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Response surface model predictions of emergence and response to pain in the recovery room: an evaluation of patients emerging from an isoflurane and fentanyl anesthetic

Noah D. Syroid, M.S.^{*,†}, Ken B. Johnson, M.D.^{*,†}, Nathan L. Pace, M.D. MStat^{*}, Dwayne R. Westenskow, Ph.D.^{*,†}, Diane Tyler, R.N.^{*}, Frederike Brühshwein, B.S.^{*}, Robert W. Albert, M.S.[†], Shelly Roalstad, M.S.^{*}, Samuel Costy-Bennett, B.A.[†], and Talmage D. Egan, M.D.^{*,†}

^{*}Departments of Anesthesiology and Biomedical Engineering, University of Utah, Salt Lake City, Utah, United States.

[†]Applied Medical Visualizations, L.L.C., Salt Lake City, Utah, United States

Abstract

Introduction—Sevoflurane - remifentanyl interaction models that predict responsiveness and response to painful stimuli have been evaluated in patients undergoing elective surgery. Preliminary evaluations of model predictions were found to be consistent with observations in patients anesthetized with sevoflurane, remifentanyl and fentanyl. The present study explored the feasibility of adapting the predictions of sevoflurane-remifentanyl interaction models to an isoflurane-fentanyl anesthetic. We hypothesized that model predictions adapted for isoflurane and fentanyl are consistent with observed patient responses and are similar to the predictions observed in our prior work with sevoflurane-remifentanyl/fentanyl anesthetics.

Methods—Twenty-five patients scheduled for elective surgery received a fentanyl-isoflurane anesthetic. Model predictions of unresponsiveness were recorded at emergence and predictions of a response to noxious stimulus were recorded when patients first required analgesics in the recovery room. Model predictions were compared to observations with graphical and temporal analyses. Results were also compared to our prior predictions following a sevoflurane-remifentanyl/fentanyl anesthetic.

Results—While patients were anesthetized, model predictions indicated a high likelihood that patients would be unresponsive ($\geq 99\%$). Following termination of the anesthetic, model predictions of responsiveness well described the actual fraction of patients observed to be responsive during emergence. Half of the patients awoke within 2 minutes of the 50% model predicted probability of unresponsiveness; 70% awoke within 4 minutes. Similarly, predictions of a response to a noxious stimulus were consistent with the number of patients who required fentanyl in the recovery room. Model predictions following an isoflurane-fentanyl anesthetic were similar to model predictions following a sevoflurane-remifentanyl/fentanyl anesthetic.

Corresponding Author: Noah Syroid, M.S., Department of Anesthesiology, University of Utah, 30 North, 1900 East, Room 3C444, Salt Lake City, Utah, 84132-2304, Phone: (801) 587-4825, FAX: (801) 581-4367, Email: Noah.Syroid@hsc.utah.edu.

Conflict of Interest: Noah D. Syroid, Ken B. Johnson, Talmage D. Egan, Dwayne R. Westenskow, Robert W. Albert, and Samuel Costy-Bennett either hold equity positions and/or receive salary/consulting fees from Applied Medical Visualizations L.L.C., a medical device development company which has a vested interest in the outcome of this study.

Implication Statement: We adapted a set of sevoflurane-remifentanyl interaction models that predict loss of responsiveness and a lack of response to 30 PSI of tibial pressure to isoflurane and fentanyl using relative potencies for opioids and potent inhaled agents. We hypothesized that observations of responses in anesthetized patients are consistent with the model predictions.

Discussion—Results confirmed our study hypothesis; model predictions for unresponsiveness and no response to painful stimuli, adapted to isoflurane-fentanyl, were consistent with observations. These results were similar to our prior study comparing model predictions and patient observations following a sevoflurane-remifentanyl/fentanyl anesthetic.

INTRODUCTION

Drug interaction models for remifentanyl and sevoflurane have been previously developed from data collected in volunteers.(1,2) A moderate synergistic interaction was observed for the model that predicts the probability of unresponsiveness, and a mild synergistic interaction was observed for the model that predicts the probability of a lack of response to noxious stimulus. We previously reported that model predictions in patients undergoing elective surgery were consistent with empirical observations for a sevoflurane, remifentanyl, and fentanyl anesthetic technique.(1)

The aim of this study is to evaluate the predictions of remifentanyl-sevoflurane models for patients' return of responsiveness (ROR) and a response to painful stimuli after an isoflurane and fentanyl anesthetic. The fentanyl to remifentanyl relative potency relationship is well established, as is the isoflurane and sevoflurane potency.(3–8) We hypothesized that these interaction models, adapted for isoflurane and fentanyl, have predictions of emergence from anesthesia and the initial need for fentanyl during postoperative recovery that are consistent with observed patient responses. We also hypothesized that isoflurane-fentanyl predictions have similar predictive behavior to our previously reported sevoflurane-remifentanyl model predictions.

METHODS

Study Protocol

After Institutional Review Board approval at the University of Utah, informed consent was obtained from twenty-five patients (8 male, 17 female) presenting for elective abdominal, gynecologic, or extremity surgeries. Patients with a history of ongoing opioid consumption were excluded. Age, weight, and height were recorded for each patient.

Experimental Protocol

Fentanyl 0.33 µg/kg was administered intravenously in the preoperative holding area. Induction consisted of starting constant infusions of fentanyl preselected from the range of 0.25 to 0.51 mcg/kg/min and propofol preselected from the range of 137–383 mcg/kg/min. Following loss of responsiveness, patients received either rocuronium (0.6 mg/kg) or succinylcholine (1.5 mg/kg). The attending anesthesiologist decided when it was appropriate to intubate the patient's trachea, and the propofol and fentanyl infusions were terminated after verification of successful tracheal intubation. Anesthesia was maintained with fentanyl and isoflurane in oxygen and air, both titrated at the anesthesiologist's discretion. Subcutaneous injection of local anesthetic was administered at the wound site, at the surgical team's discretion.

During emergence from anesthesia, each patient's level of responsiveness was assessed using the unmodified observer's assessment of alertness/sedation (OAA/S) score every 20 seconds by calling out their first name and asking, "Can you open your eyes?"(9) If eye opening did not occur, the question was repeated using a louder voice. If still unresponsive, the question was asked a third time with mild prodding of the patient's shoulder for 2 seconds. Assessments began when the isoflurane vaporizer was turned off. They ended

when the patient regained responsiveness, where the observed ROR was defined as the first of two consecutive OAA/S scores > 1.

Patients were observed in the recovery room for 30 minutes. Every five minutes patient were asked to use the visual analog scale (VAS) to report the current pain score and the pain score that was considered tolerable. Fentanyl was administered in 0.5 to 1 mcg/kg increments when the current VAS exceeded the tolerable VAS, and the recovery room nursing staff considered it appropriate (i.e. lack of excessive sedation or respiratory depression).

Time-stamped details of drug administration, surgical events, and patient responses were recorded using custom data collection software (C++ Builder 6.0, Borland Software Corporation, Austin, TX). Vital signs and end-tidal concentrations of isoflurane were collected at five second intervals using commercially available software (S/S Collect, Datex, Helsinki, Finland).

Pharmacokinetic Simulation

Fentanyl effect-site concentrations were calculated at the time of each patient's ROR and just prior to the first administration of fentanyl during postoperative recovery. Time-stamped data files of drug administration (with a resolution of 5 seconds) were used to predict weight adjusted fentanyl effect-site concentrations.(10,11) Fentanyl effect-site concentrations were converted to equivalent remifentanyl effect-site concentrations using a relative potency of remifentanyl to fentanyl = 1:1.2.(5–8)

A modified multi-compartment pharmacokinetic model used end-tidal concentration measurements (recorded at 5 second intervals) to predict isoflurane effect-site concentrations.(12,13) The isoflurane effect-site concentration is defined as the brain tissue concentration scaled to the end-tidal value. That is, the brain tissue concentration divided by the product of the blood-brain (2.4) and blood-gas (1.5) isoflurane partition coefficients. (1,13) Isoflurane effect-site concentrations were converted to equivalent sevoflurane effect-site concentrations using a potency equivalence of sevoflurane to isoflurane = 1:1.8 that is based upon the minimum alveolar concentration (MAC) and MAC_{awake} concentrations for 30–50 year old patients.(3,4) A pharmacokinetic model was used to estimate residual propofol effect-site concentrations at the time of ROR.(14)

Response Surface Models

Two previously developed Greco sevoflurane and remifentanyl interaction models were used to calculate two probabilities: (1) the probability that OAA/S = 1 (defined as no response to loud repeated verbal stimulus and mild prodding or shaking) and (2) the probability of a lack of response to 30 pounds per square inch (PSI) or 207 pascals of anterior tibial pressure. (1,15) Model parameters of the response surface models are presented in Table 1, used with the following equation:

$$Effect = \frac{E_{\max} \cdot \left[\frac{C_{er}}{C_{50r}} + \frac{C_{es}}{C_{50s}} + \alpha \cdot \left(\frac{C_{er}}{C_{50r}} \cdot \frac{C_{ep}}{C_{50s}} \right) \right]^n}{\left[\frac{C_{er}}{C_{50r}} + \frac{C_{es}}{C_{50s}} + \alpha \cdot \left(\frac{C_{er}}{C_{50r}} \cdot \frac{C_{es}}{C_{50s}} \right) \right]^n + 1}$$

$E_{\max}$ is the maximal effect, C_{50s} (sevoflurane) and C_{50r} (remifentanyl) are the concentrations that produce 50% of the maximal effect when administered individually, n dictates the slope of the response surface, and α is the interaction parameter between sevoflurane and remifentanyl. Effect ranged from 0 (0% probability of no response) to $E_{\max} = 1$ (100%

probability of no response). The model predicted probability of OAA/S = 1 was calculated once the anesthetic was terminated until ten minutes after the time of each patient's ROR. The probability of no response to 30 PSI algometry was calculated at the time just prior to when the first bolus of fentanyl was administered in the recovery room.

Data Analysis

Observed changes in responsiveness during emergence from anesthesia and the need for fentanyl in the recovery room were compared to the model predictions using the following analyses:

1. Graphical analysis—Predictions from each model were compared graphically on two plots: a plot of model prediction over time and a plot of the remifentanyl equivalent effect-site concentrations and isoflurane MAC-awake values at the time of emergence superimposed on the topographical representation of the unresponsiveness response surface model. The topographical plot included the 5%, 50%, and 95% isoboles (iso-effect lines).

2. Empirical Cumulative Distribution—(16) The model predicted probability for OAA/S = 1 was calculated for each patient at the time of observed ROR, and the model predicted probability of a lack of response to 30 PSI of anterior tibial pressure was calculated just prior to the first fentanyl administration in the recovery room. The model predictions at the transition time from unresponsive to responsive for each patient were sorted from lowest to highest. A percentage value was assigned to each patient as the fraction of all patients according to the observed probability at the transition time. The patient population percentage was plotted versus the sorted model predictions.

3. Temporal Analysis—The time from the 50% model predicted probability of unresponsiveness to the time of the observed return of responsiveness was calculated for all patients and reported as mean $\pm$ standard deviation. A negative, zero or positive time difference indicates that the observed return of responsiveness occurred prior to, exactly at, or after the 50% probability of unresponsiveness.

4. Comparison of model predictions—Model predictions from this study were compared to our previously observed model predictions in patients with a sevoflurane-remifentanyl/fentanyl anesthetic, which employed a nearly identical experimental protocol. (1) Mean model predictions recorded at the ROR (OAA/S > 1) and at the first dosing of fentanyl in the recovery room for the isoflurane-fentanyl and the sevoflurane-remifentanyl/fentanyl models were compared with an unpaired two-tailed t-test. Similarly, time differences for each anesthetic technique were compared with an unpaired two-tailed t-test.

Graphical comparisons were made by plotting the patients' observed ROR along with the response surface model predictions of unresponsiveness from both studies. Similar comparisons were made for predictions of a lack of response to 30 PSI of anterior tibial pressure at the first dose of fentanyl in the recovery room. Data from both studies are also presented on the empirical cumulative distribution plots.

RESULTS

All 25 patients completed the study. Their American Society of Anesthesiologists Physical Status (PS) classification ranged from I to II. The demographics and surgical procedures are summarized in Table 2. Fifteen different surgeons and 13 different anesthesiologists participated in the study. All patients underwent tracheal intubation prior to surgery. Estimated blood loss ranged from 0 to 2.5 mL/kg. After recovery none of the patients

reported recalling any portion of the general anesthetic from the administration of induction agents to ROR.

Return of Responsiveness

Figure 1 depicts the model's prediction of the probability of unresponsiveness for each patient during emergence from an isoflurane-fentanyl anesthetic. Differences in model-predicted probabilities of unresponsiveness at the time of ROR for the isoflurane-fentanyl and sevoflurane-remifentanyl/fentanyl combinations were not different ($p = 0.35$, Table 3).

The average effect-site concentrations at the time of ROR were $0.31 \text{ vol}\% \pm 0.13 \text{ vol}\%$ ($= 0.88 \pm 0.37 \text{ MAC}_{\text{awake}}$) for isoflurane, $1.59 \pm 0.63 \text{ ng/ml}$ for fentanyl, and $0.10 \pm 0.09 \text{ }\mu\text{g/ml}$ for propofol. Figure 2 shows the isoflurane and fentanyl effect-site concentration pairs for each patient at the time of ROR, plotted in conjunction with isoboles of the previously developed OAA/S = 1 response surface model. Effect-site concentration pairs for isoflurane and fentanyl were nearly equally distributed about the 50% model prediction, with 11 above and 14 below.

The concentration pairs were dissimilar in spatial distribution for the two anesthetics, with a greater contribution of the inhaled agent and smaller contribution of the opioid to drug effect when compared to the sevoflurane - remifentanyl/fentanyl data set. Figure 3 shows the empirical cumulative distribution plot for the model predictions of OAA/S = 1 and the observed percentage of patients that were unresponsive.

The time difference between the 50% model prediction of unresponsiveness and observed emergence are presented in Figure 4, and were not statistically different between the isoflurane - fentanyl and sevoflurane - remifentanyl/fentanyl anesthetics. There were no differences between the two anesthetic techniques with respect to the average time from the termination of the anesthetic until patient's emerged from anesthesia (Table 3).

Postoperative Recovery

Eighteen of twenty-five patients received at least one dose of fentanyl during their recovery room stay. Table 3 summarizes the results, comparing the patient observations and the model predictions just prior to the first dose of fentanyl given during postoperative recovery. When comparing the two studies, isoflurane - fentanyl model predictions were significantly lower than sevoflurane - remifentanyl/fentanyl model predictions ($p < 0.05$). The average effect-site concentrations were $0.03 \pm 0.03 \text{ vol}\%$ for isoflurane ($= 0.03 \pm 0.03 \text{ MAC}$) and $1.2 \pm 0.6 \text{ ng/ml}$ for fentanyl ($1.4 \pm 0.7 \text{ ng/ml}$ remifentanyl equivalent concentration). The average amount of fentanyl administered during the first 30 minutes in the recovery room was $93 \pm 83 \text{ mcg}$ for isoflurane - fentanyl, compared to $180 \pm 180 \text{ mcg}$ for sevoflurane - remifentanyl/fentanyl.

Figure 5 shows the isoflurane and fentanyl effect-site concentration pairs for each patient, plotted in conjunction with the previously developed model (probability of no response to 30 PSI of anterior tibial pressure). Twelve concentration pairs of isoflurane and fentanyl were below and six were above the 50% model prediction. When comparing the two anesthetic techniques, there was dissimilarity in spatial distribution appearing in the higher concentration of inhaled agent for the isoflurane - fentanyl study and higher concentration of opioid for the sevoflurane - remifentanyl/fentanyl study. Figure 6 shows the empirical cumulative distribution function for the model predictions of lack of response to tibial pressure and the observed percentage of patients that did not require fentanyl in the recovery room.

DISCUSSION

We adapted our previously described synergistic interaction models of selected drug effects for sevoflurane and remifentanyl to isoflurane and fentanyl using published opioid and volatile anesthetic MAC equivalency relationships. In this preliminary evaluation, we hypothesized that the adapted model predictions of ROR and a response to painful stimuli would be consistent with the time of emergence and the need for additional analgesia in the recovery room in patients that had received an isoflurane - fentanyl anesthetic.

The isoflurane - fentanyl model predictions of unresponsiveness were generally consistent with clinical observations. The models performed as expected; the distribution of model predictions was nearly centered about 50%, and few patients were responsive at high model predicted probabilities of unresponsiveness (and vice-versa). However, due to the small sample size, it is unclear how well model predictions discriminate between the patients' unresponsive and responsive states. With a larger data sample, other statistical methods might have provided a better estimate of model discrimination and calibration.

Patients opened their eyes on average within one minute of the model prediction probability of unresponsiveness of 50%. Just before terminating the anesthetic, the model predicted high probabilities of patient unresponsiveness, which were consistent with observations. Once the anesthetic was terminated, model predictions rapidly decreased, and patients emerged from anesthesia over a wide range of model predictions. Although more than 70% of patients awoke within ± 4 minutes of the 50% model prediction, the overall distribution of the time differences was large.

Model predictions of no response to tibial pressure at the first dose of fentanyl during postoperative recovery were generally consistent with observations. For the majority of patients who needed additional fentanyl, the model predicted probability of no response to 30 PSI of tibial pressure was less than 50%. In our prior study, we found that 50 PSI was too strong a stimulus when compared to stimuli typically encountered in the recovery room.(17) The results observed in this study may indicate that 30 PSI tibial pressure is a more appropriate surrogate but continues to be a stronger stimulus in comparison to the level of postoperative pain. Although these results are encouraging, they are difficult to interpret given that we evaluated only a small sample of patients that underwent various procedures associated with different degrees of postoperative pain.

We also hypothesized that the adapted isoflurane-fentanyl models would have similar predictive behavior to our previously reported sevoflurane-remifentanyl/fentanyl model predictions. With regard to ROR, mean model predicted probabilities of unresponsiveness were similar between isoflurane-fentanyl and sevoflurane-remifentanyl (43% versus 53%) as were the distribution of predictions (Figure 2 and Figure 3). We observed no statistical difference between models although the mean difference in predictions was 10%. This may be a function of large standard deviations and small sample sizes for both sets of predictions. Although this finding supports our study hypothesis, caution should be used in interpreting its absence of statistical significance.

In terms of temporal analysis, patients became responsive on average only 1 minute after both the sevoflurane-remifentanyl and isoflurane-fentanyl models predicted a 50% probability of unresponsiveness, but the variance in time differences for both models was large (Table 3). Although the temporal analysis results are similar for both models, the ability for each model to discriminate between responsive and unresponsive patients is limited to time intervals of approximately 5 minutes. Of note, the six longest time differences presented in Figure 4, ranging from 7.3 to 14.6 minutes were associated with older patients. These patients had an average age of 52 ± 18 years whereas the remaining 39

patients had an average age of 44 ± 14 years. The response surface models were developed in young volunteers (25 ± 4 years). (2) The predicted remifentanyl effect-site concentrations were age adjusted; however, the predicted fentanyl and inhalation agent effect-site concentrations were not. An age covariate for both pharmacokinetic and response surface models may improve model predictions.

With regard to model predictions of a response to painful stimuli in the recovery room, the isoflurane-fentanyl and sevoflurane-remifentanyl/fentanyl model predictions behaved differently. Although the distributions of predicted lack of response to a painful stimulus were wide for both models (Table 3), the mean difference of 42% between model predictions was statistically significant. Because the predicted isoflurane and sevoflurane effect-site concentrations were very low, the response surface models essentially collapsed to single drug pharmacodynamic models of opioid effect. The main difference between model predictions was that in the sevoflurane-remifentanyl/fentanyl model had higher predicted remifentanyl equivalent levels when patients requested additional analgesia (Figure 5). This may have been due to the high dose remifentanyl infusions patients received during surgery which have been known to produce transient hyperalgesic states. (18–21) This was also consistent with the almost doubling in the average amount of fentanyl required by patients that receive a sevoflurane-remifentanyl/fentanyl anesthetic versus the isoflurane-fentanyl anesthetic. Our models do not account for this phenomenon leading to model predictions that may have overestimated the analgesic effect.

There was a residual amount of propofol at ROR that was not accounted for by model predictions but likely played a minimal role in confounding the results. The contribution of propofol concentrations (0.08 ± 0.10 mcg/ml) to predict loss of responsiveness was $0.1 \pm 0.5\%$. (17) In addition, a small dose of midazolam (12.5 mcg/ml) was given as premedication prior to the sevoflurane-remifentanyl/fentanyl anesthetic, but likely had minimal contribution to effect at end of the anesthetic. (1)

When choosing appropriate volatile agent potency ratios to adapt the sevoflurane portion of the response surface model to isoflurane, there are several studies that report MAC and MAC_{awake} values over a range of patient ages. (3) For example, in the age range of 30–50 years old, MAC ranges from 1.58% to 2.05% for sevoflurane (5,22–27) and 1.15% to 1.21% for isoflurane, (7,28,29) resulting in a potency range for sevoflurane/isoflurane = 1.3 to 1.8. MAC_{awake}, ranges from 0.61% to 0.70% for sevoflurane (5,26,30) and 0.36% to 0.41% for isoflurane, (30–32) resulting in a potency range of 1.5 to 1.9. For purposes of this analysis, we chose a potency ratio of 1.8, which overlapped the potency ranges based on both MAC and MAC_{awake}. A different choice of potency ratio may alter the study's results.

In summary, pharmacokinetic models in combination with proportional relationships for inhalation agents and opioids were used to adapt previously developed response surface pharmacodynamic models. We generally observed similar model prediction behavior between the isoflurane-fentanyl and sevoflurane-remifentanyl/fentanyl models; more so with the models of unresponsiveness than the models of response to a painful stimulus. The results are encouraging that one may be able to generalize the response surface models to a variety of inhalation agent-opioid combinations, given simple relative potency relationships.

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Figure 1.

Model predictions of responsiveness during patient emergence from an isoflurane-fentanyl anesthetic. The solid black lines show the time course of model predictions of loss of responsiveness. The x axis represents the time range 10 minutes before and after emergence. The gray vertical line represents the time of patients' return of responsiveness (ROR). The gray horizontal line represents the 50% model probability of non-responsiveness.

Figure 2.

Drug effect-site concentration pairs at the time of emergence are presented in terms of MAC_{awake} for the inhaled agents and remifentanyl equivalents for opioids for each of the 25 patients. The concentration pairs are shown in context with three probabilities from the loss of responsiveness (probability OAA/S = 1) response surface model that was previously developed in a laboratory setting with human volunteers:(1,2) the dashed gray line is the 95% model predicted probability, the solid black line is the 50% model predicted probability, and the solid gray line is the 5% model predicted probability. Black dots represent isoflurane-fentanyl, and gray triangles represent our previously reported sevoflurane – remifentanyl/fentanyl results.(1)

Figure 3. The empirical cumulative distribution plot of model predictions at patients' return of responsiveness for isoflurane – fentanyl (black dots), sevoflurane – remifentanyl/fentanyl (gray triangles) models respectively. The gray diagonal dashed line is the line of identity.

Figure 4.

Time from the 50% model predicted probability of unresponsiveness to the time of the observed return of responsiveness for the isoflurane - fentanyl anesthetic in black and sevoflurane - remifentanyl/fentanyl anesthetic in gray. After termination of the anesthetic, the model predicted probability of unresponsiveness rapidly decreased over time. A negative, zero or positive number on the horizontal axis indicates that the observed return of responsiveness occurred prior to, exactly at, or after the 50% probability of unresponsiveness. The vertical axis represents each patient, sorted from shortest (top) to longest (bottom) absolute time differences.

Figure 5.

The concentration pairs just prior to when patients required a first administration of fentanyl during postoperative recovery are presented in terms of MAC for the inhaled agents and remifentanyl equivalents for opioids (18 of 25 patients needed fentanyl during postoperative recovery). The concentration pairs are shown in context with three probabilities from the pressure algometry (probability of no response to 30 PSI of anterior tibial pressure) response surface model, previously developed in a laboratory setting with human volunteers.(1,2) The dashed gray line is the 95% model predicted probability, the solid black line is the 50% model predicted probability, and the solid gray line is the 5% model predicted probability. Black dots represent isoflurane – fentanyl concentration pairs, and gray triangles represent the previously reported sevoflurane – remifentanyl/fentanyl concentration pairs.(1)

Figure 6.

The empirical cumulative distribution plot for isoflurane – fentanyl (black dots) and sevoflurane – remifentanyl/fentanyl (gray triangles) just prior to when patients required a first administration of fentanyl during postoperative recovery with respect to the pressure algometry (probability of no response to 30 PSI of anterior tibial pressure) response surface model probability. The gray diagonal dashed line is 100% - the line of identity.

Table 1

Response surface model parameters for the previously developed loss of responsiveness and probability of no response to 30 PSI of anterior tibial pressure (pressure algometry) for sevoflurane and remifentanyl using a Greco model structure.(1) The model parameters were used to evaluate isoflurane and fentanyl anesthetics by using known inhalation agent and opioid equivalencies to convert isoflurane and fentanyl effect-site concentrations to their sevoflurane and remifentanyl equivalent counterparts. OAA/S indicates Observers Assessment of Alertness and Sedation.(9)

Measure-Surrogate	C _{50 remi} (ng/ml)	C _{50 sevo}	alpha	n
Loss of Responsiveness	50.9	0.74	9.39	5.24
Pressure Algometry (30 PSI)	1.27	0.83	0.91	2.71

Table 2

Patient demographics and surgery statistics.

Weight (kg)	Height (cm)	BMI (kg/m ²)	Age (years)	# male	# female	# abdominal and gynecological cases	# extremity cases	Surgical Duration (range) (min)
79.9 ± 24.0	169 ± 10	27.9 ± 6.2	44 ± 14	8	17	5 laparoscopic 3 open 6 gynecological	11	97 ± 39 (24–198)

Table 3

Comparison of model predictions at the observed return of responsiveness (ROR) and when patients required first dose of fentanyl in the recovery room. Data are expressed as the mean $\pm$ standard deviation. ISO/FENT indicates isoflurane-fentanyl anesthetics. SEVO/REMI indicates sevoflurane-remifentanyl/fentanyl anesthetic. OAA/S indicates Observers Assessment of Alertness and Sedation,(9)

Probability of Unresponsiveness (OAA/S = 1) at ROR		
	ISO/FENT	SEVO/REMI
Time from vaporizer turned off to ROR	6.2 $\pm$ 4.1 min.	5.3 $\pm$ 6.1 min.
Time from probability unresponsiveness = 50% to time of observed ROR	1.1 $\pm$ 3.8 min.	0.9 $\pm$ 4.3 min.
Model Predictions at		
Observed ROR	42.8 $\pm$ 32.1%	52.6 $\pm$ 37.5%
5th percentile of patients	1.1%	0.4%
50th percentile of patients	40.0%	66.6%
95th percentile of patients	92.9%	93.0%
Probability of No Response to 30 PSI of Anterior Tibial Pressure at 1st dose Fentanyl given in the recovery room		
	ISO/FENT	SEVO/REMI
Opioid effect-site concentration (remifentanyl equivalents)	1.0 $\pm$ 0.5 ng/mL	1.9 $\pm$ 1.3 ng/mL
Model Predictions at		
1 st dose of fentanyl	38.2 $\pm$ 23.8%	61.0 $\pm$ 30.1%
5th percentile of patients	7.9%	9.3%
50th percentile of patients	39.6%	61.3%
95th percentile of patients	71.1%	96.8%