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When Is a Bispectral Index of 60 Too Low?

Rational Processed Electroencephalographic Targets Are Dependent on the Sedative–Opioid Ratio

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Background: **Opioids are commonly used in conjunction with sedative drugs to provide anesthesia. Previous studies have shown that opioids reduce the clinical requirements of sedatives needed to provide adequate anesthesia. Processed electroencephalographic parameters, such as the Bispectral Index (BIS; Aspect Medical Systems, Newton, MA) and Auditory Evoked Potential Index (AAI; Alaris Medical Systems, San Diego, CA), can be used intraoperatively to assess the depth of sedation. The aim of this study was to characterize how the addition of opioids sufficient to change the clinical level of sedation influenced the BIS and AAI.**

Methods: **Twenty-four 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 modified Observer's Assessment of Alertness/Sedation score, BIS, and AAI were measured at each target concentration pair. Response surface pharmacodynamic interaction models were built using the pooled data for each pharmacodynamic endpoint.**

Results: **Response surface models adequately characterized all pharmacodynamic endpoints. Despite the fact that sevoflurane–remifentanil interactions were strongly synergistic for clinical sedation, BIS and AAI were minimally affected by the addition of remifentanil to sevoflurane anesthetics.**

Conclusion: **Although clinical sedation increases significantly even with the addition of a small to moderate dose of remifentanil to a sevoflurane anesthetic, the BIS and AAI are insensitive to this change in clinical state. Therefore, during "opioid-heavy" sevoflurane–remifentanil anesthetics, targeting a BIS less than 60 or an AAI less than 30 may result in an unnecessarily deep anesthetic state.**

DOSE requirements of anesthetics vary with age, sex, physiologic condition, and many pathophysiologic factors. Therefore, to safely and efficiently provide adequate surgical anesthesia, clinical acumen must be combined with pharmacokinetic and pharmacodynamic knowledge to avoid the delivery of too much or too little anesthetic. During the past 25 yr, anesthesiologists, neuroscientists, and engineers have been searching for the method to accurately predict depth of anesthesia—the "Holy Grail." However, adequate "depth of anesthesia" is a vague term that spans from a state of sedation and amnesia that prevents explicit recall[1] to a state where there is no movement[2] or no hemodynamic response to surgical stimuli.[3] Furthermore, delivery of a single anesthetic drug class (*e.g.*, volatile anesthetic or propofol) results in a different anesthetic profile than when a balanced anesthetic is delivered.[4] Therefore, complete monitors of the "depth of anesthesia" must characterize these clinical endpoints during the administration of a variety of combinations of anesthetics.[5]

Processed electroencephalographic parameters are gaining popularity as intraoperative monitors of depth of anesthesia.[6] One depth of anesthesia monitor, the Bispectral Index (BIS®; Aspect Medical Systems, Newton, MA), is based in part on bispectral analysis of the electroencephalogram.[7] The propriety BIS algorithm was a unique step forward in the use of electroencephalographic parameters to determine anesthetic depth because it combined multiple distinct electroencephalographic parameters and a large volume of prospectively collected clinical observations into a single descriptive variable that was then prospectively tested and validated.[6] The BIS is the only processed electroencephalographic parameter that has been found to decrease the incidence of explicit recall of intraoperative events (awareness with recall) in a randomized controlled trial of patients who were at high risk for intraoperative awareness with recall.[8] In addition, titrating anesthetics to specific BIS target values has been found to effect clinical outcomes—a BIS of 40–60 results in faster emergence from anesthesia,[9] lower anesthetic drug use,[10] and possibly even an improvement in 1-yr survival of patients.[11]

During general anesthesia, the brainstem and the cortical auditory function are preserved, although meaningful interpretation of the auditory stimulus is inhibited.[12,13] These brainstem and cortical responses to an auditory stimulus correlate with motor signs of wakefulness and intraoperative awareness.[14] The A-Line Auditory Evoked Potential Index (AAI; Danmeter, Odense,

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Denmark) is a commercially available monitor that uses changes within the cortical auditory evoked potential to measure the depth of anesthesia.[15] Like the BIS, the AAI correlates well with the clinical level of sedation produced by increasing doses of sevoflurane[12,16] or propofol.[7,17]

Although adequate surgical anesthesia can be produced using a volatile anesthetic alone,[2,3] hemodynamic depression[18] and prolonged time to awakening[19] limit the practicality of utilizing a volatile anesthetic as the sole anesthetic agent. Therefore, an opioid analgesic is commonly coadministered with smaller doses of a volatile anesthetic to provided adequate analgesia and maintain a state of nonresponsiveness to surgical stimulation.[20] The addition of opioids is known to increase synergistically the clinical level of sedation produced by propofol[21,22] and volatile anesthetics.[23,24] However, the effect of the addition of an opioid on the processed electroencephalographic parameters is controversial—some reports show that the processed electroencephalogram is insensitive to opioids,[7,23–25] whereas others suggest that opioids do alter processed electroencephalographic parameters.[26–28] Therefore, the "true" effects of the addition of opioids to hypnotic drugs on the BIS (and AAI) are unclear.

The principle aim of this study was to characterize how the addition of opioids sufficient to change the clinical level of sedation influenced processed electroencephalographic parameters such as BIS and AAI. Data acquired from volunteers receiving various target concentration pairs of sevoflurane and remifentanil were used to construct response surfaces models of the observed level of sedation and the measured electroencephalographic parameters. We hypothesized that the relatively small change in the electroencephalographic parameters produced by adding remifentanil to sevoflurane would not adequately reflect the substantial change in the clinical anesthetic state. In addition, we hypothesized that with the coadministration of remifentanil and sevoflurane, attempting to maintain a target BIS of 40–60 or a target AAI of 20–30 would result in an excessively deep clinical anesthetic state—sevoflurane–remifentanil target concentration pairs well above those that provide clinically adequate anesthesia (*e.g.*, no awareness, no movement, and no hemodynamic response to stimulation).

Materials and Methods

After institutional approval (University of Utah Health Sciences Center, Salt Lake City, Utah) and informed consent, 24 volunteers were recruited for this open-label, randomized, parallel-group, crisscross-designed study to asses drug interactions (fig. 1).[29] Each volunteer was randomly assigned to receive a target-controlled infusion of remifentanil (predicted effect site concentrations of 0.5–15 ng/ml) or sevoflurane (0.3–6 vol% end-tidal alveolar concentration) as the primary agent, with the other drug acting as the secondary agent (fig. 1). The reader is referred to the previous manuscript by Manyam *et al.*[30] for complete details regarding the methods of volunteer preparation, drug administration, and data collection. For each target concentration pair, the electrophysiologic data and the sedation assessment were recorded before performing any of the surrogate pain stimulations of the protocol.

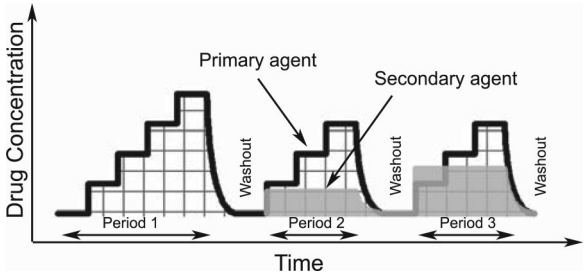

Fig. 1. A schematic summary of the infusion scheme. During each of the three study periods, the primary drug is administered in a stepwise fashion (*solid black line*), whereas in the second and third study periods, the second drug (*gray filled area*) is held at a constant predicted effect site concentration 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.

BIS and AAI Measurements

To avoid variability arising from hysteresis between plasma concentration and effect site, BIS (BIS XP®, A-2000 monitor, rev. 3.21; Aspect Medical Systems) and AAI (3300 AEP Monitor; Alaris Medical Systems, San Diego, CA) were measured at each assessment point 5 min after the targeted effect site concentration (or stable end-tidal concentration) for a primary drug "step" was reached. The electroencephalographic parameters were averaged in a 40-s interval that preceded the assessment of the modified Observer's Assessment of Alertness/Sedation score (modified OAA/S score, table 1, as described by Glass *et al.*,[7] Kearse *et al.*,[31] and our laboratory[22]). This interval was also considered a "quiet time" where no other changes or assessments were made in

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 purpose of this study, an Observer's Assessment of Alertness/Sedation (OAA/S) score of 1 or less was considered nonresponsive, whereas an OAA/S score of 4 or greater was considered "awake."

the volunteers. To control for the potential interrater variability in the modified OAA/S score, the same individual (J.L.W.) was responsible for assessments of sedation at all time points and for all study volunteers.

Definition of Adequate Anesthesia

To determine the "depth of anesthesia" at each of the target concentration pairs, adequate anesthesia was defined by the presence of all three of the following criteria: (1) modified OAA/S score of 1 or less; (2) no movement in response to a 5-s, 50-mA electric titanic stimulation; and (3) no change in heart rate (> 20%) in response to the same electrical stimulation.[30] Pharmacodynamic response surface models reported in our previous article were used to generate isoboles predicting a 95% probability of having adequate clinical sedation (modified OAA/S score ≤ 1) and a 95% probability of having clinically adequate anesthesia.

Demographic Data Analysis

Demographic data for the volunteers in each group were compared using 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.

Measurement of the Association between the Clinical Sedation Score and the Processed Electroencephalographic Parameters

The performance of each of the parameters was assessed by comparison against the sedation score (modified OAA/S). Because a direct correlation cannot be calculated between an ordinal variable (modified OAA/S score) and either of the continuous variables (processed electroencephalographic parameters), we calculated the prediction probability (P_k) as described by Smith and Dutton[32] for the association between the clinical sedation scale (modified OAA/S) and BIS and AAI using SPSS version 14 (SPSS Inc., Chicago, IL). The P_k values were also calculated for BIS and AAI to test their ability to detect the anesthetic state that corresponds with loss of "shake and shout" responses (modified OAA/S score ≤ 1).

Response Surface Models of the Processed Electroencephalographic Parameters

Response surface models were constructed for each parameter using the Greco-Berenbaum model as shown below[33]:

$$E = \frac{E_{max} \cdot \left(\frac{C_A}{EC_{50A}} + \frac{C_B}{EC_{50B}} + \alpha \cdot \frac{C_A}{EC_{50A}} \cdot \frac{C_B}{EC_{50B}} \right)^n}{\left(\frac{C_A}{EC_{50A}} + \frac{C_B}{EC_{50B}} + \alpha \cdot \frac{C_A}{EC_{50A}} \cdot \frac{C_B}{EC_{50B}} \right)^n + 1},$$

where C_A, C_B are the concentrations of the two drugs; EC_{50A}, EC_{50B} are drug concentrations causing 50% of the maximal drug effect; E_{MAX} is the maximal drug effect; α characterizes the extent of interaction between both drugs; and n is a measure of response steepness.

Table 2. Demographics of Study Volunteers

	Group 1: Sevoflurane	Group 2: Remifentanil
Age, yr	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.

For each processed electroencephalographic parameter, the data were pooled 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 ≥ 30%). The SE of the model parameters was estimated using the bootstrap method for 5,000 iterations.[34]

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

$$Error_{Prediction} = 100 \times |Observed - Predicted|/Observed.$$

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 (≥ 0.7) indicates that the responses predicted from the surface described the observed data well.[35]

Results

All 24 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 group that received sevoflurane as the primary anesthetic agent contained equal numbers of male and female volunteers, whereas the group that received remifentanil as the primary agent was predominately male volunteers.

For individual drugs, the relation among the processed electroencephalographic parameters, the measured drug concentrations, and the modified OAA/S score at each assessment point is shown in figures 2A–D and summarized in table 3. We observed that most volunteers were sedated (modified OAA/S score ≤ 1) at sevoflurane concentrations greater than 1.5 vol%. Adequate sedation could not be

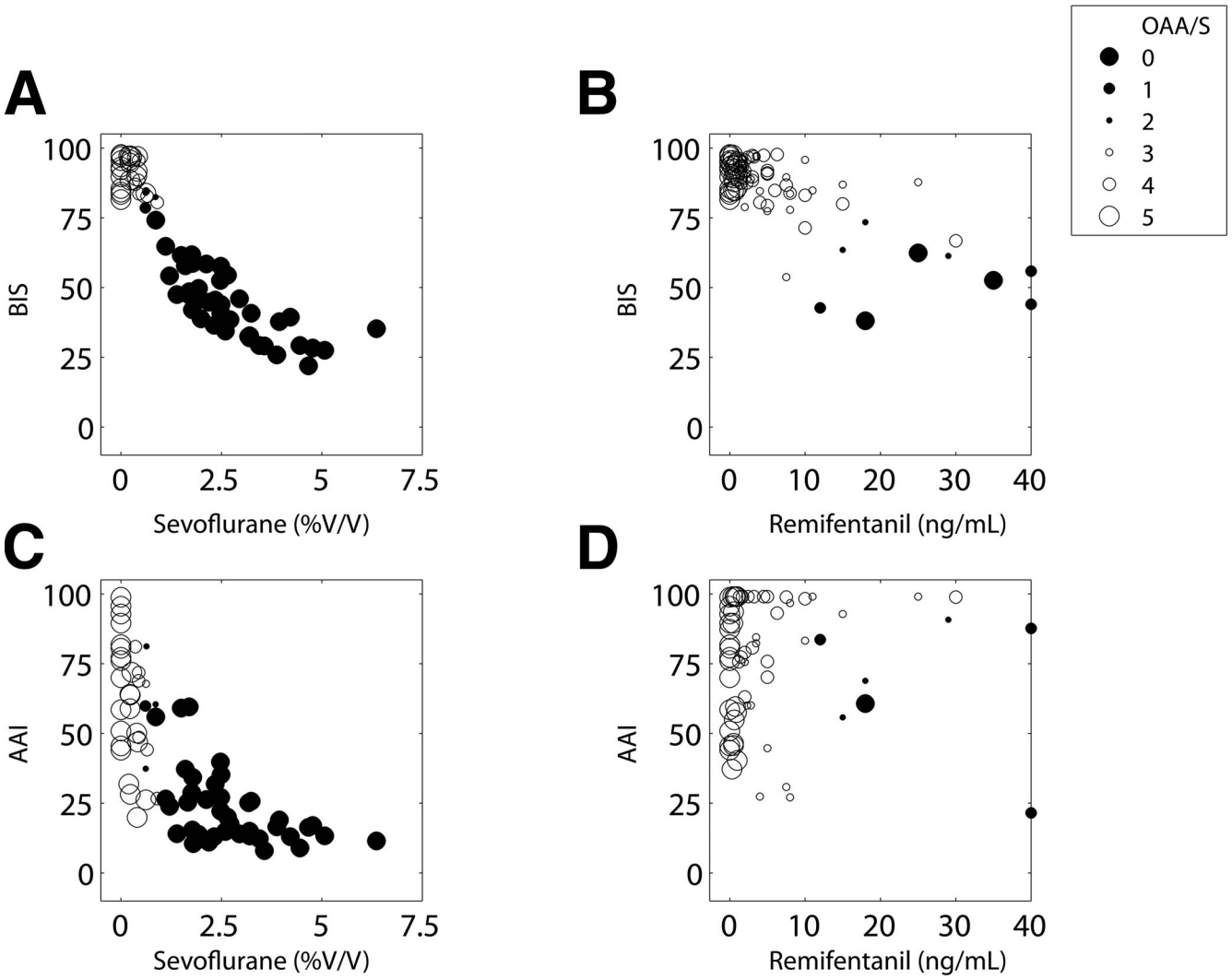

Fig. 2. ***A*** **shows a scatter plot demonstrating the relation between the Bispectral Index (BIS), the measured end-tidal sevoflurane concentration, and the clinical sedation score. Each** ***point*** **represents an assessment after target concentrations of the drug were achieved.** ***Open circles*** **represent observations classified as conscious (volunteers responded to verbal command, Observer's Assessment of Alertness/Sedation [OAA/S] score ≥ 3), whereas** ***filled circles*** **are considered unconscious.** ***B*** **shows a similar plot for the relation between the BIS, the predicted effect site concentration of remifentanil, and the clinical sedation score.** ***C*** **and** ***D*** **show similar plots for the relation between the A-Line Auditory Evoked Potential Index (AAI), the clinical sedation score, and the measured end-tidal sevoflurane concentration (*C*) or the predicted effect site concentration of remifentanil.**

achieved at remifentanil concentrations in the clinical range (5–10 ng/ml). Sedation using remifentanil could be achieved at concentrations higher than 20 ng/ml.

Figures 3A and B show the distribution of BIS and AAI at clinically relevant sedation states—loss of responsiveness to shouting (modified OAA/S score = 2), loss of responsiveness to shaking and shouting (modified OAA/S score = 1), and loss of responsiveness to noxious stimulus (modified OAA/S score = 0). The data are presented in a group where only sevoflurane was administered and in a group in which the volunteers received a combination of sevoflurane and remifentanil.

Table 3. Prediction Probability—OAA/S Score

	BIS	AAI	Sevoflurane End-tidal, vol%	Remifentanil C_e, ng/ml
SEVO	0.97 (0.01)	0.87 (0.03)	0.99 (0.01)	NA
SEVO-REMI	0.87 (0.01)	0.75 (0.02)	0.87 (0.01)	0.56 (0.03)
REMI	0.76 (0.04)	0.52 (0.05)	NA	0.93 (0.02)

SEs are given in parentheses.

AAI = A-Line Auditory Evoked Potential Index; BIS = Bispectral Index; C_e = effect site concentration; NA = not applicable; OAA/S = modified Observer's Assessment of Alertness/Sedation; REMI = remifentanil; SEVO = sevoflurane.

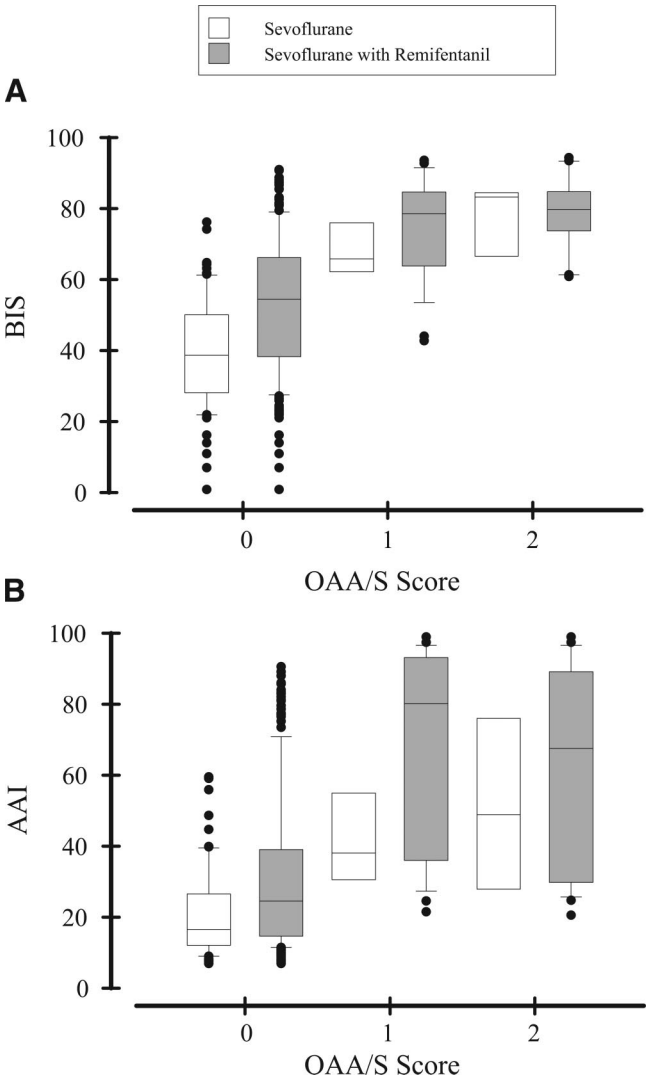

Fig. 3. *A* shows a box plot of the distribution of the Bispectral Index (BIS) at clinically relevant sedation states (Observer's Assessment of Alertness/Sedation [OAA/S] score ≤ 2). The data is presented in two groups: The first group (*open boxes*) shows the distribution in the processed electroencephalographic parameters where volunteers received only sevoflurane. The second group (*shaded boxes*) shows the distribution in the processed electroencephalographic parameters when the volunteers received a combination of sevoflurane and remifentanil. *B* shows a similar box plot of the distribution of the A-Line Auditory Evoked Potential Index (AAI) at clinically relevant sedation states (OAA/S score ≤ 2).

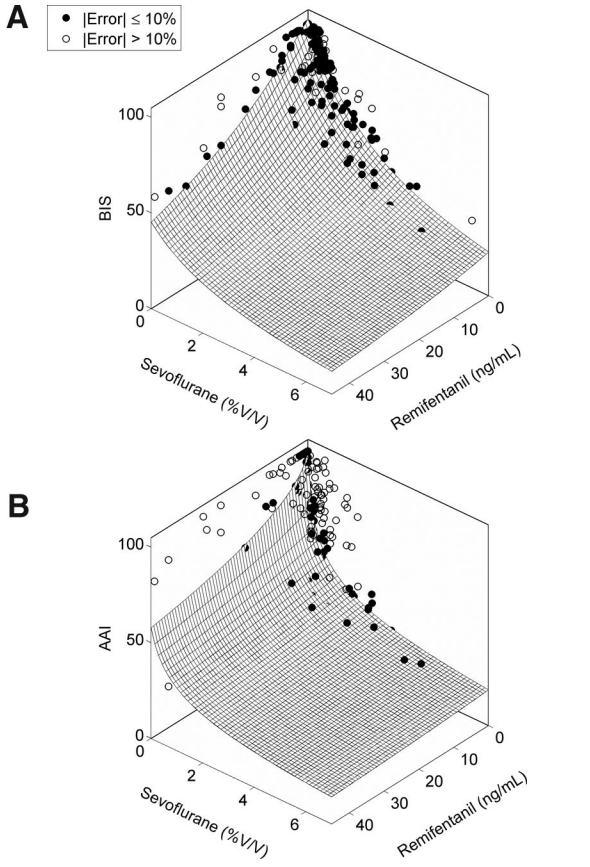

Fig. 4. *A* shows the Greco response surface model predictions of the sevoflurane–remifentanil interaction for the Bispectral Index (BIS) for unstimulated volunteers. The *symbols* show measured responses, and the surfaces predicted by the model are represented by the *grid-lined surface*. The raw data used to create this model are shaded based on the residual error. *B* shows the Greco response surface model predictions of the sevoflurane–remifentanil interaction for the A-Line Auditory Evoked Potential Index (AAI) for unstimulated volunteers.

Response Surface Models

The parameters for all the response surface models were identifiable. The Greco model parameters estimated through nonlinear regression are shown in table 4. The estimates of "goodness of fit" (*e.g.*, log likelihood, SEs, and correlation coefficient) suggest that the models described the BIS data better than the AAI data. The response surfaces that describe BIS and AAI at various target concentrations of sevoflurane and remifentanil are shown in figures 4A and B, respectively. 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%.

Isoboles from logit response surface models for clinical sedation (95% probability of modified OAA/S score ≤ 1)

Table 4. Mean Model Parameters for the Greco Response Surface for Sevoflurane and Remifentanil

	$EC_{50,Sevoflurane}$, vol%	$EC_{50,Remifentanil}$, ng/ml	Synergy, α	γ	Log Likelihood	Correlation Coefficient
BIS	2.37 (0.06)	38.02 (2.57)	0.52 (0.39)	1.12 (0.02)	−281.58	0.89
AAI	0.62 (0.06)	76.06 (17.40)	1.15 (1.33)	0.61 (0.08)	−1.24	0.60

SEs are given in parentheses.

AAI = A-Line Auditory Evoked Potential Index; BIS = Bispectral Index; $EC_{50,Remifentanil}$ = effective concentration of remifentanil (effect site) that produces a BIS or an AAI of 50; $EC_{50,Sevoflurane}$ = effective concentration of sevoflurane (alveolar) that produces a BIS or an AAI of 50.

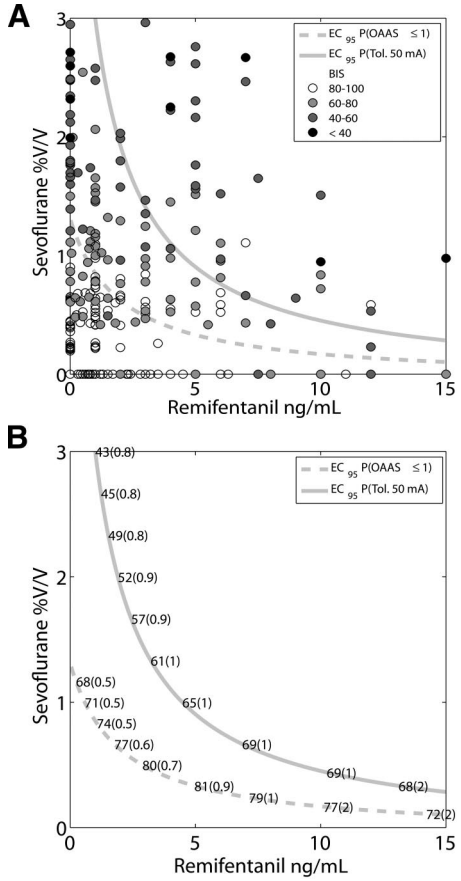

Fig. 5. ***A*** **shows a topographic view of the raw data (Bispectral Index [BIS]) overlaid on isoboles for adequate clinical sedation (95% probability of achieving an Observer's Assessment of Alertness/Sedation [OAA/S] score ≤ 1) and adequate surgical analgesia (95% probability of no movement response or hemodynamic response to a 50-mA tetanic electrical stimulation).** ***B*** **demonstrates the predictions of the BIS response surface model (mean and SD) at different concentration pairs along the isoboles for adequate clinical sedation and surgical analgesia.**

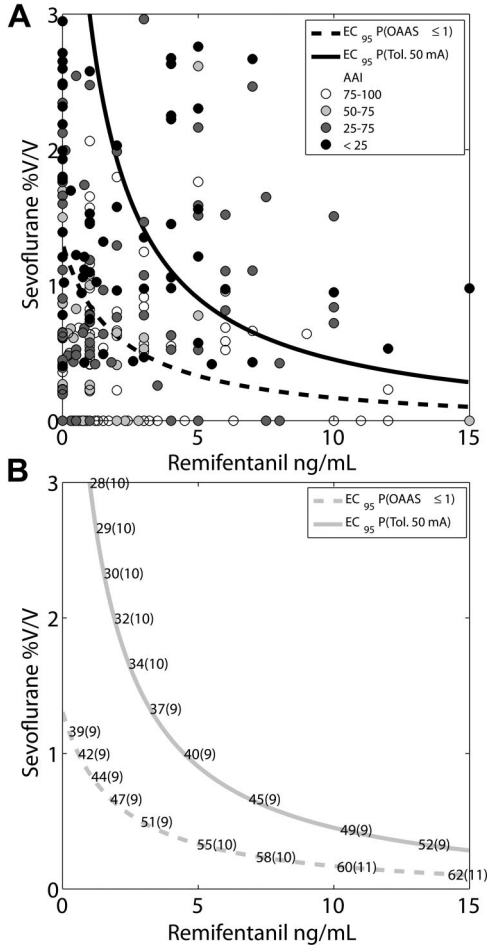

Fig. 6. ***A*** **shows a topographic view of the raw data (A-Line Auditory Evoked Potential Index [AAI]) overlaid on isoboles for adequate clinical sedation (95% probability of achieving an Observer's Assessment of Alertness/Sedation [OAA/S] score ≤ 1) and adequate surgical analgesia (95% probability of no movement response or hemodynamic response to a 50-mA tetanic electrical stimulation).** ***B*** **demonstrates the predictions of the AAI response surface model (mean and SD) at different concentration pairs along the isoboles for adequate clinical sedation and surgical analgesia.**

and tolerance of significant noxious stimulation (the 95% probability of no movement or hemodynamic response to a 50-mA electric tetanic stimulation) previously reported by Manyam *et al.*[30] are shown in figures 5 and 6. In addition, the raw data for each of the processed electroencephalographic parameters and the predicted processed electroencephalographic parameter values for the concentration target pairs on the previously described isoboles are overlaid onto the isoboles. These figures clearly demonstrate that the addition of small amounts of remifentanil (2.5 ng/ml) results in an increase in the target BIS and AAI necessary to produce clinically adequate sedation or anesthesia (figs. 5B and 6B).

Discussion

In this study, we used the volunteer paradigm previously employed by our laboratory[22,30] and others[24,36,37] to generate response surface models for anatomically distinct processed electroencephalographic parameters (BIS and AAI) during the concomitant administration of a wide range of target concentration pairs of a prototypical potent volatile anesthetic, sevoflurane, and a prototypical potent synthetic opioid, remifentanil. Although we had previously demonstrated that remifentanil synergistically potentiates the sedative effects of sevoflurane using clinical assesments,[30] we were unable to demonstrate more than a mild, additive increase in BIS and AAI with the addition of remifentanil to a sevoflurane anesthetic. The fact that the BIS and AAI are both insensitive to the observed changes in the clinical sedation state produced by the addition of a small to large dose of remifentanil to a sevoflurane anesthetic suggests that sevoflurane–remifentanil anesthetics titrated to traditional BIS or AAI targets would possibly result in a

deeper than necessary anesthetic state. With an effect site concentration of 5 ng/ml remifentanil (an infusion of approximately 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in a typical adult), approximately 1% sevoflurane is usually sufficient to produce clinically adequate anesthesia (sedation and no hemodynamic or movement response to noxious stimulation) without any concern of explicit recall, and yet our models predict that the BIS would be greater than 65 and the AAI would be greater than 40. Therefore, during sevoflurane–remifentanil anesthesia, targeting a BIS less than 60 or an AAI less than 30 may result in an excessively deep anesthetic state. This work identifies an important limitation of the currently available algorithms of two distinct processed electroencephalographic parameters in that the monitors do not indicate how dramatically the anesthetic state changes when moderate doses of opioid are added to a sevoflurane anesthetic. This work also demonstrates how the use of a small volunteer data set can rigorously derive the results of a large multicenter study without the added logistical complexity and involved pharmacokinetic–pharmacodynamic modeling previously necessary to determine the effects of varying anesthetic techniques on processed electroencephalographic parameters.[25]

Concentration–Effect Relationship

When examining the effects of prototypical anesthetic agents from a single drug class on the processed electroencephalographic parameters, the administration of sedatives–hypnotic agents (*e.g.*, sevoflurane or propofol) results in a clear dose-dependent increase in hypnosis and overall anesthetic depth. In contrast, the administration of an opioid in isolation does little to decrease the processed electroencephalographic parameter until extremely high concentrations of the opioid are achieved.[38] Our results were similar—we observed that the BIS and AAI correlate well with sevoflurane concentrations (P_k values of 0.97 and 0.87, respectively) and more poorly with remifentanil (P_k values of 0.76 and 0.52, respectively). In addition, the BIS had a wider dynamic range in response to increasing drug concentration than the AAI, consistent with previous reported response of the BIS and AAI.[39–41] The wider dynamic range available with the BIS could potentially translate into easier titration of sevoflurane than with the small dynamic range of the AAI. However, the ability of a monitor to track the concentration changes of a drug does not necessarily improve its performance in predicting an increase in hypnosis and a decreased probability of response (movement or hemodynamic) to noxious stimulation. Therefore, when developing algorithms to measure clinical depth of anesthesia, it is important to focus on capturing the various clinical anesthetic states rather than focusing only on tracking the change in the concentration(s) of the anesthetic drug(s).

We measured the concentration–central nervous system effect relation of opioids using remifentanil as a prototype opioid. Although a remifentanil effect site concentration above 15 ng/ml (an infusion of approximately 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$) is rarely used in clinical practice, we sampled remifentanil concentrations up to 60 ng/ml in an attempt to capture rigorously the sedative effects of remifentanil. Within the clinical range, remifentanil did not produce a clinically significant change in the level of sedation. At supraclinical remifentanil concentrations, remifentanil produced a clinically significant level of sedation; however, this opioid-induced sedation rarely approached a modified OAA/S score of 1. In addition, increasing the level of clinical sedation with remifentanil did not decrease the AAI in a consistent pattern, although the BIS decreased modestly. Our results are similar to previous reports that showed that the processed electroencephalographic parameters are relatively insensitive to opioids[7,42,43] within the clinical range.

Prediction Probability

Several previous reports have demonstrated that the BIS and the AAI are useful surrogates of depth of anesthesia.[6] The BIS showed less variation at each level of clinical sedation than did the AAI (figs. 3A and 4B). This may be an intrinsic characteristic of the arbitrary scaling of the AAI to have its operating range for general anesthesia between 0 and 30; therefore, small changes in clinical state might result in a large increase in AAI. An alternative explanation might be that the brainstem and cortical auditory pathways are well preserved during moderate levels of anesthesia resulting in an increased sensitivity to ascending (sensory) signals.[12,13] Finally, the increased variability may simply be the result of the more primitive (and poorer performing) electromyogram filtering algorithms available on the early model AAI compared with the more developed BIS.

Our results are in agreement with previous reports that have demonstrated that the BIS outperforms the AAI when evaluating the performances of the processed electroencephalographic parameters using prediction probabilities (P_k).[15,44] However, prediction probabilities are limited in that they report only the direction and the goodness of correlation between the clinical sedation score and the processed electroencephalographic parameter—they do not supply any information about whether the change in the parameter is large or small. Therefore, although the addition of remifentanil to a sevoflurane anesthetic resulted in a minor change in processed electroencephalographic parameters that was relatively small compared with the large change in clinical sedation, the modest decrease in the prediction probabilities does not reflect the inability of the BIS or the AAI to capture the observed clinical change.

Response Surface Models

As a complement to prediction probability analyses, response surfaces analysis was used to study the pharmacodynamic effects of adding remifentanil to a sevoflurane anesthetic. Response surface methods have been used to model the interactions between a variety of anesthetic combinations. Using the Greco form of the response surface models, we were able to characterize the relation between the effect site concentrations of remifentanil, the end-tidal concentrations, and the BIS with a low amount of error ($R^2 > 0.8$). The response surface model for AAI had moderately good correlation ($R^2 > 0.8$), with the poorer fit most likely related to the larger variability in the response and the smaller operating range. The pharmacodynamic response surface revealed that the addition of remifentanil decreased the BIS in a minor and additive fashion, whereas the AAI response surface showed that AAI is not significantly affected by the addition of remifentanil. A possible explanation for this difference is that the brainstem and auditory cortex responses are relatively resistant to opioid effects,[45] whereas the higher cortical responses associated with sedation are decreased with the inhibition of ascending sensory signals.[46] An alternative explanation for the difference between the clinical sedation response (modified OAA/S) and the minimal electrophysiologic response may simply be that the opioids are able to block the noxious (ascending) input into the central nervous system and the cortical electrophysiologic responses are unable to capture this subcortical anesthetic effect.[25,46] The anatomic distinct site of actions[47,48] of hypnotics and opioids would explain the reason why the electrophysiologic monitors are able to predict the immobility due to a large dose of sedative–hypnotic anesthetic (*e.g.*, isoflurane, *etc.*) and yet not predict the immobility produced by a combination of a sedative hypnotic and an opioid.[25]

To give clinical meaning to the predictions made by the response surface models for processed electroencephalographic parameters, we examined how the electroencephalographic parameters change with different sevoflurane–remifentanil combinations that produce a high probability of adequate anesthesia. We used the logit response surface models to define combinations of sevoflurane–remifentanil that result in a 95% probability of adequate sedation (*i.e.*, modified OAA/S score $\leq$ 1) and a 95% probability of adequate analgesia (*i.e.*, no movement of hemodynamic response to a 50-mA electrical tetanic current) previously described by our laboratory.[30] We combined these isoboles of surrogates for adequate clinical anesthesia with the BIS and AAI response surface models to show how the predicted BIS and AAI values change as the sevoflurane–remifentanil combination changes. Figures 5 and 6 demonstrate that with the addition of a remifentanil effect site concentration of 5 ng/ml (an infusion of approximately 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$), adequate sedation would be provided with a BIS of 81 and an AAI of 57, and adequate general anesthesia would be provided with a BIS of 65 and an AAI of 41—all values considerably higher than the usual target range of either of the processed electroencephalographic parameters (BIS 40–60 and AAI 15–30). Because the two processed electroencephalographic parameters are relatively insensitive to opioids, the rational target for BIS or AAI for general anesthesia increases as the opioid component of the anesthetic increases (fig. 7).

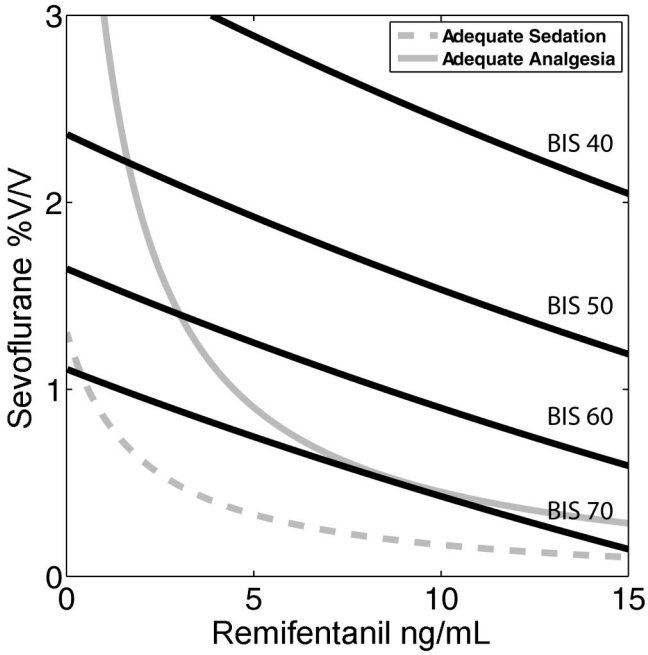

Fig. 7. The isoboles that produce target Bispectral Index (BIS) values of 40, 50, 60, and 70 are overlaid on isoboles for adequate clinical sedation (95% probability of achieving an Observer's Assessment of Alertness/Sedation score ≤ 1) and adequate surgical analgesia (95% probability of no movement response or hemodynamic response to a 50-mA tetanic electrical stimulation).

Clinical Implications

The processed electroencephalogram has emerged as an important surrogate measure of the depth of anesthesia.[7,10] Surrogate measures are used when the clinical drug effect of interest is difficult or impossible to measure. The processed electroencephalogram has many characteristics of the ideal surrogate. In contrast to more clinically oriented measures of drug effect, it is can be an objective, continuous, reproducible, noninvasive, high-resolution signal.[6] It can also be used as an effect measure when an experimental subject or patient is unconscious, whereas many of the more clinically oriented measurements of sedation require awake, cooperative subjects.[49]

The ability of the addition of even a small amount of synthetic opioid to decrease the amount of potent volatile anesthetic required to produce clinically adequate

anesthesia is well known. Previous work has demonstrated that the addition of remifentanil to sevoflurane[30] or propofol[22,50] anesthetics results in a synergistic increase in depth of anesthesia (sedation and nonresponsiveness to noxious stimulation). The inability of the two processed electroencephalographic parameters studied here to detect the increase in anesthetic depth produced by the addition of even modest amounts of a synthetic opioid has been demonstrated with response surface analysis of surgical patients.[51] Similar to our results here, response surface analysis performed by Dahan *et al.*[24] investigating the interaction of moderate levels of alfentanil and sevoflurane anesthesia has shown that there is no increase in anesthetic depth as measured by the BIS. Therefore, it would seem that despite the clinically significant increase in the clinical sedation level and the anesthetic depth produced by the addition of modest amounts of remifentanil to a sevoflurane anesthetic, there is minimal effect of even supratherapeutic doses of opioid on the depth of anesthesia measured by the BIS and the AAI. This confirms previous observations made by a large, multicenter study investigating the effects of a variety of anesthetics on the bispectral electroencephalographic analysis.[25] By avoiding the complexity in logistics and pharmacokinetic–pharmacodynamic modeling required by this large, multicenter study, the volunteer paradigm to derive response surfaces across a range on concentration pairs of a sedative–hypnotic and an opioid may be one way to quickly evaluate the performance of the next generation of depth of anesthesia monitors.

Our response surface models demonstrate that targeting the familiar operating range for a BIS of 40–60 would result in a 50–150% higher end-tidal sevoflurane concentration being administered than would be needed to provided clinically adequate anesthesia if a moderate dose of remifentanil (effect site concentration of 5 ng/ml) was administered (fig. 7). Besides the anticipated hemodynamic side effects expected from this anesthetic "overdose,"[18] anesthetics that produce and maintain low BIS values result in delayed emergence, increased anesthetic drug costs[10] and possibly an increase in 1 yr mortality—a provocative finding that requires further validation.[11] Therefore, either new "context-sensitive" operating ranges for the processed electroencephalographic parameters must be derived to account for the unmeasured effects of the addition of varying doses of opioids, or a monitor sensitive to the actual clinical conditions, with or without opioids, needs to be developed. It is possible that the combination of real-time pharmacokinetic–pharmacodynamic displays[52] with the addition of the response surfaces described here would be able to numerically and graphically provide anesthesiologists with real-time feedback as to the actual (predicted) clinical depth of anesthesia during a balanced anesthetic. However, the lack of a ready solution suggests that the delivery of a balanced anesthetic using a closed-loop controller based on any of the conventional processed electroencephalographic parameters could possibly result in clinically deeper anesthetics than desired, especially if the algorithm attempts to use the unique pharmacokinetic and pharmacodynamic characteristics of remifentanil to improve responsiveness and pharmacologic control.[53]

Previously, we had identified "optimum" target combinations of sevoflurane and remifentanil that provided adequate surgical anesthesia and minimized the time to awakening.[30] For anesthetics ranging in duration from 0.5 to 24 h, the target sevoflurane concentration varied from 1.10% to 0.75%, and the target remifentanil concentration ranged from 4.1 to 6.1 ng/ml (infusion rates of 0.15–0.22 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in typical adults). Based on our findings, targeting these optimum combinations would produce clinically adequate surgical anesthesia with BIS (64–68) and AAI (40–45) higher than the normal operating ranges suggested by the manufacturers.

Limitations

The fact that our response surface models were determined in unstimulated volunteers is a major constraint that may limit the generalizability of our results. In particular, the lack of constant stimulation from an endotracheal tube or the continuous pain form a surgical incision may result in our volunteer data underestimating the anesthetic requirements of surgical patients. However, there are numerous advantages of the volunteer study paradigm to develop response surface models—key surgical stimulation can be applied multiple times, repeated measurements can be made on the same subject, and the entire dynamic range of anesthetic combinations can be examined, all without ethical concerns of providing inadequate anesthesia during a surgical procedure—which make the volunteer study paradigm irreplaceable. In addition, this relatively small volunteer study was able to replicate what previously was only achieved with the complex retrospective pharmacokinetic–pharmacodynamic modeling of the anesthetics administered during a large, multicenter study investigating the effect of bispectral analysis on monitoring anesthetic effect.[25] Therefore, volunteer pharmacodynamic response surface analysis can provide insight into processed electroencephalographic parameters responses to a variety of anesthetic combinations.

Another source of bias in our methodology is that we did not blind our rater of clinical sedation (J.L.W.) to the dose of drug being administered. Because of the study paradigm (stepwise increasing concentrations of anesthetics), we thought that it would be difficult to blind the rater to the fact that the anesthetic concentration increased at each step. Although observer bias could have been prevented by administering the different target concentration pairs in a random fashion, the logistics

(*i.e.*, time to wash out to lower concentrations from a high concentration of drug A and/or drug B, *etc.*) would have made this complex study that took at least 6 h to perform as designed into a prohibitively long study. By using an objective measure of sedation (the modified OAA/S) and the "unbiased" measures of the processed EEG, we hoped to minimize the effects of observer bias on our results.

The fact that we use pharmacokinetic models to predict the remifentanil effect site concentration in lieu of measuring the actual blood drug concentration may compound some of the variability in the opioid-only, single-drug data.[54] However, as in our previous study,[30] there is convincing evidence to demonstrate that this may not be a major source of pharmacokinetic model error. Another source of pharmacokinetic model error may be the targeting of an end-tidal alveolar pseudo–steady state of volatile anesthetic instead of targeting the effect site concentration. The steady state partial pressure of the volatile anesthetic at the effect site correlates with the measured end-tidal alveolar partial pressure at steady state. However, achieving pseudo–steady state at the alveoli results in an effect site concentration that would most likely not reach its own pseudo–steady state. We did not choose to target a pseudo–steady state at the effect site because we would have to assume *a priori* knowledge of which an anatomical compartment contained the pharmacologic effect site for sedation and for clinical anesthesia. Given the fact that volatile anesthetics produce sedation through a supraspinal site of action whereas immobility is produced primarily at the spinal cord level,[48] the choice of effect site to target in the pharmacokinetic simulations to determine when pseudo–steady state at the effect site is achieved is one of many difficult assumptions that would be needed to address these concerns about steady state drug levels. In addition, the time involved in achieving a steady state alveolar concentration or a pseudo–steady state effect site concentration would be prohibitively longer than that required to achieve alveolar pseudo–steady state.

Although remifentanil-induced hyperalgesia has been observed in the patients[55] and volunteers[56] receiving infusions of various durations, as detailed in our previous article,[30] we did not find any differences between the baseline levels of tolerated stimuli and the levels of stimuli tolerated at the lowest doses of sevoflurane. In addition, one could conjecture that any opioid hyperalgesia that developed would not effect the clinical sedation score (modified OAA/S) or the processed electroencephalographic parameters that were determined during quiet periods before the determination of the analgesic response of each of the targeted concentration pairs.

The Greco response surface model used to describe the response surface models generated here is different than the logit model used in our previous investigation of sevoflurane–remifentanil pharmacodynamic interactions.[30] Although the logit model proved advantageous for the modeling of stimuli whose responses can be dichotomized, the Greco model[33] and the models described by Minto and Vuyk[57] and Bouillon *et al.*[50] all handle continuous response variables (*e.g.*, processed electroencephalographic parameters) well. The main advantage of the Greco model is that it assumes a sigmoidal E_{max} structure that is readily familiar to pharmacologists and clinicians. The biggest limitation of the Greco model is that it cannot account for a partial agonist—it presumes that remifentanil at sizeable concentrations will produce a BIS or an AAI of 0. This assumption causes a bias in the determination of the response surface; however, because models that adequately account for partial agonists are not well developed, there is no way to overcome this limitation. Even with the assumption that the Greco model does not account for a partial agonist, by setting the $C_{MAX,\ REMI}$ at a high enough value (*i.e.*, 400 ng/ml), the error in the response surface is not significantly large to cause a change in model predictions.

The definition of adequate anesthesia reveals many complexities of this multifaceted clinical state.[20,58] On either end of the spectrum, anesthesia can be defined in a simple model as amnesia and immobility to noxious stimulation, or it can be thought as a multifaceted condition requiring amnesia, unconsciousness, immobility, and hemodynamic stability. Because of the intricacies involved with performing repeated assessments for explicit recall in a study designed to make multiple pharmacodynamic measurements for a large number of target combinations of the target drugs, we did not test for amnesia. We thought that those patients who would be clinically sedated (modified OAA/S score ≤ 1) *and* have an end-tidal concentration of sevoflurane of approximately 1% atm (0.5 minimum alveolar concentration [MAC]) would not demonstrate any explicit recall. This is based on three premises: (1) We were administering a potent volatile anesthetic (sevoflurane) with a well-defined MAC_{AWAKE} profile (0.67 ± 0.12 5 atm or 0.36 ± 0.03 MAC)[59]; (2) the ratio of MAC_{AWAKE}/MAC does not change with age or the administration of opioids[60]; and (3) there is a reproducible finding (albeit it in small groups of volunteers) that 0.45 MAC of volatile anesthetic suppresses implicit and explicit memory formation.[61,62] This is a conservative estimate that does not take into to account the observed reduction in MAC and MAC_{AWAKE} with the administration of opioids.[59] However, given the complexity of assessing implicit and explicit memory formation in patients and volunteers[63] and the difficulty in assessing depth of anesthesia with high doses of opioids,[64] the absolute threshold for preventing of explicit recall with hypnotic–opioid combinations is not known. Therefore, to prevent a situation where a patient receiving a high dose of opioid and a low dose of volatile anesthetic is able to process com-

mands and form memories but does not care to respond to commands or stimuli, a modicum ($\geq$ 0.5 MAC) of volatile anesthetic must be administered.

If 1% sevoflurane can be accepted to reliably produce amnesia, figures 5 and 7 demonstrate that the isobole predicting the sevoflurane–remifentanil combinations that would produce a 95% probability of no movement or hemodynamic response to a surrogate for surgical incision does not advocate using less than 1% sevoflurane until the remifentanil concentration is approximately 5 ng/ml (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$). For these remifentanil "heavy" anesthetic combinations, the BIS will be between 60 and 70. In the past, there has been a concern of using opioid "heavy" anesthetic because of the occurrence of recall without movement or hemodynamic change in a "nitrous oxide– opioid–relaxant technique." With the potent volatile anesthetics, this decreases significantly because the potent volatile anesthetics are significantly more efficient in preventing memory formation and voluntary response to command (approximately two times more potent).[62] The hemodynamic stability of high-concentration opioid anesthesia[65] and the recovery profile of remifentanil[30,38] makes targeting combinations of sevoflurane and remifentanil in this range attractive.

Conclusions

Although clinical sedation increases significantly even with the addition of a small to moderate dose of remifentanil to a sevoflurane anesthetic, the BIS and AAI are insensitive to this change in clinical state. Based on this volunteer study, when using remifentanil "heavy" (0.2-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion) combinations during sevoflurane–remifentanil anesthesia, targeting a BIS less than 60 or an AAI less than 30 may result in an excessively deep anesthetic state despite providing clinically adequate sedation, analgesia/immobility, and hemodynamic stability. If providing "too deep" an anesthetic produces undesirable side effects, new target processed electroencephalographic parameters that reflect the actual measured clinical anesthetic depth would be required. Incorporation of these processed electroencephalographic parameter response surface models into a real-time, pharmacokinetic–pharmacodynamic display system[52] may allow more precise concentration pairs or target adjustments.

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