for fluid and drug administration, and electrocardiogram, pulse oximetry, noninvasive blood pressure, expired carbon dioxide, and expired anesthetic gas monitoring were applied. To measure the response to electrical tetanic stimulation, surface electrodes were placed at the posterior tibial nerve. Before administration of the study drugs, volunteers were treated with 0.2 mg glycopyrrolate to prevent bradycardia, and 1 mg pancuronium to prevent muscle rigidity due to the opioid infusion. Each volunteer received 30 ml sodium citrate by mouth.

Study Design

The study was an open-label, randomized, parallel-group study using a crisscross design as advocated by Short *et al.*[16] to assess drug interactions. Similar methodology was used in our previous report describing the interactions between propofol and remifentanil.[13] Each volunteer was randomly assigned to one of two study groups. The primary drug for the first group was remifentanil (0.5–15 ng/ml), and the primary drug for the second group was sevoflurane (0.3–6 vol%). The primary agent was administered from a low to a high concentration in random steps determined *a priori* to allow characterization of the entire concentration range when all data were pooled (fig. 1). After obtaining pharmacodynamic measurements at the highest concentration of the primary agent, a washout period was observed during which time the primary agent decayed to predicted concentrations below the initial target concentrations. This was followed by the administration of the secondary drug at a stable background level. The primary agent was administered from low to high concentration in the same steps as in the initial period. After another washout period, a higher background level of the secondary drug was administered before the primary agent was administered from low to high concentration in the same steps. Upon completion of this third set of data collection, all of the drugs were discontinued and the volunteer was allowed to recover.

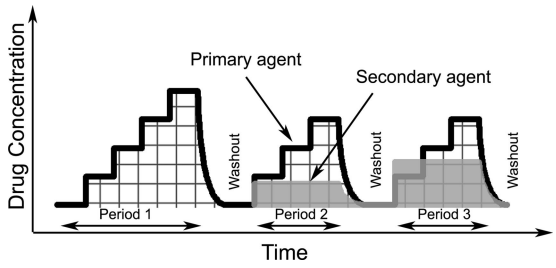

Fig. 1. A schematic summary of the infusion scheme. During each of the three study periods, the primary drug is administered in a stepwise fashion (*solid black line*), whereas in the second and third study periods, the second drug (*gray filled area*) is held at a constant predicted effect site concentration or measured alveolar concentration. In between each study period, there is a washout phase, during which the primary and secondary drugs are allowed to decay to predicted concentrations below that of the subsequent target concentration pair.

Drug Delivery

Remifentanil was administered to specific predicted effect site concentration targets using a computer-assisted infusion pump (Pump 22; Harvard Apparatus, Limited, Holliston, MA) utilizing the pharmacokinetic parameters described by Minto *et al.*[17] and controlled by STANPUMP software.†† Sevoflurane was administered in 2–10 l/min oxygen by a tight-fitting mask connected to a standard circle anesthesia circuit attached to an anesthesia machine (Drager Medical, Inc., Telford, PA).

Effect Measurements

Five minutes after achieving the targeted effect site concentration (or stable end-tidal concentration) for a primary drug "step," a battery of pharmacodynamic assessments was made. Effect measures included the Observer's Assessment of Alertness/Sedation (OAA/S) score[18] and three surrogates for surgical stimulus—

†† STANPUMP program. Available at: http://anesthesia.stanford.edu/pkpd/. Accessed October 18, 2005.

Table 1. Observer's Assessment of Alertness/Sedation Score

Responsiveness	Score
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to noxious stimulus	0

For the purposes of this study, an Observer's Assessment of Alertness/Sedation score of 1 or less was considered nonresponsive, whereas an Observer's Assessment of Alertness/Sedation score of 4 or greater was considered "awake."

pressure algometry and tetanic electrical stimulation, similar to those previously described by Kern *et al.*,[13] and thermal stimulation. All stimuli were applied until reaching supramaximal levels—50 mA, 50 pounds per square inch, and 50°C for 5 s. The maximum intensity of the stimulation was decreased from those used by Kern *et al.*,[13] because intensity levels of 60 mA and 60 pounds per square inch were found to be well above the supramaximal stimulus intensity. Sedation was measured first, and then the experimental pain stimuli were measured in random order. In terms of sedation, volunteers were considered nonresponsive if the OAA/S score was 1 or less (loss of response to "shake and shout"; table 1). After the volunteer became nonresponsive (OAA/S score $\leq$ 1), direct laryngoscopy was performed with a Macintosh No. 3 blade to achieve a Cormack grade I view[19] at each target concentration pair. The volunteer was considered responsive to the noxious stimuli when the volunteer exhibited painful verbalization, withdrawal movement, 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 were made at the start of the study day in the absence of drugs. Two kinds of data were recorded as surrogate measurements to surgical stimulus—the level of tolerated stimulus (a continuous data variable) and a quantal response of whether the volunteer could tolerate the maximal stimulus level (*e.g.*, no withdrawal, no increase in heart rate or blood pressure).[20] By convention, the maximum stimulation levels for the surrogate pain measures were 5 s of 50 mA for tetanic electrical pain, 50 pounds per square inch for pressure algometry, and 50°C for thermal stimulation.

Data Analysis

Demographic data for the volunteers in each group were compared utilizing an unpaired, two-sided *t* test using StatView version 5.0.1 (SAS Institute, Inc., Cary, NC) with $P < 0.05$ considered significant. All demographic data were reported as means with SDs.

Data points that revealed a hyperalgesic response to a noxious stimulation at low sevoflurane concentrations[21] were discarded to allow modeling of the drug response as a monotonic function.

Response Surface Models

Response surface models were constructed for each pharmacodynamic response using the Logit model as shown below[22]:

$$\text{Effect} = \frac{1}{1 + e^{(\beta_0 - \beta_1 \cdot C_s - \beta_2 \cdot C_r - \beta_3 \cdot C_s \cdot C_r)}},$$

where C_s and C_r are the concentrations of sevoflurane (alveolar end-tidal concentration, vol%) and remifentanil (effect site concentration, ng/ml, as predicted by STANPUMP), respectively, and β_i are the parameters describing the response surface. Additional details of the Logit model are provided in appendix 1.

For each pharmacodynamic response, the data were combined and used to fit the three-dimensional response surface using a naive pooled technique. Model coefficients and SEs were estimated using MATLAB (MathWorks Inc., Natick, MA). Models were built by an iterative process in which the log likelihood between the observations and the model predictions was maximized. The contribution of each coefficient was evaluated by excluding it from the model and determining whether the model deteriorated significantly using the likelihood ratio test (Δ Likelihood Ratio $\geq$ 30%). The SE of the model parameters was estimated using the bootstrap method for 5,000 iterations.[23]

Model performance was evaluated by assessment of $\text{Error}_{\text{Prediction}}$ (observed *vs.* predicted probability of effect for each dose combination) and the correlation coefficient. The $\text{Error}_{\text{Prediction}}$ is defined as the following:

$$\text{Error}_{\text{Prediction}} = 100 \times |\text{Observed} - \text{Predicted}|/\text{Observed}.$$

The correlation coefficient of the regression parameter estimates was used to evaluate how well the nonlinear regression models described the observed data. A large value of the correlation coefficient ($\geq$ 0.7) indicates that the responses predicted from the surface described the observed data well.[24]

Determination of Synergy

Using the response surfaces for surrogate surgical stimuli and sedation, it is possible to simulate two-dimensional concentration–effect relation curves for sevoflurane at a variety of remifentanil concentrations.[9] Each of these curves represents a vertical slice from the respective response surface. The synergistic effects of combining remifentanil and sevoflurane in producing sedation and analgesia are demonstrated by examining the change in the slope and the leftward shift of the sevoflurane concentration–effect curves.

Combined Pharmacokinetic and Pharmacodynamic Simulations

The time to regaining responsiveness from a single-drug anesthetic is determined by the pharmacokinetics of the individual drug, the concentration–effect relation, and the duration of administration of the drug.[2,25] For two-drug anesthetics, the time to awakening is not only dependent on the individual drug pharmacokinetics and the duration of the anesthetics, but it is also dependent on the target concentrations achieved for each of the drugs administered.[8] To provide a clinically useful context for applying the response surface models to everyday anesthesia practice, the pharmacodynamic response surface models from this study were combined with pharmacokinetic models,[17,26] using computer simulation as described by Vuyk *et al.*,[8] to identify target concentration pairs of remifentanil and sevoflurane that provided a high probability of nonresponsiveness to noxious stimulation and the most rapid emergence after cessation of anesthetic administration. Additional details are provided in appendix 2.

The sevoflurane model described by Lerou and Booij[26] and the remifentanil model reported by Minto *et al.*[17] were used to simulate a range of alveolar concentrations and effect site concentrations of sevoflurane and remifentanil, respectively, that produced a 95% probability of nonresponsiveness to the maximal tetanic stimulus of 50 mA, as determined by the response surface. Electrical tetanic stimulation is a surrogate noxious stimulus that is thought to be similar to a skin incision.[27] These alveolar and effect site concentrations were maintained at these levels for 1 h, after which time the drugs were discontinued and the "washout" of the anesthetics was simulated. The shortest time during the washout until the drug interaction model predicted an 80% probability that OAA/S score was 4 or greater was found through iterative simulation using a binary search algorithm.[28] The initial concentration pair was randomly picked from those target concentration pairs located along the EC_{95} isobole for tetanic stimulation. After calculating the recovery time (OAA/S score $\geq$ 4) for this initial target concentration pair, a fixed "step" of a 25% change in either the remifentanil concentration or the sevoflurane concentration in a random direction along the isobole was made, and the time to awakening was calculated. If this time was higher than that of the previous concentration pair, the next concentration pair was picked halfway between the previous point and this point; otherwise, the next concentration pair was picked to be the same size step change in concentration away from the previous point. This stepwise search was continued until a point was reached where recovery time was within 5% of the previously calculated recovery time at the previous concentration pair. The combination of sevoflurane and remifentanil that resulted in the quickest recovery (OAA/S score $\geq$ 4) was determined for anesthetics of 30–900 min in duration.

Table 2. Demographics of Study Volunteers

	Group 1 Sevoflurane	Group 2 Remifentanil
Age, y	25.0 ± 4.2	23.1 ± 2.7
Weight, kg	70.8 ± 13.0	74.5 ± 9.3
Height, cm	174.3 ± 9.0	177.8 ± 8.4
Sex, M:F	4:4	7:1

All values are given as mean ± SD, except for the ratio of males to females.

Results

All 16 volunteers completed the study. The demographics of the two groups are shown in table 2. There were no differences between the groups except that the remifentanil group was predominately male volunteers, whereas the sevoflurane group contained equal numbers of male and female volunteers.

Response Surface Models and Determination of Synergy

The parameters for all of the response surface models were identifiable. The Logit model parameters estimated through nonlinear regression are shown in table 3. The estimates of goodness of fit (*e.g.*, log likelihood, SE, correlation coefficient) suggest that the models describe the data well. Based on the drug concentrations required to achieve nonresponsiveness, thermal stimulation was the mildest and tetanic stimulation was the most noxious stimulus. All of the simulated concentration–effect relation curves from the response surface models showed synergy for both analgesia and sedation.

The response surface for sedation (OAA/S score $\leq$ 1) of the unstimulated volunteers is shown in figure 2A. The OAA/S response is shown topographically in figure 2B. The response surface for tetanic stimulation is shown in figure 3A, and the topographic view of the tolerance to tetanic stimulation is shown in figure 3B.

Table 3. Mean Model Parameters for the Logit Response Surface

	β_0	β_1	β_2	β_3	Log Likelihood	Correlation Coefficient
Pressure algometry	3.82	2.43	0.54	1.27	−78.90	0.78
Tetanic stimulation	3.27	0.97	0.088	1.09	−84.06	0.72
Thermal stimulation	3.38	1.32	0.55	3.47	−103.99	0.73
Laryngoscopy	3.70	2.36	0.54	1.22	−82.48	0.78
OAA/S score	7.30	7.84	0.23	3.94	−24.12	0.89

Model parameters are listed for all values. SEs for all parameters were less than 0.01, as determined by the bootstrap method.

OAA/S = Observer's Assessment of Alertness/Sedation.

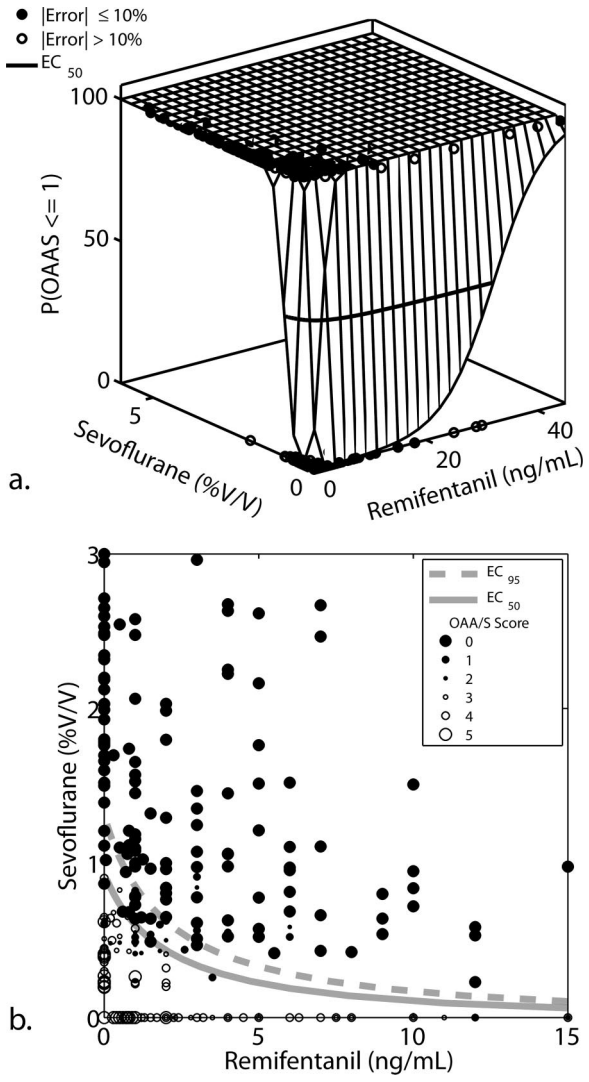

Fig. 2. Remifentanil–sevoflurane interaction for sedation. The Logit response surface model prediction for sedation for unstimulated volunteers is presented in *A*. An Observer's Assessment of Alertness/Sedation (OAA/S) score of 1 or less represents a sedated volunteer. A 0 indicates an OAA/S score of 2 or greater, and a 1 indicates an OAA/S score of 1 or less. The *symbols* show measured responses, and the surface predicted by the model is represented by the *grid-lined surface*. The raw data used to create this model are shaded based on the residual error. A topographic view of the 50% and 95% effect isoboles for probability of being sedated is presented in *B*. The OAA/S score at each target concentration pair is overlaid.

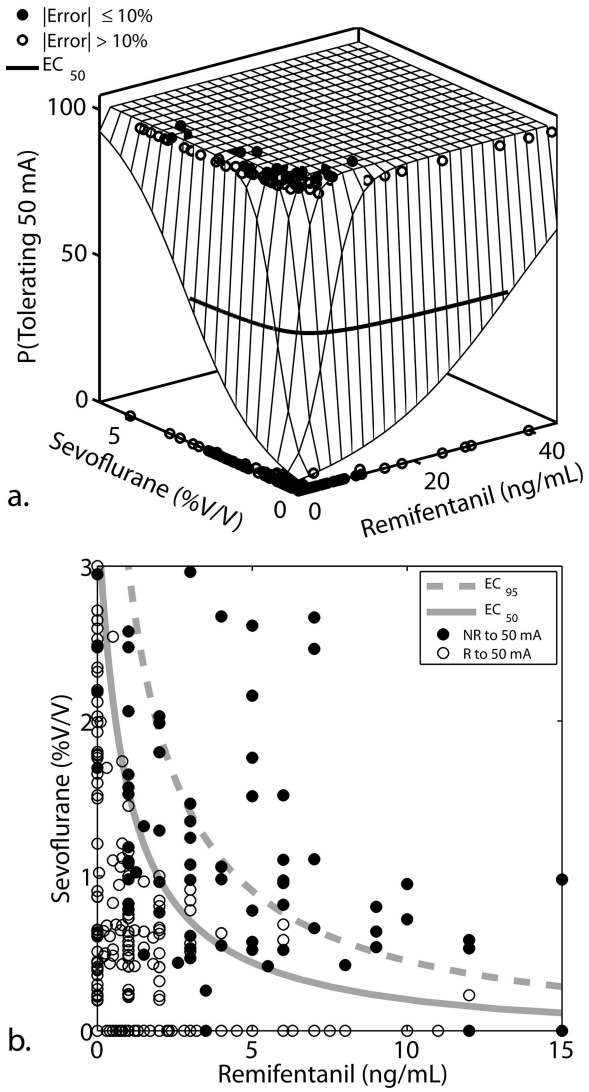

Fig. 3. Remifentanil–sevoflurane interaction for electrical tetanic stimulation. *A* shows the Logit response surface model prediction for tetanic stimulation of 50 mA. A 0 indicates a response (movement or a 10% increase in blood pressure or heart rate) to a 50-mA stimulus current, and a 1 indicates no response to a 50-mA stimulus current. The *symbols* show measured volunteer responses to 50 mA of stimulus current, and the surface predicted by the model is represented by the *grid-lined surface*. The raw data used to create this model are shaded based on the residual error. *B* shows a topographic view of the 50% and 95% effect isoboles for probability of tolerating a 50-mA stimulus current. The response to tetanic stimulation at each target concentration pair is overlaid.

The other pain stimuli surfaces (not shown) were of similar shape. The raw data used to create these surfaces are shaded based on the residual error between the measured response and model prediction. Throughout most of the clinically relevant range of concentrations (0–3 vol% sevoflurane and 0–7.5 ng/ml remifentanil), the residual error is below 10%.Figures 4A and 4B are two-dimensional concentration–response curves for sevoflurane at a variety of remifentanil concentrations that are based on the response surfaces for surrogate surgical stimuli and sedation. Each of these concentration–response curves was determined by taking a vertical slice through the respective response surface (figs. 2A and 3A and table 4).

Combined Pharmacokinetic and Pharmacodynamic Simulations

For shorter procedures, the target concentration pairs that resulted in the most rapid return to responsiveness approached the maximally synergistic combination—a combination that lies on the point of the response surface where the surface curves maximally toward the

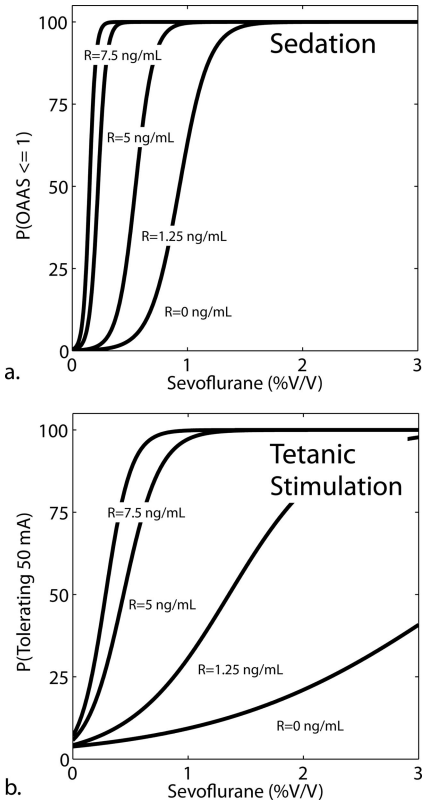

Fig. 4. Effect of adding remifentanil on the concentration–effect relations of sevoflurane for sedation (*A*) and analgesia (*B*). Each curve represents the concentration–effect relation for sevoflurane with a fixed effect site concentration of remifentanil simulated from the corresponding response surface model. The shift in the curves toward the left indicates that much less sevoflurane is needed when remifentanil is added, demonstrating the significant pharmacodynamic synergy between the sedative and the opioid. Note that the magnitude of the leftward shift decreases as the remifentanil concentration increases (*i.e.*, there is a ceiling effect). OAA/S = Observer's Assessment of Alertness/Sedation.

origin (fig. 5A). At this combination, the plasma concentrations of the drugs are both relatively low, and therefore, the plasma concentrations of the drugs decline to subclinical levels quickly (fig. 5B). As the duration of the anesthetic increases, the target concentration pairs with the shortest recovery time must be adjusted to be weighted toward the drug with the shorter acting kinetic profile, in this case remifentanil. By avoiding a large increase in the accumulation of sevoflurane in the body, the kinetics of washout of these combinations would allow rapid emergence from anesthesia. This trend plateaued at 0.75 vol% sevoflurane and 6.2 ng/ml remifentanil (fig. 6 and table 5).

Table 4. Reduction in Sevoflurane Requirements by Remifentanil

Remifentanil C_e, ng/ml	Remifentanil Infusion Rate, $\mu g \cdot kg^{-1} \cdot min^{-1}$	Sevoflurane $EC_{95\%}$ OAA/S score $\leq$ 1, vol%	Sevoflurane $EC_{95\%}$ Tetanic Stimulation, vol%
0	0	1.30	6.48
1.25	0.05	0.78	2.63
5	0.18	0.33	0.90
7.5	0.27	0.23	0.61

The reductions in the alveolar concentration of sevoflurane that produce a 95% probability ($EC_{95\%}$) of an Observer's Assessment of Alertness/Sedation (OAA/S) score of 1 or less or no movement or hemodynamic response to a 50-mA tetanic stimulation by the addition of remifentanil in doses ranging from 0 to 0.27 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (effect site concentration, C_e, 0–7.5 ng/ml) are reported. All infusion rates were calculated for a hypothetical 30-yr-old man who weighed 80 kg and was 183 cm tall, using STANPUMP (http://anesthesia.stanford.edu/pkpd/).

Discussion

In this study, we used response surface models to characterize the pharmacodynamic interactions between a potent volatile agent, sevoflurane, and a synthetic opioid, remifentanil, across a wide range of concentration pairs. With these pharmacodynamic models, we determined that the addition of remifentanil to sevoflurane anesthesia not only synergistically decreases the response to painful stimulation but also synergistically potentiates the sedative effects of the volatile anesthetic. Furthermore, using these pharmacodynamic models and previously described pharmacokinetic models,[17,26] we performed simulations to identify the target concentration pairs of remifentanil and sevoflurane that produced clinically adequate anesthesia (*e.g.*, $\geq$ 95% probability of no response to painful stimulation) while allowing the quickest time to awakening (*e.g.*, $\leq$ 20% probability of OAAS $\leq$ 4) for surgical procedures of increasing duration. These simulations demonstrated that there was a plateau in the utility of remifentanil to decrease the amount of sevoflurane necessary to produce clinically adequate anesthesia (sedation and nonresponsiveness to noxious stimulation).

Response Surface Models

Response surface methods have been used to model the interactions between a variety of combinations of anesthetics, the most common being that of propofol and remifentanil.[8,13,14,29–31] Our results are similar to the findings with propofol and remifentanil, in that our data demonstrate that the addition of remifentanil to sevoflurane results in a synergistic effect for both analgesia and sedation. Our results do not agree with the study by Dahan *et al.*,[32] who found that alfentanil produced no synergistic effect on sevoflurane-induced sedation. Dahan *et al.* used Bispectral Index rather than OAA/S score to measure sedation and used a relatively lower concentration of alfentanil. Our data evaluated the contribution of higher levels of opioid effect (remifentanil) relative to the alfentanil concentration range studied by these investigators. Furthermore, we specifically evaluated the effects of combinations of sevoflurane and remifentanil on clinical sedation, as measured by the OAA/S score, as opposed to the surrogate marker of the Bispectral Index.

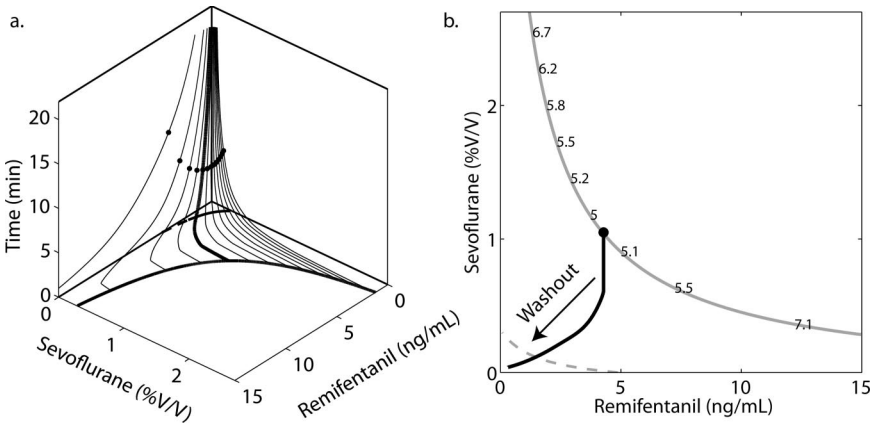

Fig. 5. Results of computer simulations designed to identify optimal target concentration pairs of remifentanil and sevoflurane that minimize the time to responsiveness. *A* shows the predicted decline in effect site and alveolar concentrations for remifentanil and sevoflurane after stopping drug administration regimens targeted to reach the EC_{95} isobole for tetanic stimulation for 1 h. The EC_{95} isobole is on the "floor" of the cube; the vertical axis represents time elapsed since stopping the administration of the drugs. The isobole representing an 80% probability of the return of responsiveness (Observer's Assessment of Alertness/Sedation score ≥ 4) is shown by a *dotted line* that is superimposed on the concentration decay curves. The *highlighted curve* is the sevoflurane and remifentanil target concentration pair that resulted in the fastest return of responsiveness. *B* shows the time in minutes to the return of responsiveness after a 1-h procedure in which sevoflurane and remifentanil were administered to target concentration pairs on the EC_{95} isobole for tetanic stimulation. The *highlighted trace* on the panel on the left is shown topographically. The minimum time to regain responsiveness represents the target concentration pairs for a 1-h procedure.

The limitations of the Bispectral Index algorithm, specifically its insensitivity to the effect of an opioid on sedation,[33] may explain differences in our results. Alternatively, the fact that we used the Logit model for our response surface data, whereas Dahan *et al.* used the Minto response surface models, may have resulted in a "forced fit" of our data to the relatively constrained model. However, the response surface generally predicted the observed data extremely well (figs. 2A and B and table 3) and therefore is most likely not a forced fit.

During the past few years, several investigators have used response surface models to determine the interactions between propofol and remifentanil,[8,11,13,30] propofol and alfentanil,[34,35] and sevoflurane and alfentanil.[32]

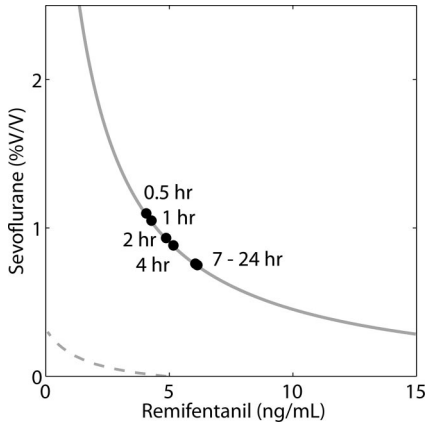

Fig. 6. Optimal combinations of remifentanil and sevoflurane to maintain adequate anesthesia and promote rapid emergence. The combinations that produced the quickest time to regain responsiveness (Observer's Assessment of Alertness/Sedation score ≥ 4) at various durations (in hours) are shown. For example: In a 1-h procedure, target concentrations of 1.05 vol% sevoflurane and 4.3 ng/ml remifentanil result in the fastest return of responsiveness. The simulations show that optimal combination changes as a function of duration of procedure. Although a target concentration pair with higher remifentanil concentrations provides a faster recovery in longer cases, remifentanil–sevoflurane mixtures in which sevoflurane is less than 0.75 vol% show no significant advantage.

Each of these authors used a single type of pharmacodynamic model to develop their response surface models. The pharmacodynamic model described by Greco *et al.*[12] and used by Kern *et al.*[13] differs from the pharmacodynamic model developed by Minto *et al.*[15] and used by Dahan *et al.*,[32] in that it requires the exponent of the response to be fixed, therefore limiting the flexibility of the model to fit optimally the response data. However, the Greco form of this model provides a specific parameter that examines the interaction between the two drugs. The models proposed by Bouillon *et al.*[11] and Bol *et al.*[30,36] and the Logit model also differ in their mathematical complexity and physiologic plausibility. Choosing the right model to describe the data is an empirical process in which the error statistics of each model are used to determine whether increasing the level of complexity allows a better fit of the measured response data.[23] However, if a model that has many degrees of freedom is chosen, it is possible to fit a surface to data

Table 5. Simulation Results for Anesthetics 30–900 min in Duration

Duration of Anesthetic, h	Shortest Recovery Time, min	Remifentanil C_e, ng/ml	Remifentanil Infusion Rate, $\mu g \cdot kg^{-1} \cdot min^{-1}$	Sevoflurane Alveolar, vol%
0.5	4.5	4.1	0.15	1.10
1	5.0	4.3	0.16	1.05
2	5.8	4.9	0.18	0.93
4	6.7	5.2	0.19	0.88
7	7.2	6.1	0.22	0.75
10	7.4	6.1	0.22	0.75
15	7.5	6.2	0.23	0.74
20	7.6	6.1	0.22	0.75
24	7.7	6.1	0.22	0.75

The effect site concentration (C_e) and infusion rate for remifentanil and the alveolar end-tidal concentration of sevoflurane that produced the shortest recovery times are reported for anesthetics lasting 0.5–24 h. All simulations were performed for a hypothetical 30-yr-old man who weighed 80 kg and was 183 cm tall.

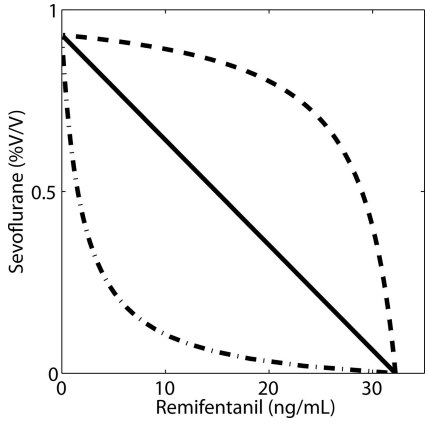

Fig. 7. The isoboles derived from simulated Logit model of the sedation response surface (Observer's Assessment of Alertness/Sedation score ≤ 1) to demonstrate additive, synergistic, and antagonistic interactions, by only modifying the β_3 coefficient. In the Logit model, the β_3 coefficient controls the interaction between the two drugs—$\beta_3 = 0$, $\beta_3 > 0$, and $\beta_3 < 0$, producing additive, synergistic, and antagonistic interactions. The *solid line* represents the isobole predicted by the Logit model when the drug interaction is simply additive ($\beta_3 = 0$), whereas the *dashed line* and the *dotted-dashed line* represent the predicted isoboles when there is a synergistic ($\beta_3 = 3.94$) or antagonistic ($\beta_3 = -0.22$) drug interaction.

from poorly designed trials or studies with inadequate response sampling.[15]

For the analysis of our data, we chose the Logit model because it easily allowed the analysis of data from volunteers with different baseline and maximal responses to the surrogate pain stimuli and the clinical assessment of sedation. Given the diversity of different response surfaces models published in the anesthesia literature, the fact that we were able to characterize adequately our data set with the Logit model, which is a moderately constrained model compared with those proposed by Greco *et al.*,[12] Minto and Vuyk,[14] or Bol *et al.*,[36] may indicate that the synergism observed by these surfaces is accurate. Minto *et al.* have proposed that there are several criteria necessary for an "ideal pharmacodynamic interaction model."[14] The Logit model is able to predict additive, synergistic, and antagonistic interactions. Simulations of the isoboles that result with changes in the Logit model's β_3 coefficient—the coefficient that controls the interaction between the two drugs—produce isoboles consistent with those of Bernebaum[37] (fig. 7). The response surfaces derived from the Logit model were easily derived from a relatively small number of volunteers from predicted effect site remifentanil concentrations and measured alveolar end-tidal sevoflurane concentrations covering the entire clinical range of concentration pairs. In addition, the response surface reduces to single-drug concentration–response curves that are similar to those that would be derived by single-drug analysis[17,38] as shown in figures 4A and B. However, the mathematics of logarithms dictates that when there is no drug present (*i.e.*, sevoflurane–remifentanil target concentration pair of 0 vol% and 0 ng/ml), there is still a slight effect (approximately 0.0007 probability of no response). Therefore, the Logit model that we have chosen as the basis of our response surface analysis meets all but one of the criteria proposed by Minto *et al.*, [15] albeit that the predictions made when there are no drugs present is close to no drug effect.

Combined Pharmacokinetic and Pharmacodynamic Simulations

The simulations using pharmacokinetic models and our pharmacodynamic response surfaces to determine the combination of sevoflurane and remifentanil that would produce the fastest return of responsiveness for anesthetics of varying durations provided interesting insight into the role of pharmacokinetics and pharmacodynamics in optimizing clinical anesthetics. As shown in figure 5A, for a 1-h duration anesthetic, the "optimum" combination of sevoflurane and remifentanil is at the point in the center of the "edge" of the plateau of maximum response—on the isobole that defines 95% probability of not responding to electrical tetanic stimulation. As the duration of the anesthetic increases, the optimal combinations shifted toward higher remifentanil concentrations due to the rapid elimination of remifentanil.

Despite the synergistic interactions between remifentanil and sevoflurane in providing analgesia and sedation, there was a discrete plateau in the sevoflurane–remifentanil combinations for the longest of procedures (fig. 6). This plateau occurs at a sevoflurane concentration of 0.75 vol%, which correlates with an approximately 66% reduction in the MAC of sevoflurane (2.2 vol% for adult men and women aged between 20 and 50 yr).[38] The 66% reduction in sevoflurane requirements coincidentally is between the amount of reduction of MAC (61%) and MAC_{BAR} (blocks autonomic responses, 83%) expected when high doses of opioids are combined with the modern, potent volatile anesthetics.[3,7,38,39] Furthermore, this value is similar to the MAC_{awake} of sevoflurane (0.35 MAC, approximately 0.75 vol%),[40] thereby demonstrating that these response–surface models may account for the fact that opioids themselves cannot provide complete anesthesia.[41–43] The major factor preventing a further decrease in the sevoflurane requirement may be the limited reduction of the MAC_{awake} observed with opioids.[44] That these sevoflurane–remifentanil response surface pharmacodynamic models predict interactions that are consistent with clinical practice further demonstrates that these response surfaces may be useful tools for understanding anesthetic interactions in the clinical realm.[45]

Clinical Implications

These response surface models allow the creation of two-dimensional concentration–effect curves that dem-

onstrate an approximately sixfold decrease in the EC_{95} for sedation and an approximately 10-fold decrease in the EC_{95} for tolerance of tetanic stimulation with the addition of 7.5 ng/ml remifentanil (0.27 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion) to a sevoflurane anesthetic (figs. 4A and B and table 4).

Based on the synergistic interaction between sevoflurane and remifentanil in preventing a response to the surrogate surgical stimuli and in producing sedation, the response surfaces from this study confirm the utility of administrating "balanced" anesthetics with a combination of a volatile anesthetic and an opioid. The pharmacokinetic–pharmacodynamic simulations illustrate the benefit of minimizing the administered dose of even a low solubility volatile anesthetic to near 0.5 MAC in the presence of remifentanil, an opioid with rapid elimination. This is especially true for anesthetics with duration of more than 5 h. Whether this results in a pharmacoeconomic advantage of combining a low dose of sevoflurane with a higher dose of remifentanil will require prospective studies, because the pharmacoeconomic advantages of a drug are certainly not limited to just minimizing the time until awakening or the drug acquisition costs.[46]

Limitations

One of the limitations of our study design is that the response surface model for sedation was determined in unstimulated volunteers. Because the level of stimulation can change the depth of sedation, it is possible that our unstimulated volunteer response surface analysis for sedation may not accurately predict the sedation response of patients undergoing surgical procedures. In particular, the lack of an endotracheal tube in the volunteers may have resulted in our measuring deeper levels of sedation than would be apparent if the endotracheal tube was stimulating a patient or volunteer receiving the same target concentration pairs of sevoflurane and remifentanil. However, the difficulty in measuring the level of sedation during stimulation in a volunteer setting (*e.g.*, confounding sedation score by stimulation response) prevented us from collecting the data that would be needed to estimate a surface with continual stimulation.

A further limitation of our study design was that the surrogate pain stimuli used to measure the analgesic response in volunteers is only a surrogate of intraoperative surgical pain. By including a range of experimental pain stimuli to cover the range expected during a surgical procedure, it is probable that the most stimulating intraoperative events—surgical incision and laryngoscopy—have been recreated in the volunteer laboratory. However, because key surgical stimuli can only be applied once (*e.g.*, skin incision), and because surgical patients cannot ethically be provided with subtherapeutic combinations of anesthetics or serve as their own pharmacologic control, volunteer studies are essential to allow the collection of the high-resolution data needed to achieve the goal of mapping the interaction surface between two agents over the entire concentration spectrum.

Another limitation in this study is that we used a pharmacokinetic model to predict remifentanil effect site concentrations rather than drawing blood samples during pseudo–steady state to measure remifentanil plasma concentrations. This limitation may explain the variability found in the single-drug dose–response data for remifentanil.[47] Mertens *et al.*[48] determined that remifentanil can be delivered accurately by target-controlled infusions. However, they found that the most accurate and least biased delivery was achieved when the pharmacokinetic sets determined by Egan *et al.*[49–51] were used. Given the fact that the pharmacokinetic set used (by Minto *et al.*[17]) was determined in a population similar to that being studied here, the accuracy and bias of the target-controlled infusion should be at least as accurate as using the pharmacokinetic sets of Egan *et al.*[49] Although we had an unequal number of males and females in our groups, it is unlikely that this accounted for the pharmacodynamic variability given that sex has little influence on the pharmacokinetics or pharmacodynamics of remifentanil[17] or sevoflurane.[52] Other sources of pharmacokinetic variability (*e.g.*, age, body weight, cardiac output) most likely did not contribute much to the pharmacodynamic variability, given the similarities between groups in the important covariates.

For the analgesic response measurements, we were forced to both limit the maximum stimulus applied and discard those responses that were below the respective baseline values. We limited the maximum stimulus applied to prevent irreversible tissue damage in the volunteers. In a previous investigation in our laboratory,[13] we found levels of the pressure, temperature, and electrical current that could be tolerated without any evidence of long-lasting damage. However, this approach may result in censored data that can result in pharmacodynamic response curves that predict potency lower than the true values. Therefore, extending the application of these response surfaces beyond the range of concentrations examined by these response surfaces may result in erroneous conclusions.

Just as difficult of a statistical problem is how to deal with those analgesic responses that were below the baseline values. This hyperalgesic response has been observed when low doses of volatile anesthetics are administered to animals and humans.[21] Unfortunately, the models used to construct response surfaces require a monotonic function and therefore are unable to characterize this phenomenon. Other investigators often do not observe this hyperalgesic response because the step change in inhaled anesthetic concentration is either so large that the hyperalgesic concentrations are "jumped

over" or the variability in the analgesic response measurement is so large that this small hyperalgesic effect is unidentifiable.

The hyperalgesia associated with the presence of low concentrations of volatile anesthetics[21] is different from the hyperalgesia phenomenon occasionally observed after the administration of remifentanil.[53–55] The hyperalgesia observed by some investigators after remifentanil administration is associated with a rightward shift in the subsequent analgesic concentration–response curves. Although we did not design this study to specifically address the presence or absence of remifentanil-induced hyperalgesia, we did not find any difference between the baseline levels of tolerated stimuli (*e.g.*, before remifentanil administration) and the levels of stimuli tolerated at the lowest level of remifentanil with the first doses of sevoflurane (study period II, remifentanil group, one-sided paired *t* test, $P > 0.05$ for all three stimuli). This is consistent with the observations of Lotsch and Angst[55] where hyperalgesia to pressure and electrical stimulation was not induced by remifentanil.

The Logit model offered the advantage of being able to easily compensate for data from volunteers with different baseline and maximal responses to the surrogate pain stimuli and the clinical assessment of sedation. However, the mathematics of logarithms dictates that when there is no drug present (*i.e.*, sevoflurane–remifentanil target concentration pair of 0 vol% and 0 ng/ml), there is still a very slight effect (approximately 0.0007 probability of no response). Furthermore, the Logit model requires a dichotomous response—response *versus* no response to a single stimulus intensity. For the surrogates for surgical stimulus, this was the equivalent of having no movement and no hemodynamic change when a volunteer received the maximum possible intensity of the pain surrogate. However, the OAA/S is an ordinal scale that consists of five different scores (table 1). The Logit model mandated that we choose which OAA/S scores defined patients who were "awake" and those who were "asleep." To represent the state most consistent with adequate sedation for surgery, the response surface model for "general anesthesia" was based on an OAA/S score of 1 or less (no response to "shake and shout). On the other hand, to most accurately represent the emergence from general anesthesia (*i.e.*, suitable for extubation), we chose an OAA/S score of 4 or greater (response to normal voice) as the basis of the response surface for awakening from anesthesia. Although this dichotomous view of general anesthesia is not reflected by the OAA/S score, it is more consistent with "adequate" general anesthesia—for any given stimulus at any given time point, anesthesia can be considered either adequate or not.[20] The models described by Greco *et al.*,[12] Minto and Vuyk,[14] and Bouillon *et al.*[11] would have avoided this complexity because all of these models easily handled continuous response variables. However, each of these alternative model architectures would have had difficulty resolving the intersubject variability that naturally exists in the baseline and maximal tolerated stimulus.

Future Work

Our response surface models for sevoflurane and remifentanil interactions were developed in volunteers exposed to a variety of surrogate pain stimuli. These models will need to be validated in a variety of surgical patients receiving these two drugs as the only anesthetic agents. Further work will need to be conducted to determine whether the surrogate pain stimuli accurately predict the responses to different surgical stimuli (*e.g.*, skin incision, abdominal insufflation, placement of Mayfield head fixation). In addition, there are conceivably 15 different sedative–opioid combinations that could be generated when one considers the pharmacodynamic and pharmacokinetic differences between the clinically available volatile anesthetics (desflurane, sevoflurane, and isoflurane) and commonly used opioids (morphine, fentanyl, alfentanil, sufentanil, and remifentanil), not to mention the alternative of a propofol-based anesthetic. Response surface models of these combinations would be necessary to develop a comprehensive library of models for use in everyday anesthesia practice that would not constrain the clinician to a single pair of anesthetics (*i.e.*, sevoflurane and remifentanil only).

Conclusion

In summary, the sevoflurane–remifentanil response surfaces estimated in this study demonstrate clear and profound synergism for both analgesia and sedation. Furthermore, combined with pharmacokinetic models, the response surfaces provide the scientific foundation to identify the "optimal" combinations of sevoflurane and remifentanil required to produce the fastest return to alertness (OAA/S score ≥ 4) after anesthetics varying in duration from 30 to 900 min. The reduction in sevoflurane requirements predicted by these simulations plateaus at a value (0.75 vol%, 0.34 MAC) comparable with that of MAC_{awake} (0.35 MAC) of sevoflurane and in the range of the maximum reduction in MAC (61%) and MAC_{BAR} (85%) that results from coadministration of high doses of remifentanil with sevoflurane, acting as indirect validation of the response surfaces. These response surfaces may potentially be used to clinical advantage, such as their incorporation into real-time, pharmacokinetic–pharmacodynamic display systems.[45,56]

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Appendix 1: The Logit Model for Pharmacodynamics

The pharmacodynamic response to a single drug can be described by the logistic regression model. In the logistic regression model, the natural logarithm of the odds ratio of drug effect (the Logit) is described as a function of drug concentration (C):

$$\text{Logit} = \ln(\text{oddsratio}) = \ln\left(\frac{P}{1-P}\right) = -\beta_0 + \beta_1 \cdot C. \quad (1)$$

where P is the probability of the desired effect, and β_0 and β_1 are estimated parameters. The Logit model can be generalized to multiple drugs, using the linear function of the concentrations of the two drugs sevoflurane (C_s) and remifentanil (C_r)[22]:

$$\text{Logit} = \ln(\text{oddsratio}) = \ln\left(\frac{P}{1-P}\right) = -\beta_0 + \beta_1 \cdot C_s + \beta_2 \cdot C_r + \beta_3 \cdot C_s \cdot C_r. \quad (2)$$

where P is the probability of the desired effect, and β_0, β_1, β_2, β_3 are estimated coefficients of the linear function.

Rearranging equation 2 to solve for the probability of effect, P, results in equation 3:

$$P = \frac{1}{1 + e^{(\beta_0 - \beta_1 \cdot C_s - \beta_2 \cdot C_r - \beta_3 \cdot C_s \cdot C_r)}}. \quad (3)$$

Equation 3 can be rearranged to compute the 50% (equation 4A) and 95% (equation 4B) probability isoboles for sevoflurane:

$$EC_{50,S} = \frac{\beta_0 - \beta_2 \cdot C_r}{\beta_1 + \beta_3 \cdot C_r} \quad (4A)$$

$$EC_{95,S} = \frac{\ln\left(\frac{1}{0.95} - 1\right) + \beta_0 - \beta_2 \cdot C_r}{\beta_1 + \beta_3 \cdot C_r}. \quad (4B)$$

The Logit model reduces to a simpler form that allows calculation of the concentration–effect relation for sevoflurane or remifentanil when administered alone. By substituting into equation 3 a value of 0 for remifentanil or sevoflurane, respectively, the concentration of each drug needed to produce 50% probability of effect (EC_{50}) when each of the drugs is used individually, can be calculated by equations 5A and B.

$$EC_{50,S} = \frac{\beta_0}{\beta_1} \quad (5A)$$

$$EC_{50,R} = \frac{\beta_0}{\beta_2}. \quad (5B)$$

Appendix 2: Pharmacokinetic–Pharmacodynamic Simulations

Pharmacodynamic Endpoints

Examining the response surface models generated for adequate sedation (95% probability of OAA/S score ≤ 1) and adequate analgesia (95% probability of having no movement or hemodynamic response to a 50-mA electrical stimulus), it is clear that there are many target concentration pairs of sevoflurane and remifentanil that would provide adequate surgical anesthesia. The concentration pairs on the $EC_{95\%}$ isobole for no response to a 50-mA electrical stimulation (fig. 3B) is consistently greater than the concentration pairs on the $EC_{95\%}$ isobole for adequate sedation (fig. 2B). Therefore, providing combinations of sevoflurane and remifentanil that are on the electrical stimulation $EC_{95\%}$ isobole will provide adequate surgical anesthesia.

Clinical recovery from surgical anesthesia is characterized by the ability to follow simple commands (*e.g.*, eye opening, squeezing hands) upon discontinuing drug administration. The state of clinical recovery from anesthesia corresponds to an OAA/S score of 4 or greater (table 1). Therefore, to model the response surface for clinical recovery from administration of combinations of sevoflurane and remifentanil, a Logit model can be constructed with an OAA/S score of 4 or greater defined as adequate recovery and an OAA/S score of less than 4 defined as asleep. This model has a correlation coefficient of 0.83, and the model coefficients β_0, β_1, β_2, β_3 are estimated as 2.97, 4.98, 0.33, and 3.15, respectively. Because the Logit model has the limitation that a small effect remains when no drug is administered, the $EC_{80\%}$ isobole for an OAA/S score of 4 or greater was used to determine the sevoflurane–remifentanil concentration pairs that resulted in clinical recovery after discontinuing administration of sevoflurane and remifentanil.

Pharmacokinetic Models

As detailed above, the time until clinical recovery after the discontinuation of the administration of sevoflurane and remifentanil can be defined as the time that it takes for the sevoflurane and remifentanil concentrations to reach a combination on the $EC_{80\%}$ isobole for an OAA/S score of 4 or greater. To simulate the elimination of sevoflurane and remifentanil, it is necessary to know the concentrations in all of the pharmacokinetic compartments before the cessation of drug administration. Administration and elimination of sevoflurane was simulated using the 14-compartment physiologic model described by Lerou and Booij,[26] with the volumes and blood flows reported by Lowe and Ernst,[57] and partition coefficients reported by Kennedy *et al.* [58] Simulation of the administration of remifentanil required the use of the target-controlled infusion algorithm described by Van Puocke *et al.*,[59] using the remifentanil pharmacokinetic model described by Minto *et al.*,[17] to maintain a remifentanil effect site concentration on the $EC_{95\%}$ isobole for no response to 50-mA electrical stimulus.

Determination of the Shortest Time to Awakening from Adequate Anesthesia

The $EC_{95\%}$ isobole for no response to a 50-mA electrical stimulus provides a large number of concentration pairs of sevoflurane and remifentanil. An initial concentration pair was randomly picked from those concentration pairs located on the $EC_{95\%}$ isobole for tetanic stimulation. The alveolar concentration of sevoflurane and the effect site concentration of remifentanil were maintained constant for the predetermined duration (30–900 min). For example, to simulate the administration of 1.05 vol% sevoflurane and 4.53 ng/ml remifentanil, the uptake and distribution of sevoflurane throughout the body were simulated to maintain an alveolar concentration of 1.05%, and the uptake and distribution of remifentanil were simulated for using the target-controlled infusion algorithm to maintain a constant value of 4.53 ng/ml at the effect site. At the end of the predetermined duration of drug administration, the decay of the effect site concentration of remifentanil and alveolar concentration of sevoflurane were observed. The time at which these combinations decreased below levels on the $EC_{80\%}$ isobole for an OAA/S score of 4 or greater were noted. For this example, the recovery time was 5 min (fig. 5B). This procedure was repeated with a binary search algorithm to determine the combination of sevoflurane and remifentanil that started on the $EC_{95\%}$ isobole for tetanic stimulation and had the fastest recovery time for the predetermined duration of drug administration. Using the same methods, the ratio that had the fastest recovery time was determined for each procedure duration (0.5, 1, 2, 4, 7, 10, 15, 20, and 24 h).

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