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Validation of remifentanil propofol response surfaces for sedation, surrogates of surgical stimulus, and laryngoscopy in patients undergoing surgery

Ken B Johnson, M.D., Noah D. Syroid, M.S., Dhanesh K. Gupta, M.D., Sandeep Manyam, B.S., Talmage D. Egan, M.D., Jeremy Huntington, B.S., Julia L. White, R.N., Diane Tyler, R.N., and Dwayne K. Westenskow, Ph.D.

Departments of Anesthesiology and Biomedical Engineering, University of Utah, Salt Lake City, Utah, United States.

INTRODUCTION

Recent work in our laboratory has characterized the synergistic interaction between remifentanil and propofol in volunteers using surrogate and actual measures of sedation and analgesia[1]. In this prior study, a wide range of remifentanil and propofol effect site concentrations were achieved using target controlled infusions. Metrics of sedation (the Observers Assessment of Alertness/Sedation scale – OAA/S scale[2]) and analgesia (response to tetanic stimuli, pressure algometry, and laryngoscopy) were made at numerous remifentanil/propofol effect site concentration pairs with the intent of characterizing the synergistic relationship between these two intravenous anesthetics.

From this data, using a response surface approach [3], interaction models were developed to predict the probability of loss of responsiveness and loss of response to tetanic stimuli, pressure algometry, and laryngoscopy. Electrical tetany consisted of applying a small current through electrodes over the posterior tibial nerve until subjects considered the pain intolerable up to 50 mA and pressure algometry consisted of 1 cm diameter piston that applied pressure to the anterior aspect of the mid shaft of the tibia until subjects considered the pain intolerable up to 50 lb-in⁻² [4]. As has been reported by other authors [5,6], results from this analysis revealed significant synergism between remifentanil and propofol for both sedation and analgesia. Specifically, the co-administration of remifentanil with propofol led to a more pronounced sedating effect at lower concentrations of propofol than with propofol alone. Similarly, the co-administration of propofol with remifentanil led to a more pronounced analgesic effect at lower remifentanil concentrations than with remifentanil alone.

The aim of this present work is to explore how well these interaction models developed from human subject volunteers would predict pertinent events of anesthetic care in patients undergoing elective surgery. An assessment of loss of responsiveness and the presence or absence of a response to laryngoscopy are easily observed in patients undergoing elective

Corresponding Author: Ken B. Johnson, M.D., Associate Professor, Learned Family Associate Professorship, Department of Anesthesiology, University of Utah, 30 North, 1900 East, Room 3C444, Salt Lake City, Utah 84132-2304, Phone: (801) 205-1039, FAX: (801) 581-4367, Email: ken.b.johnson@hsc.utah.edu.

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surgery. By contrast, interaction model predictions of a response to electrical tetany and pressure algometry, as surrogates of surgical pain, are more difficult to interpret clinically[1]. Of note, in our prior work, pressure algometry was found to be significantly less stimulating than electrical tetany. For example, the remifentanyl effect site concentrations at which 50% of the volunteers did not respond to maximal settings for pressure algometry and electrical tetany were 8.8 and 21.3 ng/mL respectively. Some investigators have suggested that electrical tetany is a surrogate stimulus to skin incision [7].

In this present study, we intended to explore how model predictions of no response to 50 lb-in⁻² of pressure algometry and 50 mA of electrical tetany compared to the observed response of selected stimulating events during elective surgery to include skin incision, surgical stimulus 5 minutes after skin incision, at the start of wound closure, at the start of skin closure, and requirement for administration of analgesics in the post anesthesia care unit.

One metric of anesthetic behavior that was not characterized by an interaction model in our prior work was a prediction of loss of responsiveness. In our prior work, we used a transition from an OAA/S score of 4 to 3 to represent the onset of sedation. [1] Of equal, or perhaps, even more interest to an anesthetist, is a prediction of the onset and offset of responsiveness during the delivery of an anesthetic. With this in mind, we developed an additional interaction model that characterized the transition from an OAA/S score from 2 to 1.

Our hypotheses were that these set of response surface models would predict with high probability (i) loss and return of responsiveness, (ii) the presence or absence of a response to laryngoscopy and tracheal intubation, and (iii) the presence or absence of a no response to skin incision, wound closure, and painful stimuli in the post anesthesia care unit.

METHODS

Patient Selection

After Internal Review Board approval at the University of Utah, potential subjects were recruited from patients presenting for elective surgery at the University of Utah Health Sciences Center where a general anesthetic would be appropriate. An equal number of male and female potential subjects were solicited to participate in the study. Patients with a history of opioid consumption were excluded because of likely tolerance to the opioids administered during the experimental protocol making their response different from the general population. Baseline blood pressure and heart rate, gender, age, weight, height and surgical procedure were recorded for each patient enrolled in the study.

Computer Simulations to Identify Dosing

In our prior work, using target controlled infusions, levels of sedation and analgesia were evaluated over wide ranges of effect site concentrations for remifentanyl (0 to 80 ng/mL) and propofol (0 to 12 mcg/mL)[1]. Using a response surface model approach described by Greco *et. al.* [8], interaction models were constructed that estimated the synergistic interaction and the slope of the response surface. The interaction models are represented by the following relation:

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

C_r and C_p represent the effect site concentrations for remifentanyl and propofol respectively. E_{max} is the maximal effect of propofol and remifentanyl for a given effect measure (i.e. no response to laryngoscopy). The C_{50p} and C_{50r} represent the effect site concentrations for each drug 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 a unique parameter that characterizes the nature and extent of interaction between propofol and remifentanyl for a given drug effect. Model parameters estimated for each of the effect measures in our prior study are presented in Table 1.

Using OAA/S data collected in our prior work, an interaction model for loss of responsiveness was developed. The probability of loss of responsiveness was assigned a value of 1 if the subject's OAA/S score was 1 and 0 if the OAA/S score was 2, 3, 4, or 5. As previously described, remifentanyl and propofol concentration pairs were used to fit a three dimension response surface using a naïve pooled technique [9]. Using modeling software (Matlab, Mathworks, Natick, MA), this binary data of OAA/S was fit to a Greco model adjusted for categorical data [10] to estimate model parameters. Nonlinear regression analysis of the concentration-response data [11] revealed that the interaction model was able to fit to the loss of responsiveness data with an r^2 value of 0.82. The regression coefficient of the interaction term (α) was 3.6 indicating a strong degree of synergistic interaction between remifentanyl and propofol. Model parameters for loss of responsiveness are also presented in Table 1.

One unique feature of the interaction models is that they allow identification of an infinite number of effect site concentration combinations of propofol and remifentanyl that can produce the same level of effect. Equivalent effects over a range of possible drug pair combinations on the response surface are called an isobole. Prior to taking the patient to the operating room, a set of pharmacokinetic simulations were performed to identify the induction infusion rates for propofol and remifentanyl that would result in a 95% probability of loss of response to laryngoscopy. To explore different effect site concentration combinations, patients were randomly assigned to one of 5 groups along the isobole for a 95% probability of loss of response to laryngoscopy (Figure 1). Target effect site concentrations ranged from Group 1 which targeted relatively high propofol and low remifentanyl levels to Group 5 which targeted low propofol and high remifentanyl levels.

Using previously published pharmacokinetic-pharmacodynamic models for propofol [12,13] and remifentanyl [14,15] that accounted for age and body size, infusion rates for each drug were individually identified for each patient. To minimize the transient effects associated with rapidly changing effect site concentration, infusion rates were designed to reach effect site concentration of propofol and remifentanyl associated with a 95% probability of loss of response to laryngoscopy in 10 minutes. In an iterative fashion, sequential simulations were performed of continuous high rate remifentanyl and propofol infusions to identify the proper infusion rates that yielded the target propofol-remifentanyl effect site concentrations within 10 minutes. This was done to allow for a gradual rise in effect site concentrations so that the concentrations of propofol and remifentanyl at the time of laryngoscopy could be determined with greater accuracy. Should doses of propofol and remifentanyl be inadequate to perform laryngoscopy at the end of the 10 minute infusions, additional propofol or remifentanyl was administered at the discretion of the attending anesthesiologist. The infusion rates for each group are presented in Table 2.

Patient Instrumentation and Equipment

Each patient was instrumented with a pulse oximeter, noninvasive blood pressure cuff set to cycle every 5 minutes, a five lead electrocardiogram, and following induction, an oral or nasal temperature probe. Inspired and expired oxygen and carbon dioxide were monitored

with a gas analyzer. Data from these sensors was monitored using a physiologic monitor (AS/3 Anesthesia Monitor, Datex-Ohmeda, Helsinki, Finland) and stored every 5 seconds using a computerized data acquisition system (S/5 Collect, Datex-Ohmeda, Helsinki, Finland).

Syringe pumps (Medfusion 2010I or 3010I, Medex Inc, Duluth, GA) were used to deliver remifentanyl and propofol. An anesthesia machine (Aestiva, Datex-Ohmeda, Madison, WI, USA) was used to administer a mixture of oxygen and air and provide mechanical ventilation. The inspired oxygen content and ventilator settings were at the discretion of the anesthesiologist providing care to the patient.

Experimental Protocol

Anesthesiologists routinely assigned to provide anesthetic care to patients enrolled in the study were asked to participate in the protocol. They were asked to administer an intravenous dose of midazolam 12.5 mcg/kg in the pre-operative holding area. Patients were then taken to the operating room, instrumented as described above, and then asked to take a minimum of five vital capacity breaths of 100% oxygen. Infusions of remifentanyl and propofol were started approximately ten minutes after the midazolam was administered. Anesthesiologists were advised to terminate the induction infusions at any time should they believe that patient safety was compromised.

During induction, anesthesiologists were asked to determine when the patients were suitably anesthetized for laryngoscopy. If the anesthesiologists felt that the continuous infusions of remifentanyl and propofol were inadequate to render patients unconscious prior to laryngoscopy, they were asked to give additional propofol or remifentanyl as they deemed appropriate. Following loss of consciousness, at the discretion of the anesthesiologist, patients received either rocuronium (0.6 mg/kg) or succinylcholine (2 mg/kg) to optimize conditions for laryngoscopy and tracheal intubation.

Following tracheal intubation, remifentanyl and propofol were titrated at the anesthesiologist's discretion. Anesthesiologists were asked to verbalize their intent to administer a bolus or change an infusion rate and when the bolus or rate change was completed. All dosing regimen changes were recorded.

The times for skin incision, 5 minutes following skin incision, start of wound closure, and start of skin closure were recorded for each patient. At these time points anesthesiologists were asked whether the patient had developed a response to the surgical stimulus. For patients that did respond, the nature of the response was recorded in terms of hemodynamic change or patient movement.

Prior to emergence from anesthesia, anesthesiologists were asked to use fentanyl as a transition opioid as needed. Upon completion of surgery, the remifentanyl and propofol infusions were terminated and patients were allowed to emerge from anesthesia. Subsequently, they were taken to the post anesthesia care unit for a minimum of 30 minutes.

In the post anesthesia care unit, an assessment of post operative pain was based on the need to administer additional fentanyl. Every five minutes, using the visual analog scale (VAS), patients were asked to give a current pain score and what pain score the patient would consider to be tolerable. Additional fentanyl was administered in 25 to 150 mcg increments if (1) the recovery room nursing staff considered it appropriate (*i.e.* lack of excessive sedation or respiratory depression) and (2) the actual VAS was greater than the tolerable VAS. The time and amount of each fentanyl dose in the post anesthesia care unit was recorded.

Metrics of Response

Measures of drug effect included the OAA/S score (Table 3) for sedation and a response in hemodynamics at selected points during the anesthetic for analgesia.

During induction, the patient's level of sedation was assessed every 20 seconds using the OAA/S score beginning with the simultaneous start of remifentanyl and propofol infusions until laryngoscopy and tracheal intubation. Similarly, during emergence, the patient's level of sedation was assessed every 20 seconds from when the remifentanyl and propofol infusions were both turned off until the patient regained responsiveness (an OAA/S > 1). Two to three additional subsequent OAA/S assessments were made when possible. During induction, the point at which the patient lost responsiveness was defined as two consecutive OAA/S scores less than 2 and during emergence, the point at which the patient regained responsiveness was defined as two consecutive OAA/S scores greater than one.

The presence or absence of a response to laryngoscopy and tracheal intubation was evaluated when the trachea was successfully intubated and the endotracheal cuff was inflated. The presence or absence of a response to painful stimuli was evaluated at skin incision, 5 minutes after skin incision, and wound skin closure. A hemodynamic response was considered present if the heart rate developed an increase that was more than 20% above baseline.

Once in the post anesthesia care unit, a measure of adequate analgesia was estimated every five minutes by the need to give additional fentanyl.

Computer Simulations of Delivered Anesthetic

An investigator recorded the dosing regimens for propofol, remifentanyl, and fentanyl for the entire anesthetic for each patient. Using this information and previously established pharmacokinetic-pharmacodynamic models [12–16], simulated effect-site concentrations for remifentanyl, fentanyl, and propofol were performed for the duration of the anesthetic for each subject.

Effect site concentrations for fentanyl were converted to remifentanyl equivalent effect site concentrations by developing a ratio between the C_{50} 's for remifentanyl and fentanyl that produce 50% of the maximal effect in the electroencephalogram [17]. Several studies have identified the C_{50} for fentanyl [18–21] ranging from 6.9 ± 1.5 ng/mL to 9.8 ± 8.3 ng/mL. A mean value of 8.2 ng/mL was used for the C_{50} for fentanyl. The C_{50} for remifentanyl has been reported as 19.9 ± 5.2 ng/mL by Egan et al [22]. From these data, an opioid equivalency based on the C_{50} 's for remifentanyl and fentanyl are 19.9 to 8.2 ng/mL with a ratio of 2.4. As described by Egan et al [17], the opioid equivalency for other opioid effects, such as respiratory depression and analgesia have the same ratio, but lower absolute C_{50} 's.

Data analysis

Loss of Responsiveness Interaction Model—Two methods were used to assess the performance of the loss of responsiveness interaction model during induction: (1) a temporal analysis and (2) an assessment of model accuracy and bias.

To assess the temporal accuracy for the loss of response interaction model, for each subject, a comparison was made between when the model predicted patients would lose responsiveness (OAA/S < 2) and when the patient actually became unresponsive. The time point at which patients lost responsiveness was defined as 0. Times from when the loss of responsiveness interaction model predicted, with a probability of 0.5, that patients would lose responsiveness either prior to or after the onset of actual loss of responsiveness were

reported as negative and positive respectively. In a similar fashion, during emergence, a comparison was made between when the loss of responsiveness model predicted, with a probability of 0.5, that patients would be responsive ($OAA/S > 1$) and when patients actually developed a return of responsiveness.

The performance of the loss of responsiveness interaction model was evaluated in terms of its ability to predict loss and return of responsiveness. Performance parameters included a measure of accuracy (median absolute weighted residual), bias (median weighted residual), root mean squared error analysis, and visual assessment of observed versus predicted loss of responsiveness during induction and emergence[16,23].

Laryngoscopy and Surrogates of Surgical Stimuli Interaction Models—It is important to point out that proper assessment of the interaction models for laryngoscopy and surrogates of surgical stimuli requires an assessment of remifentanyl propofol concentration pairs over the entire range of each response surface. Constraints of meeting the anesthetic requirements of surgical procedures prohibited full exploration of each model.

With this in mind, an assessment of the laryngoscopy interaction model was made at the time of laryngoscopy and tracheal intubation. Model predictions at the time of endotracheal tube cuff inflation were used for this analysis. An assessment of the surrogates of surgical stimuli interaction models (electrical tetany and tibial pressure algometry) were made at selected time points during the surgical procedure to include skin incision, five minutes after skin incision, onset of wound closure, and onset of skin closure. Each interaction model was assessed at each of these time points in terms of how many patients were above or below probabilities of 0.95 and how many patients developed a response to surgical stimuli.

Surrogates of Painful Stimuli in the Recovery Room—Interaction models for surrogates of painful stimuli were evaluated during the first 30 minutes of patient recovery in the post anesthesia care unit. Similar to the performance assessments (measures of accuracy, bias, and root mean squared error) for the loss of responsiveness interaction model, model predictions of response to pressure algometry and electrical tetany were compared to when patient required a first dose of fentanyl in the recovery room.

RESULTS

Twenty one patient subjects were enrolled and all subjects completed the study. Their American Society of Anesthesiology classification ranged from I to III. Patient demographics are presented in Table 4. Surgical procedures included open (9) and laparoscopic (7) abdominal surgery, lower extremity orthopedic surgery (1), upper extremity orthopedic surgery (1) cervical spine surgery (1), throat surgery (1) lower extremity vascular surgery (1). Fourteen different surgeons and seven different anesthesiologists participated in the study.

Computer Simulations to Identify Dosing

The time from the start of the infusions to laryngoscopy and tracheal intubation are presented in Table 2. Laryngoscopy with tracheal intubation, on average, was performed 9.3 ± 2.7 minutes after the start of the infusions and one patient required additional remifentanyl or propofol prior to laryngoscopy. Pharmacokinetic model estimates of remifentanyl-propofol effect site concentration pairs at the time of tracheal intubation are presented by group in Figure 1. Resultant remifentanyl-propofol effect site pairs were distributed about the 5 target effect site pairs along the isobole representing a 95% probability of no response to laryngoscopy.

Example Subject

The time course of the intravenous opioid and sedative dosing regimens, the resultant opioid and sedative effect site concentrations, the OAA/S scores, selected painful stimuli, and the predicted probability of loss of responsiveness are presented in Figure 2 for a typical patient subject (59 year old 75 kilogram 180 cm tall male undergoing an open bilateral inguinal hernia repair) enrolled in this study. In addition, model predictions for sedation, loss of responsiveness, loss of response to laryngoscopy, and loss of response to pressure algometry and electrical tetany are presented in Figure 2.

The anesthetic consisting of bolus doses and continuous infusions of intravenous anesthetics is presented in panel A and the resultant effect site concentrations for each drug are presented in panel B. For this subject, the anesthetic quickly achieved a high probability of sedation shortly after initiating the infusions of remifentanyl and propofol that persisted until after emergence and extubation. The anesthetic induction quickly achieved a high probability of loss of responsiveness and quickly dropped once the infusions were terminated. The probabilities of loss of responsiveness were consistent with the measured OAA/S scores < 2 . From these simulations, it is evident that propofol is the primary contributor to the loss of responsiveness. The addition of opioid minimally increased the probability of loss of responsiveness during the anesthetic. Once in the post anesthesia care unit, the addition of opioid did not make a large contribution to the probability of loss of responsiveness (Panels C).

During induction, the dosing regimen led to tracheal intubation within 9.4 minutes from the start of the remifentanyl and propofol infusions. The patient exhibited no response to laryngoscopy. The interaction model for loss of response to laryngoscopy predicted greater than a 95% probability of no response to laryngoscopy within 9.3 minutes from the start of the remifentanyl and propofol infusions. The addition of sedatives markedly increased the probability of loss of response to laryngoscopy. In fact, the remifentanyl alone, at the time of laryngoscopy provided only a 1% probability of no response to laryngoscopy (Panel D).

The interaction model predictions for loss of response to shin pressure algometry of 50 lb-in⁻² and loss of response to posterior tibial nerve electrical tetany of 50 mA as a result of the dosing regimen revealed that (1) the anesthetic technique achieved high probabilities of no response for both of these surrogates of surgical pain and (2) the addition of sedatives markedly increased the analgesic effect of the opioid. The patient developed no response at skin incision, 5 minutes after skin incision, at the start of wound closure, or at the start of skin closure. Similar to the interaction model for loss of response to laryngoscopy, these interaction models revealed little analgesic effect with opioid alone (~1%) compared to the overall analgesic effect of the anesthetic.

Following completion of surgery and termination of the remifentanyl and propofol infusions, the pressure algometry and electrical tetany interaction models behaved differently in response to the dosing of additional fentanyl in the post anesthesia care unit. The pressure algometry interaction model predicted with high probability no response to 50 lb-in⁻² during extubation (black triangle) and shortly after the first dose of fentanyl in the post anesthesia care unit. By contrast, the electrical tetany interaction model consistently predicted a low probability of no response to a current of 50 mA during extubation and despite all of the additional doses of fentanyl in the post anesthesia care unit (Panels E and F).

Performance Assessment of the Loss of Responsiveness Interaction Model during Induction and Emergence from Anesthesia

The loss of responsiveness interaction model predicted a mean probability of $95 \pm 6\%$ that patients would have an OAA/S < 2 at the onset of loss of responsiveness. Figure 3, panel A,

presents the predicted remifentanyl-propofol effect site concentration pairs at the observed onset of loss of responsiveness. A majority of the data points are above the 95% isobole (solid line) but four patients were between the 50 and 95% isoboles.

Analysis of model performance during induction revealed that model predictions of probability of loss of responsiveness were higher than the observed percentage of patients found to be unresponsive (Panel B). Estimates of accuracy (median absolute weighted residual), bias (median weighted residual), and root mean squared error analysis were 48.9%, 88.4% and -88.4% respectively.

The loss of responsiveness interaction model predicted the onset of loss of responsiveness on average, earlier than it was observed to occur. The mean time from when the loss of responsiveness model predicted a 50% of the onset of loss of responsiveness was 3.5 ± 2.5 minutes before that actual onset of loss of responsiveness. The difference in time between model predicted onset of loss of responsiveness and actual onset of loss of responsiveness for each patient are presented in Figure 3, panel C.

The loss of responsiveness interaction model predicted a mean probability of $55 \pm 31\%$ that patients would be unresponsive at the point where patients began to respond during emergence from anesthesia. Figure 4, panel A, presents the predicted remifentanyl-propofol effect site concentration pairs at the observed return of responsiveness. The data points are distributed about the 50% isobole (9 below and 12 above) and four patients had propofol-remifentanyl levels above the 5% isobole.

Analysis of model performance during emergence revealed that model predictions of probability of loss of responsiveness were similar to observed percentage of patients found to be unresponsive (Panel B). Estimates of accuracy (median absolute weighted residual), bias (median weighted residual), and root mean squared error analysis were 7.8%, 15.2% and 15.2% respectively.

Unlike induction, with return of responsiveness, the interaction model predicted the return of responsiveness shortly after the observed return of responsiveness. The mean time from when the loss of responsiveness model predicted a 50% probability of loss of responsiveness was 1.5 ± 8.8 minutes after the actual return of responsiveness. The difference in time between model predicted return of responsiveness and actual return of responsiveness for each patient are presented in Figure 5, panel C.

Laryngoscopy Interaction Model

The mean probability of no response to laryngoscopy at tracheal intubation was $94 \pm 3\%$. The remifentanyl-propofol effect site concentrations at the time of tracheal intubation and the 50% and 95% isoboles predicted by the loss of response to laryngoscopy model are presented on Figure 5. Seven patients had a probability above the 95% isobole and the remaining patients were between the 50% and 95% isoboles. Four patients developed an increase in heart rate that was 20% above their heart rate just before tracheal intubation. The remifentanyl-propofol effect site concentration pairs for these four subjects at the time of tracheal intubation were associated with probabilities of no response to laryngoscopy of 96, 92, 94, and 97% respectively. Heart rate changes are presented in Table 5. With all four patients, the anesthesiologists did not give additional propofol or remifentanyl at the time of tracheal intubation or within 5 minutes following tracheal intubation.

Surrogate of Surgical Stimuli Interaction Models During Surgery

The remifentanyl-propofol effect site concentrations at skin incision, 5 minutes after skin incision, at the start of wound closure, and at the start of skin closure for each patient along

with the 50 and 95% isoboles for no response to pressure algometry and electrical tetany interaction models are presented in Figure 6. All of the patients were above the 95% isobole for no response to pressure algometry at all assessment points during the surgical procedure. Similarly, all of the patients were at or above the 95% isobole for no response to electrical tetany. One patient demonstrated a heart rate response at skin incision and a different patient demonstrated a heart rate response 5 minutes after skin incision. The patient who responded at skin incision had a remifentanyl-propofol effect site concentration pair that was associated with probabilities of no response to pressure algometry and electrical tetany of 100% and 99% respectively. Similarly the patient who responded 5 minutes after skin incision had a remifentanyl-propofol effect site concentration pair that was associated with probabilities of no response to pressure algometry and electrical tetany of 100% and 100% respectively. Heart rate changes for these patients are presented in Table 5. With the patient who exhibited a response 5 minutes after skin incision, the remifentanyl infusion rate was subsequently increased from 0.1 mcg/kg/min to 0.15 mcg/kg/min.

Surrogate of Surgical Stimuli Interaction Models During Recovery

The remifentanyl-propofol effect site concentrations when patients required fentanyl to treat post operative pain during the first 30 minutes in the post anesthesia care unit along with the 50 and 95% isoboles for no response to pressure algometry and electrical tetany interaction models are presented in Figure 7. The mean probabilities of no response to pressure algometry and electrical tetany for patient assessments that required additional fentanyl were $46 \pm 40\%$ and $14 \pm 24\%$ respectively. The majority of patient assessments were below the 50 and 95% isoboles for electrical tetany and the 95% isobole for pressure algometry. All data points above the 95% isobole for pressure algometry came from one patient.

Analysis of model performance of surrogates of surgical pain in the recovery room revealed that the pressure algometry model predictions of the probability of not tolerating a maximal stimulus (50 lbs-in^{-2}) were similar to the percent of patients that required their first dose of fentanyl to treat pain in the recovery room. By contrast the electrical tetany model predictions of the probability of not tolerating a maximal stimulus (50 mA), under predicted the percentage of patients that would require their first dose of fentanyl in the recovery room (Panel B). Estimates of accuracy (median absolute weighted residual), bias (median weighted residual), and root mean squared error analysis for pressure algometry were 22.8%, -11.4% and 14.3% respectively and for electrical tetany were 681%, 681% and 30.9% respectively.

Discussion

Prior work from our human volunteer laboratory characterized the synergistic interaction between remifentanyl and propofol in a series of surrogate and actual measures of analgesia and sedation. Several models of remifentanyl-propofol interaction were constructed to quantify the synergistic interaction between these two drugs. The aim of this study was to explore how well these interaction models developed from human volunteers would predict pertinent events of anesthetic care in patients undergoing elective surgery. We hypothesized that these models would predict with high probability (i) loss and return of responsiveness, (ii) the presence or absence of a response to laryngoscopy and tracheal intubation, (iii) the presence or absence of a no response to skin incision, wound closure, and painful stimuli in the post anesthesia care unit.

Our results in part confirmed our hypotheses. In general, the loss of responsiveness interaction model performed poorly during induction of anesthesia. Predictions of loss of responsiveness, although accurate at the time loss of responsiveness actually occurred where predicted to occur too early. By contrast, the loss of responsiveness interaction model

performed well on emergence from anesthesia. The interaction models built for laryngoscopy and surrogates of surgical stimuli (pressure algometry and electrical tetany) were difficult to evaluate during the intraoperative period because resultant remifentanyl-propofol effect site concentration pairs were typically well above the 50% and 95% isoboles. However, for the most part, they indicated that patients would be unresponsive to noxious stimuli and patients behaved accordingly. Using the administration of additional fentanyl as a metric of inadequate analgesia, the pressure algometry interaction model performed well in predicting patients would respond to a noxious stimulus (in this case postoperative incisional pain) whereas the electrical tetany model predicted that all of the patients except one would not respond to a noxious stimulus while in the recovery room.

Computer Simulations to Identify Dosing

Computer simulations were performed prior to induction of each patient to identify the propofol and remifentanyl infusion rates that would be required to achieve a 95% probability of no response to laryngoscopy within 10 minutes for a given target propofol-remifentanyl concentration pair assignment (groups 1 through 5). This was done to minimize the potential error in pharmacokinetic estimates of effect site concentrations under non steady state conditions between plasma and effect site compartments. The experiment was designed to explore 5 different groups of remifentanyl-propofol effect site concentration pairs along the 95% isobole for no response to laryngoscopy. Although the time at which laryngoscopy was performed was at the discretion of the anesthesiologist, laryngoscopy and tracheal intubation were performed at concentration pairs near their target for each group (Figure 1). For all groups except group 1, the mean time required prior to laryngoscopy and tracheal intubation was near 10 minutes. In group 1, with a high propofol infusion rate, the time to laryngoscopy and tracheal intubation was shorter.

Temporal Analysis of the Sedation and Loss of Responsiveness Interaction Models during Induction of Anesthesia

During induction, the loss of responsiveness interaction model predicted the onset of loss of responsiveness much sooner than was actually observed. This was found to be the case for a majority of patients (Figure 3). The discrepancy in this result may be in part a (i) misspecification in the pharmacokinetic – pharmacodynamic link model and/or (ii) a misspecification in the three compartment pharmacokinetic model[24] for either remifentanyl or propofol or both. Specifically, the parameter of the model that accounts for the lag time between changes in the plasma concentration and changes in the effect site concentration (i.e. the biophase typically described by k_{e0}) may predict more rapid equilibration between the plasma and effect site compartments than actually occurs. In this evaluation we chose the k_{e0} of 0.46 ($t_{peak} = 1.7$ min). [12,13] However, Doufas et. al. reported that when a k_{e0} of 0.17 ($t_{peak} = 2.7$ min), the effect-site concentrations were not affected by rate changes in propofol administration. The observed results by Doufas may partly explain the poor model performance observed during induction in our study[25].

Another source potential source of error influencing the temporal performance of the loss of responsiveness interaction model may have been (i) higher degrees of anxiety in patients taken to the operating room than in volunteers in a study laboratory and (ii) more tactile and verbal stimuli in the operating room than in the study laboratory. Both of these may have led to increased drug requirements for sedation and loss of responsiveness in patients versus volunteers.

In terms of model accuracy, at the time of actual onset of loss of responsiveness, the loss of responsiveness interaction model predicted with high probability that the patients would indeed lose responsiveness. However, the accuracy of the model of data points collected

over the response surface for this model revealed large errors that led to poor accuracy and a large bias.

During emergence from anesthesia, the loss of responsiveness interaction model performed better than during induction. The actual return of responsiveness occurred near the time when the loss of responsiveness interaction model predicted 50% of the patients would become responsive (Figure 4). In comparison to the induction of anesthesia, the rate of change in propofol and remifentanyl effect site concentrations were much slower (Table 6). Slower rates of change in effect site concentrations more closely approximate the steady state condition assumed by the model.

Of course these interaction models were estimated during pseudo steady state conditions whereas the model was applied during a period of rapidly changing drug concentrations. It is perhaps unrealistic to expect the models to perform well when applied during rapidly changing states such as induction.

In terms of model accuracy, the model performed well in that at the time of actual onset of responsiveness, nearly half of the patients emerged with remifentanyl-propofol concentrations below and above the 50% isobole. This finding is in line with what would be expected of population estimates of return of responsiveness along the 50% isobole. Model accuracy and bias were significantly improved during emergence from anesthesia.

Laryngoscopy Interaction Model

The laryngoscopy interaction model predicted with high probability that none of the patients would develop a response to laryngoscopy (a mean probability of 94%). Four patients, however, did develop a small heart rate response during laryngoscopy and tracheal intubation. Several points merit discussion here. First, the responses were very mild and no additional anesthetic was required to address these responses. The clinical implications of these heart rate changes are most likely inconsequential. This conclusion is supported by the fact that anesthesiologists did not administer additional anesthetic following tracheal intubation. In fact in all instances, they reduced the infusion rates for propofol and remifentanyl. Second, the laryngoscopy interaction model was built from data collected from volunteers where laryngoscopy only was performed as a stimulus. By contrast, in this study, the stimulus consisted of laryngoscopy and tracheal intubation. Intubation of the trachea may have increased the stimulus when compared to laryngoscopy alone. [6],

The accuracy of the laryngoscopy model is difficult to evaluate given that all of the data points were near or above the 95% isobole. However, the laryngoscopy model did predict that patients would not respond to laryngoscopy, and with the exception of minor responses in four patients, the model performed well.

Surrogate of Surgical Stimuli Interaction Models

As with the laryngoscopy interaction model, it is difficult to assess the accuracy of the models of surrogate surgical pain at skin incision, 5 minutes after skin incision, at the start of wound closure, and at the start of skin closure. This was because again all of the data points were at or above the 95% isobole for both the electrical tetany and the pressure algometry interaction models. Of note, in the assessments of all 21 patients at each of these four events, only 2 patient assessments were found to have a response to surgical stimuli and only one was treated with a modest increase in the infusion rate of remifentanyl.

Since all the anesthetic techniques led to remifentanyl-propofol concentration pairs that were at or above the 95% isoboles for both surrogates of surgical stimuli, from this analysis it is difficult to determine which surrogate is more reflective of stimuli encountered during these

surgical procedures. It is likely that the procedures varied in the stimulus intensity and perhaps in some cases, the electrical tetany better mimicked surgical pain whereas in other cases, pressure algometry better mimicked surgical pain.

During the recovery phase in the post anesthesia care unit, responses were more varied, spanning concentration pairs above and below the 50% and 95% isoboles for electrical tetany and pressure algometry making evaluation of surrogate surgical pain models possible. As expected for patients with relatively good pain control, remifentanyl-propofol effect site concentration pairs of patient assessments that did not require additional fentanyl were below the 50% isobole for both the electrical tetany and pressure algometry models. However, with patients that required supplemental fentanyl, all patient assessments, except for three (from the same patient) were below the 50% isobole for electrical tetany while all of the responses straddled the 50% isobole for the pressure algometry model. These results suggest that the algometry model is a better surrogate of pain encountered in the post anesthesia care unit than electrical tetany. Electrical tetany appears to be too strong a stimulus compared to what is encountered in the post anesthesia care unit. Model accuracy and bias assessments confirmed this finding.

Limitations

There are several limitations with this line of investigation. For example, one potential confound of this study is the effect of midazolam during induction and laryngoscopy. Each patient received a 12.5 mcg/kg bolus of midazolam in the pre-operative area, approximately five to ten minutes before the propofol and remifentanyl infusions were started. Pharmacokinetic simulations predicted an average peak effect-site concentration of 26.4 ± 5.3 ng/ml with this bolus. This effect site concentration is $8.9\% \pm 1.8\%$ of the concentration necessary for an OAA/S score ≤ 3 and $6.8\% \pm 1.4\%$ of the concentration required for apparent sleep[9]. Although the influence, by itself, on sedation and loss of responsiveness are small, midazolam may have had a larger influence because of its additive interactions with propofol and potentially synergistic interactions with remifentanyl. Despite this confound, the experimental design included a small dose of midazolam in order to mimic "standard-practice" and to help decrease patient anxiety prior to surgery. It is interesting to point out that patients lost responsiveness substantially later than predicted, even with the addition of midazolam.

Another inherent limitation of this type of investigation was that it was difficult to intentionally administer less anesthetic to illicit a response to surgical stimuli during an elective surgical procedure. This limitation made it difficult to explore the transition from a responder to non responder and hence quantify how well each model performed.

Summary

This study set out to explore how a set of interaction models for loss of responsiveness and painful stimuli developed from data collected from volunteers would predict responses to events in patient undergoing elective surgery. The loss of responsiveness interaction model predicted with high probability that patients would be unresponsive when they were found to be unresponsive. However, this interaction model inaccurately reported that patients should have become unresponsive much earlier during induction. This error is potentially due to a misspecified biophase for either the remifentanyl or propofol pharmacokinetic models. The laryngoscopy interaction model predicted with high probability no response to laryngoscopy. In all but four of the patients, no response was noted. The remaining four developed a small response in heart rate that was most likely clinically inconsequential. Surrogate models of surgical pain (electrical tetany and pressure algometry) predicted with high probability no response to selected stimulating events during surgery. Since the

anesthetic technique led to remifentanyl-propofol effect site concentration pairs that were well above the 95% isoboles for both surrogate pain models, it was difficult to determine which model best represented intraoperative surgical stimuli. During emergence from anesthesia, the loss of responsiveness interaction model effectively predicted return of responsiveness. In recovery, surrogate models of surgical pain were compared to patient assessments that led to the administration of additional fentanyl for post operative pain control. The pressure algometry interaction model better described the patient responses to pain experienced in the recovery room than the electrical tetany model.

In conclusions, this preliminary assessment of a series of remifentanyl-propofol interaction models demonstrated that these models can predict responses to pertinent selected events during elective surgery. However, significant model error is evident during rapid changes in effect site concentrations and this study was limited in how well it could assess the full response surface of each interaction model because of practical limitations in assessing responses to painful stimuli during surgery.

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Figure 1.

Response surface interaction model for loss of response to laryngoscopy illustrating the remifentanyl-propofol effect site concentration pairs associated with a 95% probability of no response to laryngoscopy known as the 95% isobole (solid line). The five patient group assignments are superimposed on the 95% isobole. Groups 1 through 5 are represented by circles, triangles, squares, diamonds, and hexagons respectively. The open shapes represent the five target remifentanyl-propofol concentration pairs for each group. The solid shapes represent the predicted remifentanyl-propofol concentration pairs at the time of tracheal intubation for patients in each group.

F. Probability of Loss of Response to Pressure Algometry

G. Probability of Loss of Response to Electrical Tetany

Figure 2.

Plot of dosing (Panel A), resultant effect site concentrations (Panel B), probability of loss of responsiveness (Panel C), probability of loss of response to laryngoscopy, (Panel D), and probability of loss of response to a pressure algometry and electrical tetany (Panels E and F) for a typical patient enrolled in this study. The black and gray bar along the horizontal axis of each plot presents segments of time associated with preoperative period (PO), induction (I), maintenance of anesthesia, emergence from anesthesia (E), and time in the post anesthesia care unit (PACU). The start of emergence was defined as the time from which the remifentanil and propofol infusions were turned off. In panel A, the midazolam and fentanyl bolus doses are represented by vertical lines. The remifentanil and propofol infusions rates

are plotted over time. For Panels C – F, the time of laryngoscopy and tracheal intubation, skin incision, wound closure, and tracheal extubation are presented as a TI, SI, WC, and TE respectively.

In panel C, the probability of loss of responsiveness (probability of the Observers Assessment of Alertness/Sedation score (OAA/S) < 2) is plotted for all drugs and for just the sedative drugs alone (dashed lines) illustrating the magnitude of the increase in sedative effect when opioids are co-administered with sedative hypnotics (grey area). Also presented in this panel is the OAA/S over time.

In panels D, E, and F the probability of no response to laryngoscopy, no response to pressure algometry, and to electrical tetany are plotted for all drugs and for just the opioids alone (dashed line near the bottom of the plot) and opioid co-administered with sedative hypnotics (gray area). With the addition of a sedative hypnotic, the analgesic effect of opioids is markedly increased. The F represent time points where fentanyl was administered.

Figure 3.

Loss of responsiveness interaction model predictions during induction of anesthesia. Panel A presents the remifentanyl-propofol effect site concentrations at the onset of loss of responsiveness. The solid and dashed lines represent the 50% and 95% probability of OAA/S < 2 (interaction model for loss of responsiveness) respectively. A comparison between model predictions of the percent of patients that will have a loss of responsiveness to the percent of patients that actually have a loss of responsiveness is presented in Panel B. Time between onset of loss of responsiveness defined as OAA/S < 2 and model predictions of a 50% probability of an OAA/S < 2 are presented in panel C. The horizontal axis represents the time between the onset of observed and predicted OAA/S scores < 2. Negative and

positive numbers indicate that the predicted onset of loss of responsiveness occurs before and after the observed onset of loss of responsiveness respectively. The vertical axis represents each subject.

Figure 4.

Return of responsiveness interaction model predictions during emergence from anesthesia. Panel A presents the remifentanyl-propofol effect site concentrations at the onset of return of responsiveness. The solid and dashed lines represent the 50% and 5% probability of OAA/S > 1 respectively. A comparison between model predictions of the percent of patients that will have a return of responsiveness to the percent of patients that actually have a return of responsiveness is presented in Panel B. Time between onset of return of responsiveness defined as OAA/S > 1 and model predictions of a 50% probability of an OAA/S > 1 is presented in panel C. The horizontal axis represents the time between the onset of observed and predicted OAA/S scores > 1. Negative and positive numbers indicate that the predicted

onset of return of responsiveness occurs before and after the observed onset of return of responsiveness respectively. The vertical axis represents each subject.

Figure 5.

Remifentanyl-propofol effect site concentration 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 respectively as predicted by the loss or response to intubation interaction model.

Figure 6.

Remifentanil-propofol effect site concentration pairs for each subject at skin incision, 5 minutes after skin incision, wound closure, and skin closure (Panels A-D respectively) for each patient. Solid circles and open triangles represent patients with no response and a response to surgical stimuli respectively. The black solid and dashed lines represent the 50% and 95% probability of no response to 50 lbs-in⁻² pressure applied to the anterior surface of the mid-shaft of the tibia (interaction model for pressure algometry). The gray solid and dashed lines represent the 50% and 95% probability of no response to 50 mA of electrical current applied over the surface of the posterior tibia nerve (interaction model for electrical tetany).

Figure 7.

Panel A presents the remifentanil-propofol effect site concentration pairs where additional analgesic (fentanyl) at the discretion of the recovery room nursing staff during the first 30 minutes in the post anesthesia care unit (open triangles). The black solid and dashed lines represent the 50% and 95% probability of no response to 50 lbs-in⁻² pressure applied to the anterior surface of the mid-shaft of the tibia (interaction model for pressure algometry). The gray solid and dashed lines represent the 50% and 95% probability of no response to 50 mA of electrical current applied over the surface of the posterior tibia nerve (interaction model for electrical tetany). A comparison between model predictions of the percent of patients that will not tolerate maximal stimulus to the percent of patients that require a first dose of

fentanyl is presented in Panel B. Open triangles represent the probability of no response to pressure algometry and solid circles represent the probability of no response to electrical tetany.

Table 1

Interaction model parameters for loss of responsiveness, loss of response to a painful stimulus, and loss of response to laryngoscopy.

	C50p	C50r	n	α
Loss of response to pressure algometry*	4.2	8.8	8.3	8.2
Loss of response to electrical tetany*	4.6	23.1	6.0	14.7
Loss of response to laryngoscopy*	5.6	48.9	2.2	33.2
Loss of responsiveness	2.2	33.1	5.0	3.6

C50p (mcg/mL) and C50r (ng/mL) represent the effect site concentrations for each drug that produce 50% of the maximal effect, n is the slope of the pharmacodynamic response curve, and α is the extent of interaction between propofol and remifentanyl for a given drug effect.

* Interaction model parameters taken from Kern et al [1]

Table 2

Remifentanyl and propofol infusion rates during induction for each study group

Induction Group Mean $\pm$ SD	Propofol (mcg/kg/min)	Remifentanyl (mcg/kg/min)	Time to LOR (minutes)	Time to TI (minutes)	Remifentanyl Ce (ng/mL)	Propofol Ce (mcg/mL)
1	317 $\pm$ 39	0.145 $\pm$ 0.018	3.6 $\pm$ 0.5	6.9 $\pm$ 1.7	3.2 $\pm$ 0.3	5.7 $\pm$ 0.7
2	199 $\pm$ 20	0.337 $\pm$ 0.034	6.0 $\pm$ 1.2	9.7 $\pm$ 2.5	7.0 $\pm$ 0.7	3.8 $\pm$ 0.3
3	158 $\pm$ 11	0.524 $\pm$ 0.038	5.5 $\pm$ 1.2	9.2 $\pm$ 1.3	9.6 $\pm$ 1.9	2.6 $\pm$ 0.6
4	97 $\pm$ 20	0.534 $\pm$ 0.113	6.7 $\pm$ 4.2	10.9 $\pm$ 4.5	13.0 $\pm$ 1.1	2.2 $\pm$ 0.6
5	79 $\pm$ 6	0.691 $\pm$ 0.050	6.9 $\pm$ 2.8	10.2 $\pm$ 2.1	16.5 $\pm$ 1.5	1.6 $\pm$ 0.1
Overall Mean $\pm$ SD	177 $\pm$ 93	0.432 $\pm$ 0.206	5.6 $\pm$ 2.5	9.3 $\pm$ 2.7	9.6 $\pm$ 5.0	3.3 $\pm$ 1.6

Table 3

The Observers Assessment of Alertness/Sedation (OAA/S) score [2].

Value	Description
5	Responds readily to name spoken in normal tone.
4	Lethargic response to name spoken in normal tone.
3	Responds only after name is called loudly and/or repeatedly for the individual to open their eyes.
2	Responds only after moderate prodding or shaking.
1	Does not respond to moderate prodding or shaking

Table 4

Patient Demographics

Weight (kg)	Height (cm)	Age (Years)	Gender (Female/Male)
79.0 ± 17.1	79.0 ± 17.1	79.0 ± 17.1	11/10

Data are presented at mean ± standard deviation

Table 5

Patients that had a greater than 20% change in heart rate over pre-stimulus baseline at selected points during the surgical procedure.

Subject	Surgical Stimulus	Baseline HR*	Peak HR** (absolute change)	% Change	Clinician Response
5	Tracheal Intubation	56	68 (12)	21%	None
16	Tracheal Intubation	67	89 (22)	33%	None
17	Tracheal Intubation	62	87 (25)	40%	None
19	Tracheal Intubation	72	96 (24)	33%	None
11	Skin Incision	61	109 (48)	79%	None
5	5 min after skin incision	66	80 (14)	20%	Increase infusion of remifentanyl from 0.12 to 0.15 mcg/kg/min

HR = heart rate

* Heart rate just prior to stimulus (skin incision, 5 minutes after skin incision, wound closure, or skin closure)

** Peak heart rate within 1 minute following the stimulus.

Table 6

Mean rate of change of propofol and remifentanyl (equivalent) effect site concentrations at loss or responsiveness LOR and return of responsiveness (ROR).

	propofol effect-site conc. slope (mcg/mL/min)	remifentanyl effect-site conc. slope (ng/mL/min)
LOR	0.5 ± 0.37	1.16 ± 0.79
ROR	-0.14 ± 0.08	-0.52 ± 0.36

Data are presented at mean $\pm$ standard deviation