An Evaluation of Remifentanil Propofol Response Surfaces for Loss of Responsiveness, Loss of Response to Surrogates of Painful Stimuli and Laryngoscopy in Patients Undergoing Elective Surgery

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INTRODUCTION: In this study, we explored how a set of remifentanil-propofol response surface interaction models developed from data collected in volunteers would predict responses to events in patients undergoing elective surgery. Our hypotheses were that these models would predict a patient population's loss and return of responsiveness and the presence or absence of a response to laryngoscopy and the response to pain after surgery.

METHODS: Twenty-one patients were enrolled. Anesthesia consisted of remifentanil and propofol infusions and fentanyl boluses. Loss and return of responsiveness, responses to laryngoscopy, and responses to postoperative pain were assessed in each patient. Model predictions were compared with observed responses.

RESULTS: The loss of responsiveness model predicted that patients would become unresponsive 2.4 ± 2.6 min earlier than observed. At the time of laryngoscopy, the laryngoscopy model predicted an 89% probability of no response to laryngoscopy and 81% did not respond. During emergence, the loss of responsiveness model predicted return of responsiveness 0.6 ± 5.1 min before responsiveness was observed. The mean probability of no response to pressure algometry was 23% ± 35% when patients required fentanyl for pain control.

DISCUSSION: This preliminary assessment of a series of remifentanil-propofol interaction models demonstrated that these models predicted responses to selected pertinent events during elective surgery. However, significant model error was evident during rapid changes in predicted effect-site propofol-remifentanil concentration pairs.

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Drug interaction studies have characterized the synergy between remifentanil and propofol over a wide range of predicted effect-site concentrations.[1–4] From these data, drug interaction models have been developed that relate predicted remifentanil and propofol effect-site concentrations to patient states that are of interest to an anesthesiologist such as the probability of loss and return of responsiveness. As has been done with pharmacokinetic models to drive target-controlled infusions, a natural extension of this work is to explore the use of drug interaction models to drive real-time displays of predicted drug effects. Should these models be able to predict patient responses with sufficient accuracy, the use of interaction models in real-time may better match opioid and sedative delivery to patient analgesic and sedation needs.

A volunteer study in our laboratory characterized the synergistic interaction between remifentanil and propofol by measuring sedation and antinociception over a wide range of effect-site concentrations.[2] Response surface interaction models were developed to relate concentration pairs to the probability of loss of responsiveness (LOR) and loss of response to tetanic stimuli, pressure algometry, and laryngoscopy.[5]

The aim of this present study was to explore how well these interaction models predict patient responses during surgery. We expect that LOR and loss of response to laryngoscopy will occur at the same drug concentrations in patients as in volunteers. Our hypotheses were that response surface models developed in volunteers will accurately predict (i) LOR and return of responsiveness, (ii) the presence or absence of a hemodynamic response to laryngoscopy, and (iii)

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when patients would require administration of additional analgesic after surgery.

METHODS

Patient Selection

After IRB approval at the University of Utah, informed consent to perform the study was obtained from 21 patients presenting for elective surgery. An equal number of male and female subjects were solicited to participate in the study. Patients with a history of continuing opioid consumption were excluded. Baseline arterial blood pressure and heart rate, gender, age, weight, and height were recorded for each patient.

Response Surface Models

In our prior work, levels of sedation and antinociception were measured over wide ranges of targeted propofol and remifentanil effect-site concentrations.[2] Metrics of sedation (the Observers Assessment of Alertness/Sedation scale—OAA/S scale[6]) and antinociception (response to tetanic stimuli, pressure algometry, and laryngoscopy) were made at numerous concentration pairs with the intent of characterizing the synergistic relationship between these two IV anesthetics. Using a response surface model approach,[7] interaction models were constructed and represented by the following relation:

$$\text{Effect} = \frac{E_{\max} \cdot \left[\frac{C_e r}{C_{50r}} + \frac{C_e p}{C_{50p}} + \alpha \cdot \left(\frac{C_e r}{C_{50r}} \cdot \frac{C_e p}{C_{50p}} \right) \right]^n}{\left[\frac{C_e r}{C_{50r}} + \frac{C_e p}{C_{50p}} + \alpha \cdot \left(\frac{C_e r}{C_{50r}} \cdot \frac{C_e p}{C_{50p}} \right) \right]^n + 1} \quad (1)$$

$E_{\max}$ is the maximal effect of propofol and remifentanil for a given effect measure (i.e., no response to laryngoscopy), C_{50p} and C_{50r} are the C_e that produce 50% of the maximal effect (i.e., 50% probability of no response to laryngoscopy), n is the slope of the pharmacodynamic response curve, and α is the interaction between propofol and remifentanil. Model parameters taken from Kern et al.[2] are presented in Table 1. The range of effect was from 0 (100% probability of response) to 1 (100% probability of no response).

In our prior work, we used a transition from an OAA/S score of 4 to 3 to represent the onset of sedation[2] but did not characterize LOR. In this present work, characterized LOR was based on a transition from response to loss of response to prodding and shaking (OAA/S score from 2 to 1). Measured remifentanil and propofol concentration pairs were used to fit a three dimension response surface using a naïve pooled technique.[8] Using modeling software (Matlab, Mathworks, Natick, MA), these binary data of OAA/S were fit to a Greco model adjusted for categorical data[9] to estimate the new model parameters. Nonlinear regression analysis of the concentration-response data[10] revealed that the new interaction model fit to the LOR data with an r^2 value of 0.82. Model parameters for LOR are presented in Table 1.

Table 1. Interaction Model Parameters

	C_{50p}	C_{50r}	n	Alpha
Loss of responsiveness	2.2	33.1	5.0	3.6
Loss of response to laryngoscopy[a]	5.6	48.9	2.2	33.2
Loss of response to pressure algometry[a]	4.2	8.8	8.3	8.2
Loss of response to electrical tetany[a]	4.6	23.1	6.0	14.7

C_{50p} (mcg/mL) and C_{50r} (ng/mL) represent the predicted effect-site concentrations for each drug that produce 50% of the maximal effect, n is the slope of the pharmacodynamic response curve, and alpha is the extent of interaction between propofol and remifentanil for a given drug effect.

[a] Interaction model parameters taken from Kern et al.[2]

Patient Monitoring

Each patient was instrumented with a pulse oximeter, noninvasive blood pressure cuff set to cycle every 5 min, a 5-lead electrocardiogram and, after induction, an oral or nasal temperature probe. Inspired and expired oxygen and carbon dioxide concentrations were continuously monitored (AS/3 Anesthesia Monitor, Datex-Ohmeda, Helsinki, Finland) and stored every 5 s using a computerized data acquisition system (S/5 Collect, Datex-Ohmeda, Helsinki, Finland).

Experimental Protocol

Midazolam 12.5 mcg/kg was administered IV in the preoperative holding area. Patients were then taken to the operating room. Infusions of remifentanil and propofol were started approximately 10 min after midazolam was administered. Using pharmacokinetic models for propofol[11,12] and remifentanil,[13,14] infusion rates for each drug were calculated to reach desired remifentanil and propofol effect-site concentrations within 10 min. Patients were randomly assigned to one of the five groups. Group 1 had high propofol and low remifentanil target concentrations. Group 5 had low propofol and high remifentanil target concentrations. Table 2 lists the infusion rates for each group. Syringe pumps (Medfusion 2010I or 3010I, Medex, Duluth, GA) were used to deliver remifentanil and propofol.

During induction, a study nurse assessed the patient's level of sedation every 20 s using the OAA/S score. Assessments began when the remifentanil and propofol infusions started and ended with LOR (two consecutive failures to respond to their name called out in a loud voice and moderate prodding). Anesthesiologists were asked to determine when the patient was ready for laryngoscopy. If they believed that the amount of remifentanil and propofol were inadequate after 10 min, they were asked to give additional propofol or remifentanil as needed. They were not made aware of any model predictions.

Table 2. Remifentanil and Propofol Infusion Rates During Induction for Each Study Group

Induction group	Propofol ($mcg \cdot kg^{-1} \cdot min^{-1}$)	Remifentanil ($mcg \cdot kg^{-1} \cdot min^{-1}$)	Time to LOR (min)	Time to TI (min)	Estimated remifentanil C_e (ng/mL)	Estimated propofol C_e (mcg/mL)
1	317 ± 39	0.145 ± 0.018	3.6 ± 0.5	6.9 ± 1.7	2.5 ± 0.4	2.4 ± 0.5
2	199 ± 20	0.337 ± 0.034	6.0 ± 1.2	9.7 ± 2.5	6.0 ± 0.5	2.3 ± 0.3
3	158 ± 11	0.524 ± 0.038	5.5 ± 1.2	9.2 ± 1.3	8.0 ± 1.9	1.6 ± 0.3
4	97 ± 20	0.534 ± 0.113	6.7 ± 4.2	10.9 ± 4.5	10.8 ± 1.7	1.1 ± 0.8
5	79 ± 6	0.691 ± 0.050	6.9 ± 2.8	10.2 ± 2.1	14.0 ± 2.6	0.9 ± 0.3s
Overall	177 ± 93	0.432 ± 0.206	5.6 ± 2.5	9.3 ± 2.7	8.0 ± 4.4	1.7 ± 0.8

Data are expressed as mean ± standard deviation.

Estimated remifentanil and propofol concentrations are at the time of TI.

LOR = loss of responsiveness; TI = tracheal intubation; C_e = effect-site concentration at the time of LOR.

After LOR, patients received either rocuronium (0.6 mg/kg) or succinylcholine (2 mg/kg). The presence or absence of a heart rate response to laryngoscopy and tracheal intubation was evaluated when the endotracheal cuff was inflated. A heart rate response was considered present if it increased more than 20% above baseline. After tracheal intubation, remifentanil and propofol were titrated at the anesthesiologist's discretion.

Before emergence, the anesthesiologists gave fentanyl as per their standard practice to manage postoperative pain. During emergence, the patient's level of sedation was assessed every 20 s. Assessment began when the remifentanil and propofol infusions were turned off and ended when the patient regained responsiveness (two consecutive OAA/S scores >1).

Patients were observed in the recovery room for 30 min. Every 5 min, a study nurse asked the patients to use the visual analog scale (VAS) to give a pain score and a pain score that the patients considered tolerable. Fentanyl was administered in 25 to 150 mcg increments when the actual VAS was more than the tolerable VAS and the recovery room nursing staff considered it appropriate (i.e., lack of excessive sedation or respiratory depression).

Data Analysis

Using previously reported pharmacokinetic-pharmacodynamic models,[13–16] estimates of propofol, remifentanil, and fentanyl effect-site concentrations were made for each subject's anesthetic. Fentanyl effect-site concentrations were converted to equivalent remifentanil effect-site concentrations using a fentanyl to remifentanil potency ratio of 1:1.2.[17] We used the pharmacodynamic model in Eq. 1 to convert effect-site concentrations to drug effects.

LOR Interaction Model

To measure the temporal accuracy, the time differences between when the model predicted 50% of the patients would lose responsiveness and when patients actually lost responsiveness to shaking and shouting during induction and when patients actually regained responsiveness during emergence were calculated.

To assess model performance, we compared observed changes in responsiveness to model predictions during induction and emergence from anesthesia. Using estimated remifentanil and propofol effect-site concentrations as input into the LOR model, predicted LOR (from 0 to 100%) were estimated for each patient at the time of observed LOR. Model predictions from each patient were organized according to increasing probability. A percentage value was assigned to each patient as a percentage of all 21 patients according to increasing probabilities. Residuals between model predictions and the observed percentage of patients with LOR were made for each patient during induction and emergence. Residuals were used in accuracy, bias, and root mean squared error analyses.[16,18] In general, a good model fit resulted in an equal distribution of model predictions of LOR above and below the 50% isobole.

Laryngoscopy Interaction Model

After induction, patient response to laryngoscopy, intubation, and inflation of the endotracheal tube cuff were recorded for each patient. Patient responses were compared with the 95% isobole for no response to laryngoscopy.

Surrogates of Painful Stimuli Interaction Models

Probabilities of response to surrogates of painful stimuli (pressure algometry and electrical tetany) were compared with dosing of additional fentanyl during the first 30 min in the recovery room. Accuracy, bias, and root mean squared error were calculated as described for the LOR model. All data are presented as mean ± SD.

RESULTS

Twenty-one patient subjects (10 men, 11 women) were enrolled and all subjects completed the study. Their ASA Physical Status classification ranged from I to III. The height, weight, Body Mass Index, and age were 172 ± 10 cm, 79 ± 17 kg, 26.6 ± 5.7 kg/m^2, and 41.7 ± 17 yr, respectively. None of the patients were taking a β-blocker and no β-blockers were administered during their surgery. Surgical procedures included

open (nine) and laparoscopic (seven) abdominal surgery, lower extremity orthopedic surgery (one), upper extremity orthopedic surgery (one), cervical spine surgery (one), throat surgery (one), and lower extremity vascular surgery (one). Estimated blood loss was <100 mL for all surgeries. Fourteen different surgeons and seven different anesthesiologists participated in the study.

The time from the start of the remifentanil and propofol infusions to LOR and tracheal intubation and the predicted remifentanil and propofol effect-site concentrations for each induction group are presented in Table 2. At the discretion of the attending anesthesiologist, laryngoscopy with tracheal intubation was performed on average 9.3 ± 2.7 min after the start of the infusions.

LOR Interaction Model

This model predicted a mean probability of 81% ± 22% that patients would not respond to moderate shaking and prodding at the time of the onset of LOR. Figure 1A presents the predicted concentration pairs at the time of the observed onset of LOR. Data points are distributed about the 95% isobole (10 above and 11 below). Model predictions were higher than the observed percentage of patients found to be unresponsive (Fig. 1B). Accuracy, bias, and root mean squared error analysis are presented in Table 3. The observed LOR occurred on average 2.4 ± 2.6 min after the model predicted a 50% probability of LOR (Fig. 1C).

Figure 2A presents the predicted concentration pairs at the observed return of responsiveness. The data points are distributed about the 50% isobole (14 above and 7 below). During emergence, the mean model probability of response was 60% ± 30% at the time patients responded. Model predictions were consistent with the observed percentage of patients found to be responsive (Fig. 2B). Accuracy, bias, and root mean squared error analysis are presented in Table 3. The observed return of responsiveness occurred on average 0.6 ± 5.1 min after the model predicted a 50% probability of LOR (Fig. 2C).

After surgery, one patient (subject 5) was observed to return to responsiveness 7 min before the model prediction. The predicted propofol and remifentanil effect-site concentrations for this subject (11.5 ng/mL and 2.0 mcg/mL, respectively) at the time of emergence (after surgery was completed) were substantially higher than most other patients. This patient was receiving chronic benzodiazepine therapy.

Laryngoscopy Interaction Model

The mean probability of no response to laryngoscopy was 89% ± 5%. Nine patients received rocuronium and 12 patients received succinylcholine. Figure 3 shows the concentration pairs at the time of tracheal intubation. One patient had a probability above the 95% isobole with the remainder between the 50% and 95% isoboles. Four patients responded to tracheal intubation with an increase in heart rate (20% above their heart rate just before tracheal intubation). For these responders, the probabilities of no response to laryngoscopy were 69%, 94%, 78%, and 92% (Table 4). With all four patients, the anesthesiologists did not deem the heart rate increase as clinically significant enough to warrant treatment. The patient receiving chronic benzodiazepine therapy was one of the responders.

Surrogates of Painful Stimuli Interaction Models

Figure 4 shows the concentration pairs when patients received their first dose of fentanyl to treat postoperative pain during the first 30 min after surgery. Four of the 21 patients did not require fentanyl during this time period. The mean probabilities of no response to pressure algometry at the time patients required additional fentanyl were 23% ± 35% and 9% ± 24% for the pressure algometry and electrical tetany models, respectively. For the pressure algometry model, 14 of the 17 patient assessments were below the 50% isobole. One patient was above the 95% isobole and was the patient receiving chronic benzodiazepine therapy. For the electrical tetany model, all of the patients were below the 50% isobole except, as with the pressure algometry model, the one patient receiving chronic benzodiazipine therapy which was above the 95% isobole.

DISCUSSION

The aim of this study was to explore how well remifentanil propofol interaction models developed in volunteers would predict selected drug effects in patients undergoing elective surgery. We hypothesized that these models would predict LOR and return of responsiveness and presence or absence of a response to painful stimuli. Our results in part confirmed these hypotheses.

LOR Interaction Model

During induction, observed LOR came after model predictions of LOR in all but 2 of the 21 observed LOR on average by 2 min (Fig. 1). Model performance during induction was fair (Table 3) with 10 of 21 patients requiring predicted remifentanil propofol levels above the 95% isobole to achieve LOR. Reasonable model performance would have been one to two subjects above the 95% isobole and 10 to 11 patients above the 50% isobole.

A reason why patients required higher drug levels than volunteers to achieve LOR may have been due to higher levels of anxiety for patients in the operating room along with an increase in tactile and verbal stimuli just before the induction, whereas volunteers received escalating doses of remifentanil and propofol over several hours to become comfortable with their surroundings and external stimuli. Increased anxiety can also increase cardiac output which alters initial drug distribution and drug behavior.[19,20]

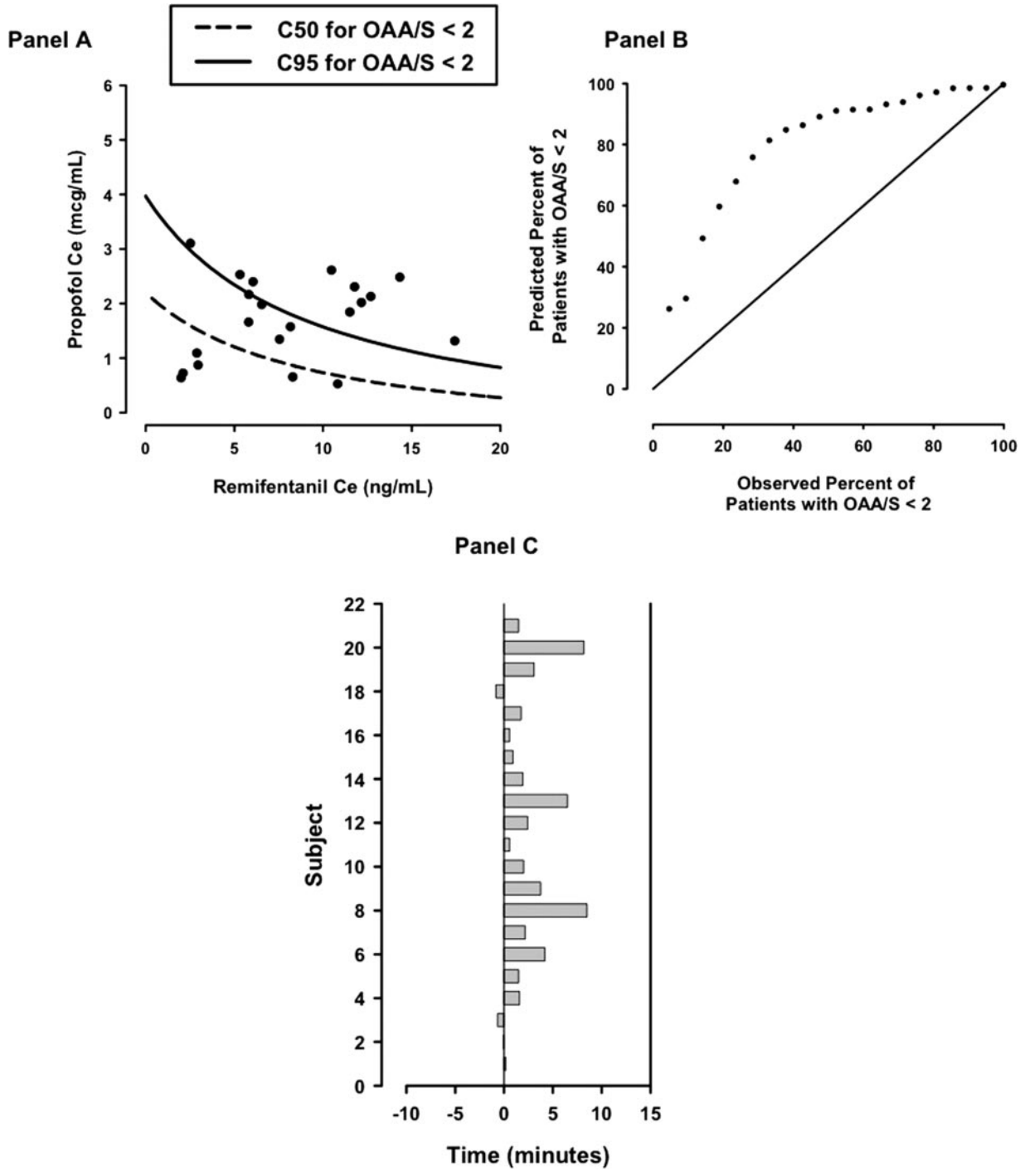

Figure 1. Loss of responsiveness (LOR) interaction model predictions during induction of anesthesia. Panel A presents the predicted remifentanil-propofol effect-site (C_e) concentrations at the onset of LOR. The solid and dashed lines represent the 50% and 95% probability of LOR, respectively. Panel B presents a comparison between model predictions to the percent of patients who had a LOR. Panel C presents the time between onset of LOR and model predictions of a 50% probability of LOR. The horizontal axis represents the time between the onset of observed and predicted LOR. Positive and negative numbers indicate that the predicted onset occurs before and after the observed onset of LOR, respectively. The vertical axis represents each subject.

Table 3. Accuracy, Bias, and Root Mean Squared (RMS) Error Analysis

Model	Accuracy	Bias	RMS
Loss of responsiveness (induction)	42.3%	42.3%	31.9%
Return of responsiveness (emergence)	15.7%	13.6%	9.3%

In contrast to induction, during emergence, model predictions were very similar to the observed return of responsiveness (Fig. 2). Model performance was good (Table 3) with a near-even spread of data above and below the 50% isobole (13 patients above and 8 below). Although the time differences between predictions and observations were small

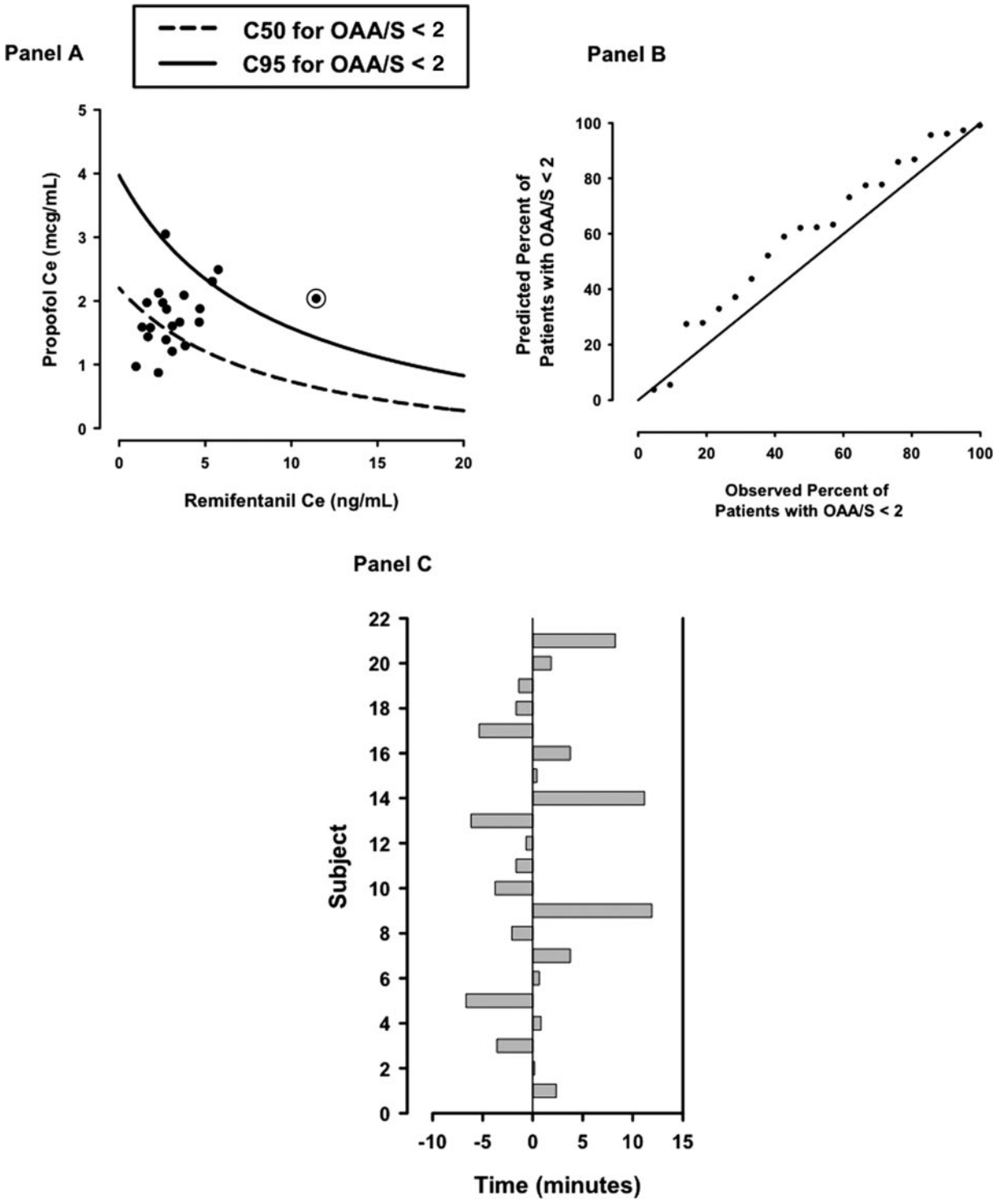

Figure 2. Loss of responsiveness (LOR) interaction model predictions during emergence from anesthesia. Panel A presents the predicted remifentanil-propofol effect-site (C_e) concentrations at the onset of return of responsiveness (ROR). The solid and dashed lines represent the 50% and 95% probability of LOR, respectively. Panel B presents a comparison between model predictions of the percent of patients that will have a ROR to the percent of patients that actually have a ROR. Panel C presents the time between onset of ROR and model predictions of a 50% probability of ROR. The horizontal axis represents the time between the onset of observed and predicted ROR. Positive and negative numbers indicate that the predicted onset of ROR occurs before and after the observed onset of ROR, respectively. The vertical axis represents each subject. The observed ROR for subject 5 was 7 min before model predicted ROR. This subject is identified in Panel A by a circle around the predicted remifentanil propofol C_es.

(on average, <1 min), the variance was much wider for the mean than during induction. This may have been a reflection of the wide variability in surgical stimulus (i.e., location and length of incision, extent of surgery, presence or absence of wound infiltration with local anesthetic, etc.). Model predictions

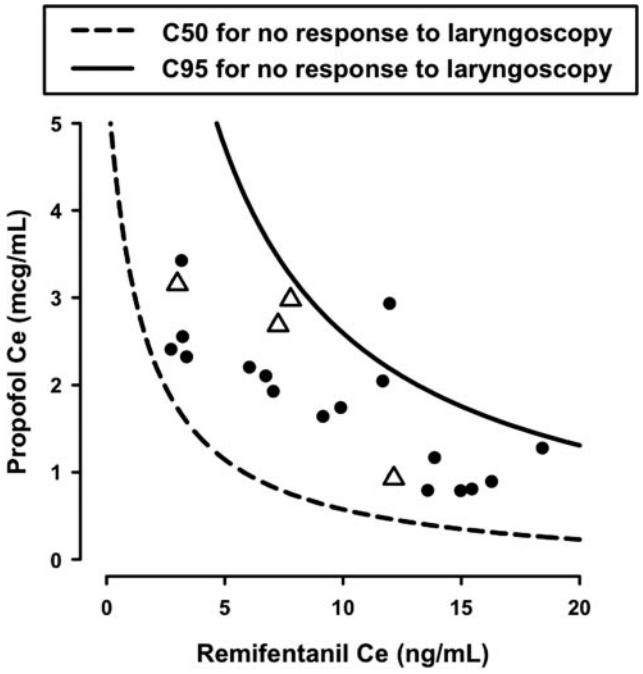

Figure 3. Predicted remifentanil-propofol effect-site concentration (C_e) pairs for each subject upon completion of tracheal intubation. Solid circles and open triangles represent patients with no response and a response to laryngoscopy and tracheal intubation, respectively. The solid and dashed lines represent the 50% and 95% probability of no response to laryngoscopy.

Table 4. Heart Rate Changes During Laryngoscopy

Subject	Baseline HR[a]	Peak HR[b] (absolute change)	% Change	Clinician response
4	80	98 (18)	23	None
5	56	68 (12)	21	None
17	62	87 (25)	40	None
19	72	96 (24)	33	None

Values within the parentheses represent the increase from baseline in beats per minute.
HR = heart rate.
[a] Heart rate just before stimulus.
[b] Peak heart rate within 1 min after the stimulus.

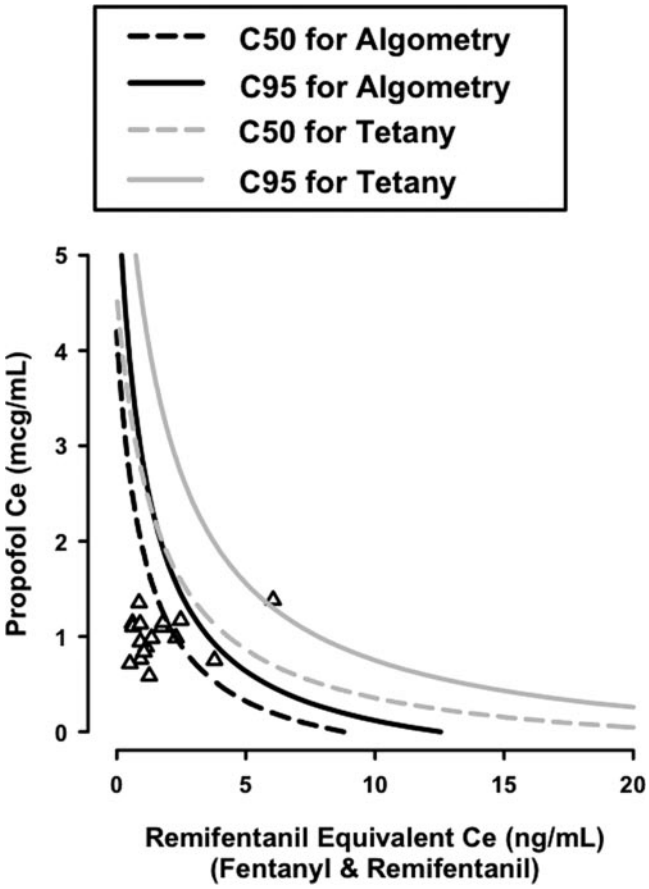

Figure 4. Predicted remifentanil-propofol effect-site concentration (C_e) pairs where additional fentanyl was administered during the first 30 min after surgery. The black and gray lines represent the probability of no response to pressure algometry and no response to electrical tetany, respectively. The solid and dashed lines represent the 50% and 95% isoboles, respectively.

were sensitive to opioid dosing (which was variable among practitioners) but was unable to account for the extent of surgical stimulus during emergence.

During emergence, one patient who had a Body Mass Index of 41 and had a history of chronic benzodiazepine use returned to responsiveness earlier than expected. The propofol pharmacokinetic model used did not account for variances in body size, but the remifentanil model did. The pharmacodynamic models did not compensate for chronic use of opioids and benzodiazepines because there are no such pharmacodynamic models. Future work is warranted to identify methods of scaling model parameters to account for chronic consumption of opioids and benzodiazepines.

A potential reason why our LOR model worked well during emergence, but not during induction, is a miss-specified biophase in either the propofol or remifentanil models. Biophase is frequently described in pharmacokinetic models using a k_{eo} parameter. We used a propofol pharmacokinetic set developed by Marsh et al.[11] with a k_{eo} parameter (k_{eo} = 0.51, t-peak = 2.7 min[21]) described from a time to peak effect approach described by Minto et al.[12] A miss-specified k_{eo} parameter would impact model performance during rapid changes in effect-site concentrations such as during induction as opposed to slower changes during emergence.

Laryngoscopy Interaction Model

The laryngoscopy model performed well over the limited range of the 50% and 95% isoboles that we were able to explore using patient responses. From the concentration pairs at the time of laryngoscopy, the model predicted that, on average, 89% of patients would not respond to laryngoscopy and 81% did not respond. Four patients developed at least a 20% increase in heart rate. The responses were transient requiring no additional anesthetic. The clinical implications of these heart rate changes are most likely inconsequential since none of the anesthesiologists treated the increased heart rate. These findings

suggest that the model may be too sensitive and detect responses that are, from a clinical standpoint, unimportant.

It is important to indicate that the laryngoscopy model was built from volunteer data in which only laryngoscopy was performed. In this study, the stimulus consisted of laryngoscopy and tracheal intubation. As presented by Mertens et al., in patients undergoing a remifentanil-propofol-based anesthetic, tracheal intubation was more stimulating than laryngoscopy. Higher remifentanil-propofol concentration pairs were required to blunt the response to tracheal intubation than to laryngoscopy alone.[3] Nevertheless, despite the apparent increase in stimulus, our model predictions were consistent with the observations.

Surrogates of Painful Stimuli Interaction Models

In this segment, the observed response (need for the first dose of fentanyl to treat postoperative pain) and the predicted response (a probability of response to 50 PSI of shin pressure algometry or 50 mA of electrical tetany) are not well matched. In our prior work, we found electrical tetany to be a more painful stimulus than pressure algometry requiring higher remifentanil propofol effect-site concentrations to blunt a response (Fig. 4). In this present analysis, we plotted remifentanil propofol effect-site concentrations at which patients requested analgesia on the electrical tetany and pressure algometry response surfaces to see if either model may have predictive utility. We found that, in the recovery room, predicted concentration pairs were for the most part below the 50% isobole for both models (Fig. 4). These results suggest that both models were of a stimulus more than that which is typically encountered in the recovery room.

A limitation to this segment of the study was a function of our experimental design. We studied patients enrolled in a variety of surgical procedures. Our intent was to evaluate the pressure algometry and electrical tetany response surface models over a wide range of postoperative stimuli. This approach, however, did not allow us to explore model performance for a specific surgical stimulus (i.e., predict supplemental analgesia needs for a laparoscopic cholecystectomy).

Limitations

The experimental design included a small dose of midazolam in order to mimic "standard-practice" and to help decrease patient anxiety before surgery. One potential confounder of this study is the effect of midazolam during induction and laryngoscopy. Each patient received a small midazolam bolus in the preoperative area about 10 min before the propofol and remifentanil infusions were started. Pharmacokinetic simulations predicted a peak effect-site concentration of 26 ± 5 ng/mL 9 min after the bolus. This predicted effect-site concentration is 9% ± 2% of the concentration necessary for an OAA/S score ≤3 and 7% ± 1% of the concentration required for apparent sleep.[8] Although midazolam may have an additive interaction with propofol, it may have a synergistic interaction with remifentanil. It is interesting to note that patients lost responsiveness substantially later than predicted, even with the addition of a small dose of midazolam.

Evaluating the ability of these response surface models to predict responsiveness in a patient population is limited with respect to the ability to explore a wide range of drug concentrations over the entire range of the surface. For example, anesthesiologists performed laryngoscopy when they felt the patient would be unresponsive and hence responders and nonresponders were observed at isoboles on the laryngoscopy response surface that were more than 75%. Thus, we can conclude little about the lower portions of this model. Similarly, clinicians directed anesthetic maintenance, which led to a "clustering" at return of responsiveness (Fig. 2A). Thus, although we were able to evaluate clinically interesting segments of the response surface, some portions of the LOR model were not evaluated (e.g., remifentanil effect-site concentrations more than 7 ng/mL).

Summary

The LOR model accurately predicted when patients would be unresponsive. However, it inaccurately predicted that patients would lose responsiveness earlier than observed during induction. This error is potentially due to a miss-specified biophase for either the remifentanil or propofol pharmacokinetic models. The laryngoscopy model predicted with high probability no response to laryngoscopy in all of the patients. Four patients, however, developed a small heart rate response. During emergence from anesthesia, the LOR model effectively predicted return of responsiveness. In recovery, surrogate models of surgical pain were compared with the administration of additional fentanyl for postoperative pain control. The pressure algometry model better described responses to pain experienced by this patient group in the recovery room than the electrical tetany model but both models of surrogate stimuli were most likely more intense than stimuli routinely encountered in the recovery room.

In conclusion, this preliminary assessment of a series of remifentanil-propofol interaction models demonstrated that these models predicted responses to selected pertinent events during elective surgery. However, significant model error is evident during rapid changes in predicted effect-site propofol-remifentanil concentration pairs.

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