IDENTIFICATION OF OPTIMAL DOSING REGIMENS FOR PROCEDURES REQUIRING ESOPHAGEAL INSTRUMENTATION THROUGH MULTIOBJECTIVE OPTIMIZATION

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

The use of propofol and propofol in combination with remifentanil by nonanesthesiologists is a controversial topic. Much of the concern centers on adverse respiratory effects: loss of responsiveness, respiratory depression, and airway obstruction. The aim of this study was to investigate these adverse drug effects at propofol-remifentanil combinations commonly used in procedures requiring esophageal instrumentation and build response surface models of drug effects. A second aim was to investigate published dosing regimens through simulation with these models. A third aim was to develop an optimization algorithm to identify an ideal propofol-remifentanil dosing regimen for upper endoscopy procedures.

Twenty-four volunteers received escalating target controlled remifentanil and propofol infusions. Responses to insertion of a bougie (40 cm), responsiveness, respiratory rate, and tidal volume were recorded at 384 targeted concentration pairs. Four published dosing regimens of propofol alone or in combination with opioids were simulated for a 10-min procedure. An optimization algorithm was developed to identify an optimal propofol-remifentanil dosing regimen from a set of possibilities.

Models for loss of response to esophageal instrumentation, intolerable ventilatory depression, and respiratory compromise were built. Simulations of published dosing regimens showed that once drug administration ended, loss of responsiveness, and respiratory depression effects dissipated quickly. Respiratory compromise dissipated more quickly in propofol only techniques compared to propofol-opioid techniques. An optimal dosing recommendation was identified for a simulated 55 year-old, 75 kg, 175

cm male undergoing an anticipated 10-min upper endoscopy and consisted of a propofol bolus of 0.8 mg/kg and infusion rate of 40 mcg/kg/min and a remifentanil bolus of 0.2 mcg/kg and an infusion rate of 0.05 mcg/kg/min.

High propofol-low remifentanil concentration pairs can block the response to esophageal instrumentation while avoiding intolerable ventilatory depression in spontaneously breathing volunteers. Propofol combined with remifentanil or fentanyl improved conditions for esophageal instrumentation and had a rapid return to responsiveness. Optimization techniques identified a remifentanil propofol dosing regimen that minimizes the duration of loss of responsiveness, respiratory depression, and airway obstruction and, according to expert opinion and models of drug effect, provides conditions that will permit upper endoscopy procedures. This dosing regimen merits clinical validation in patients undergoing brief endoscopic procedures.

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PREFACE

The work presented in this thesis represents several years of careful study into the analgesic and sedative effects resulting from propofol-remifentanil dosing combinations. There has been some debate on whether it is safe for nonanesthesiologists to administer these drugs. This work will address this question in the realm of gastrointestinal procedures requiring esophageal instrumentation.

In Chapter 2, we present probabilistic models of drug effect for loss of response to esophageal instrumentation, loss of responsiveness, and intolerable ventilatory depression and conclude that there is an area where a high percentage of volunteers tolerated esophageal instrumentation and avoided concentrations that would lead to involuntary respiratory depression. However, there was no concentration that achieved these conditions and avoided loss of responsiveness in a majority of volunteers. This chapter was published in Anesthesia & Analgesia in September 2011 with an accompanying editorial.

Chapter 3 improves upon our models for loss of response to esophageal instrumentation and intolerable ventilatory depression. A revised model is introduced that more accurately reflects clinically acceptable conditions for esophageal instrumentation. A new model for both intolerable ventilatory depression and airway obstruction is presented and called respiratory compromise. In addition, simulations of published upper endoscopy dosing protocols are performed. Because models for respiratory compromise and loss of responsiveness were built from data collected in unstimulated patients, it was decided they only are accurate in unstimulated patients

following termination of the procedure. An abstract presented on this work was awarded a Best of: Clinical Science award at the American Society of Anesthesiologists 2011 Conference. Anesthesiology, the official journal of the American Society of Anesthesiologist, extended an invitation to submit a manuscript from this work for publication in their April 2012 issue and it is currently under final review.

Reviewers from both manuscripts have encouraged us to use our expert position to provide a dosing recommendation. However, the complexity involved in addressing this issue required this be addressed in its own manuscript. Chapter 4 presents our work into providing an a priori dosing recommendation using multiobjective optimization techniques and our previously published propofol-remifentanil interaction models. This work has not yet been submitted to a journal for publication.

CHAPTER 1

INTRODUCTION

Each day, thousands of patients undergo gastrointestinal endoscopy, with the number continually increasing. The advent of new, fast acting drugs such as propofol and remifentanil has helped decrease procedure and recovery times but also introduces the risk of cardiopulmonary complications.[1] Of particular concern is that for the procedures, the anesthetics are commonly administered by nonanesthesiologists. This is worrisome because of the rapid onset of drug effects and lack of reversal agents, placing patients in potentially harmful situations very rapidly and leaving the clinician with a narrow window in which to react. The American Society of Anesthesiologists has issued a statement that the use of propofol be limited to those properly trained.[2]

1.1 Background

Propofol or propofol in combination with an opioid is commonly used to provide sedation and analgesia for gastrointestinal procedures such as upper endoscopy.[3] Propofol is a sedative that also provides amnesia but offers only minimal analgesia. It has a time to peak effect of 1.6 min.[4] While it is possible to perform upper endoscopy without any anesthesia, sedatives and analgesics are commonly administered to improve patient comfort and procedure quality.

While mild to moderate sedation is the ideal target, it is often not possible to place a scope in the esophagus and avoid deep sedation. Also, if propofol is dosed alone, there is also a tendency to oversedate in an attempt to compensate for its lack of

analgesic properties. Elevated levels of propofol can lead to apnea, ventilatory depression, desaturation, and hypotension.

Opiates commonly used in combination with propofol include midazolam, fentanyl, alfentanil, and remifentanil. This work will focus on remifentanil, which has a time to peak effect of around 1 min.[4-6] As an opiate, remifentanil has analgesic properties but little sedative or amnesic properties. High doses of remifentanil can lead to respiratory depression.

Administering propofol in combination with an opioid is common, allowing the patient to receive the benefits of both drugs. In addition, the interaction between these propofol and opioids is synergistic for most effects, meaning that when both are administered, less of each drug is needed to reach the same effect as if either drug were given alone. However, this is not limited to just the desired effects – the patient is also exposed to the adverse effects of both drugs and the interaction for these effects may also be synergistic.

1.2 Goals

The question this dissertation seeks to answer is “does a dosing combination exist that provides adequate sedation and analgesia for esophageal instrumentation while minimizing the risk of adverse effects?” Because remifentanil is a relatively new drug, its effects have not been thoroughly characterized. Studies do exist that report a propofol C50 for endoscopy procedures with propofol alone and in the presence of an opioid, but to our knowledge no interaction model exists. In order to determine if propofol and remifentanil can be safely administered for upper endoscopy, interaction models between propofol and remifentanil needed to be built for several drug effects. Research needs to be conducted to identify current dosing strategies, and an algorithm needs to be developed to identify the optimal dosing combination.

1.2.1 Pharmacodynamic models of drug effect

The first aim of this study was to characterize the interaction between propofol and remifentanil for loss of response to esophageal instrumentation, intolerable ventilatory depression, and respiratory compromise (intolerable ventilatory depression and airway obstruction). Response surface models would be built that could predict the probability of effect for any drug combination.

1.2.2 Evaluation of common dosing strategies

A second aim was to explore through simulation the behavior of common dosing regimens for loss of response to esophageal instrumentation, loss of responsiveness, respiratory depression, and respiratory compromise. Focus will be on evaluating the adverse effects encountered by these protocols following the end of the procedure, a time when patients are unstimulated and therefore at greatest risk. This aim would also partly serve as a validation of the models developed in the first aim.

1.2.3 Identification of optimal drug combination and dosing

Once drug effect models are created, we will have a “view of the landscape”, meaning we will know where the various effects occur and how they interact. This will help identify what if any propofol-remifentanil combination will provide a high probability of loss of response to esophageal instrumentation yet avoid loss of responsiveness, respiratory depression, and respiratory compromise. In addition, simulation of common dosing protocols would serve to validate these models as well as comment on which strategy may be best. Ultimately, these steps would contribute to our making a final dosing recommendation.

With the experience obtained in the first two aims, objective functions will be constructed that will define the properties of the ideal dose. It will include time until the procedure can begin, time needed to perform the procedure, and total recovery time.

Ideal times for each objective will be obtained from experts in the field. Finally, an optimization algorithm will be developed to identify the dosing combination that comes closest to these ideal times. The algorithm will evaluate the tradeoff between the various objectives and select the best compromise solution.

Algorithm performance will be evaluated by comparing recommendations from the optimization routine to actual dosings administered to patients. Objective scores for the actual and recommended dosings will be computed and a final recommendation made.

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CHAPTER 2

REMIFENTANIL-PROPOFOL PHARMACODYNAMIC MODELS FOR INTOLERABLE VENTILATORY DEPRESSION, LOSS OF RESPONSIVENESS, AND LOSS OF RESPONSE TO ESOPHAGEAL INSTRUMENTATION[*]

2.1 Abstract

2.1.1 Introduction

Remifentanil and propofol are increasingly used for short duration procedures in spontaneously breathing patients. In this setting, it is preferable to block the response to moderate stimuli while avoiding loss of responsiveness (LOR) and intolerable ventilatory depression (IVD). The aim of this study was to explore selected effects of combinations of remifentanil-propofol effect-site concentrations (Ces) that lead to a loss of response to esophageal instrumentation (EI), a LOR, and/or onset of IVD. A secondary aim was to use these observations to create response surface models for each effect measure. We hypothesized that (1) in a high percentage of volunteers, selected remifentanil and propofol Ces would allow EI yet avoid LOR and IVD and (2) the drug interaction for these effects would be synergistic.

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2.1.2 Methods

Twenty-four volunteers received escalating target controlled remifentanil and propofol infusions over ranges of 0-6.4 $ng \cdot mL^{-1}$ and 0-4.3 $mcg \cdot mL^{-1}$, respectively. At each set of target concentrations, responses to insertion of a blunt end bougie into the mid-esophagus (40 cm), level of responsiveness, and respiratory rate were recorded. From these data, response surface models of loss of response to EI and IVD were built and characterized as synergistic, additive, or antagonistic. A previously published model of LOR was used.

2.1.3 Results

Of the possible 384 assessments, volunteers were unresponsive to EI at 105 predicted R-P Ces; in 30 of these, volunteers had no IVD; in 30 of these, volunteers had no LOR; and in 9 of these, volunteers had no IVD or LOR. Many other assessments over the same concentration ranges, however, did have LOR and/or IVD. The combinations that allowed EI and avoided IVD and/or LOR primarily clustered around remifentanil propofol Ces ranging from 0.8 to 1.6 $ng \cdot mL^{-1}$ and 1.5 to 2.7 $mcg \cdot mL^{-1}$, respectively, and to a lesser extent around 3.0 to 4.0 $ng \cdot mL^{-1}$ and 0.0 to 1.1 $mcg \cdot mL^{-1}$, respectively. Models of loss of response to EI and IVD both demonstrated a synergistic interaction between remifentanil and propofol.

2.1.4 Discussion

Selected remifentanil-propofol concentration pairs, especially higher propofol-lower remifentanil concentration pairs, can block the response to EI while avoiding IVD in spontaneously breathing volunteers. It is, however, difficult to block the response to EI and avoid both LOR and IVD. It may be necessary to accept some discomfort and blunt rather than block the response to EI in order to consistently avoid LOR and IVD.

2.2 Introduction

Propofol in combination with remifentanil is useful for medical procedures that require moderate sedation and analgesia. Both drugs are rapid acting and quickly dissipate once administration is terminated. They interact synergistically with one another,[1] requiring less of each drug to achieve a desired effect when used in combination. For example, a synergistic interaction is present for loss of response to laryngoscopy[1-3] and moderately painful stimuli,[4] and to a lesser extent for loss of responsiveness.[1-3,5]

Propofol and combinations of propofol with an opioid have been used to block the response to noxious stimuli during procedures in spontaneously breathing patients in the context of moderate sedation.[6-11] In this setting, it is preferable to block the response to moderate noxious stimuli while avoiding intolerable ventilatory depression and minimizing loss of responsiveness.

The aim of this study was to explore the effects of selected combinations of remifentanil and propofol. Effects of interest included a loss of response to esophageal instrumentation, a loss of responsiveness, and intolerable ventilatory depression. A secondary aim was to use these observations to create response surface models for each effect measure. We hypothesized that in a high percentage of volunteers, selected remifentanil-propofol effect-site concentrations would allow esophageal instrumentation yet avoid intolerable ventilatory depression and that the drug interaction for these effects would be synergistic.

2.3 Methods

2.3.1 Volunteer recruitment and instrumentation

After approval by the Institutional Review Board at the University of Utah, informed written consent was obtained from 12 male and 12 female

(nonpregnant/nonlactating) volunteers. Eligible volunteers had an American Society of Anesthesiologists' Physical Status of I or II, were nonsmokers 18 years of age or older, and had a body mass index between 18 and 28. Volunteers were not eligible if they had a history of significant alcohol or drug abuse, allergy to opioids or propofol, sleep apnea, or chronic drug requirements or medical illness that are known to alter the pharmacokinetics or pharmacodynamics of opioids or intravenous anesthetics.

2.3.2 Monitoring

Following overnight fasting, volunteers had a 20-gauge intravenous catheter placed for fluid and drug administration. A maintenance infusion of 0.9% sodium chloride was administered at 1 $mL \cdot kg^{-1} \cdot hour^{-1}$ throughout the study period. In addition, a 20-gauge arterial catheter was placed in a radial artery for continuous blood pressure monitoring and intermittent arterial blood gas analyses. Volunteers were monitored with an electrocardiogram, pulse oximeter, noninvasive blood pressure, and expired carbon dioxide and inspired oxygen monitor. Inspired and expired airway flow and volumes were measured using a pneumotachometer (Novametrix, Louisville, KY) attached to a tight fitting mask. All volunteers received oxygen by face mask at 2 $L \cdot min^{-1}$. A Mapleson E circuit was used to provide manual ventilation if required to maintain adequate oxygenation and ventilation. Before administration of the study drugs, volunteers were treated with 0.2 mg glycopyrrolate to prevent bradycardia and 30 mL sodium citrate by mouth.

2.3.3 Experimental design

The study was an open-label, randomized, parallel group study using a crisscross design as described by Short et al. to assess drug interactions.[12] Each volunteer was randomly assigned to one of two groups: a basal infusion group of remifentanil or propofol. Each group was further randomized to receive three of six

possible sets of escalating predicted target effect-site concentrations (Ces) (Appendix A). For each set, one drug was stepped through five predetermined Ce targets (primary agent) while the second drug was held at a constant Ce (secondary agent). Following each set, the infusions were stopped until predicted Ces for both drugs returned to near 0, at which time the next set would begin. This design provided a total of 61 possible pairs: one at baseline prior to drug administration, 30 for the remifentanil basal infusion group, and 30 for the propofol basal infusion group.

Based on prior work,[1,5,13] 8 to 9 volunteers were randomly assigned to eight of the twelve sets (sets 1-4 of the remifentanil and propofol groups) of concentration pairs in the anticipated transition zone (less than 5.0 $ng \cdot mL^{-1}$ and 3.3 $mcg \cdot mL^{-1}$ for remifentanil and propofol, respectively) and one to two volunteers to the remaining four sets (sets 5 and 6 of the remifentanil and propofol groups) anticipated to be near maximal effect. The predicted target effect-site concentrations ranged from (0.0–6.4 $ng \cdot mL^{-1}$) for remifentanil and (0.0–4.3 $mcg \cdot mL^{-1}$) for propofol. The study was designed so each experiment could be completed within 10 hours.

2.3.4 Drug delivery and effect measures

Target controlled infusions were administered using computer controlled infusion pumps (Pump 22; Harvard Apparatus, Limited, Holliston, MA) and drug infusion software (STANPUMP, Available from Steven L. Shafer, M.D., at http://www.opentci.org/doku.php?id=code:code. Posted November 25, 2008. Last accessed June 3, 2010). Pharmacokinetic parameters published by Minto et al. were used for remifentanil[14] and Schnider et al. for propofol.[15] Effect measurements began 5 min after predicted Ces reached the targeted concentrations.

At each target concentration pair, volunteers underwent an assessment period consisting of three measures. First, an assessment of responsiveness was made using

the Observers Assessment of Alertness and Sedation (OAA/S) scale (Table 2.1).[16] A loss of response was defined as an OAA/S score = 1. Second, an assessment of respiratory rate was made using the capnography tracing. Intolerable ventilatory depression was defined as a respiratory rate of 4 or less breaths in a 1-min time window. During pilot studies, we arrived at this respiratory rate cutoff based on several observations: Below 4 breaths per minute, volunteers consistently began to (1) have a drop in their SpO2 levels (a rapid decline from 100 to low 90s), (2) the ETCO2 began to rise above 50 mmHg, and (3) without manual bag mask ventilation, the volunteers would become hypoxic. Third, an assessment of response to esophageal instrumentation was made. A 42 French (14 mm diameter, 215542, Teleflex Medical, RTP, NC) blunt end bougie was placed through the oropharynx and advanced 40 cm into the esophagus. Loss of response to esophageal instrumentation was defined as no gag reflex, no voluntary or involuntary movement, and no change in heart rate or blood pressure greater than 20% from baseline values recorded just prior to instrumentation. Each volunteer underwent a total of 16 assessment periods (one at baseline and five in each of three sets).

Volunteers were verbally prompted to breathe if there were less than 2 breaths in 30 seconds. If SpO2 was below 95% on 2 liters per min of face mask oxygen or expired carbon dioxide levels were greater than 55 mmHg and they did not respond to prompts to breathe, mask ventilation was provided. If airway obstruction was present, the airway was opened using a head tilt and chin lift and/or placement of an oral pharyngeal airway. If volunteers developed a mean arterial blood pressure or heart rate less than 20% of baseline, drug administration was terminated and the washout period begun. Ephedrine 5-10 mg was administered intravenously to treat hypotension as needed.

Table 2.1: The Observers Assessment of Alertness/Sedation (OAA/S) score[16]

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
2	Responds only after moderate prodding or shaking.
1	Does not respond to moderate prodding or shaking

An Observer's Assessment of Alertness/Sedation score of 1 was considered unresponsive.

2.3.5 Response surface models

Using modeling software (MATLAB R2008b, The MathWorks, Inc., Natick, MA), binary data (presence or absence of a response) for loss of response to esophageal instrumentation and onset of intolerable ventilatory depression were fit to a Greco model[17] adjusted for categorical data[18] using equation 2.1. For loss of responsiveness, a previously reported model based on data collected in volunteers in a similar fashion was used.[5]

$$P(LR=1 \mid C_R, C_P) = \frac{E_{\max} * \left(\frac{C_R}{C_{50R}} + \frac{C_P}{C_{50P}} + \alpha \cdot \frac{C_R}{C_{50R}} \cdot \frac{C_P}{C_{50P}} \right)^{\gamma}}{\left(\frac{C_R}{C_{50R}} + \frac{C_P}{C_{50P}} + \alpha \cdot \frac{C_R}{C_{50R}} \cdot \frac{C_P}{C_{50P}} \right)^{\gamma} + 1} \quad 2.1$$

$P(LR = 1|C_R, C_P)$ is the probability of loss of response at a given remifentanil (C_R) and propofol (C_P) concentration. E_{max} is the maximal effect (i.e. loss of response to esophageal instrumentation) and is 1 for categorical data. C_R and C_P are the predicted Ces of remifentanil and propofol ($ng \cdot mL^{-1}$ and $mcg \cdot mL^{-1}$) as predicted by Stanpump. C_{50R} and C_{50P} are the concentrations of remifentanil and propofol that alone achieve 50% probability of no response. The parameter γ (gamma) determines the slope along the sigmoid surface, and α (alpha) is the drug interaction term.

Models were built using a naïve pooled technique.[19] Effect ranged from 0 (100% probability of response) to 1 (100% probability of no response). Model parameters were determined using an iterative approach minimizing the -2 Log Likelihood (-2LL), presented in equation 2.2.

$$-2LL = -2 \cdot \sum_{i=1}^{N} (R_i \cdot \ln(P) + (1 - R_i) \cdot (1 - P)) \quad 2.2$$

N is the number of observations made for all volunteers combined, R_i is the observed

response, and *P* is the corresponding probability of loss of response.

To characterize variability, coefficients of variation (CV) for each model parameter were estimated using a bootstrap technique. One thousand subsamples were randomly drawn (with replacement) from the raw data, with each subsample containing the same number of data points as the raw data set. Estimates of model parameters were generated from each subsample using the same techniques described previously. The mean (μ) and standard deviation (σ) of the 1000 estimates were used to compute the CV for each model parameter (equation 2.3).

$$CV = \frac{\sigma}{\mu} \qquad 2.3$$

The CV was computed in this manner at least 10 times for each effect measure. It was continued until the percent change between the average of all iterations and the average from all previous iterations was less than 5%. The final averaged CV was reported.

For each effect measure, model fits were evaluated using a Chi-square (χ^2) goodness-of-fit test. Response/no response data were divided into probability bins with at least 5 no response data points in each bin. The expected frequency of no response for each bin (P_i) was calculated by multiplying the mean predicted probability by the total number of observations in the bin. Observed frequency of no response (O_i) was the number of observations where no response occurred. The χ^2 test statistic was computed using equation 2.4:

$$\chi^2 = \sum_{i=1}^{k} \frac{(O_i - P_i)}{P_i} \qquad 2.4$$

k is the number of bins. The null hypothesis was that the expected (based on the

model's prediction of probability of no response) and observed frequencies were from the same distribution and was rejected if the χ^2 test statistic exceeded the χ^2 critical value at a significance level of 5% with k-5 degrees of freedom (four parameters used to compute expected frequency are estimated from the data).

Two graphical approaches were used to assess model fits. The first plot presented the observed responses and a topographical rendering of model predictions. A graphical representation of the model was created by plotting the 5, 50, and 95% iso-effect lines (isoboles) representing predicted remifentanil-propofol Ces that produce an equivalent effect. This format was used to illustrate the number of volunteers that developed a loss of response alongside model predictions of the same effect measure. The second plot presented the observed responses and a three-dimensional rendering (response surface) of model predictions. This format was used to illustrate the differences between model predictions (ranging from 0 to 1 using equation 2.1) and observed responses (either 0 or 1). An assessment of how well the model predictions fit the observations was made by calculating the percentage of predictions that agreed with observations. Agreement was defined as an absolute difference less than 0.5.

2.3.6 Comparison of model profiles

Topographical plots of models of loss of response to esophageal instrumentation, loss of responsiveness, and intolerable ventilatory depression were superimposed on one another. Each plot included the 5, 50, and 95% isoboles. Visual inspection of superimposed isoboles was used to identify potential concentration pairs with a high probability of loss of response to esophageal instrumentation, but avoid loss of responsiveness or intolerable ventilatory depression.

2.4 Results

All twenty-four volunteers (12 male and 12 female) completed the study. The mean ± standard deviation of the height, weight, body mass index, and age were 174 ± 8 cm, 71 ± 12 kg, 23 ± 3 $kg \cdot m^{-2}$, and 25 ± 4 years, respectively.

Appendix A presents the observed responses for each effect measure over the 61 concentration pairs investigated. Seventeen assessment periods were completely or partially aborted at higher target concentrations because blood pressure and/or heart rate were less than 20% of baseline. Portions of three assessment periods were aborted due to inadequate oxygenation after maneuvers to correct it failed. Of the possible 384 evaluations and 61 possible concentration pairs, 367 were made for esophageal instrumentation at 56 concentration pairs, 373 were made for loss of responsiveness at 58 concentration pairs, and 376 were made for intolerable ventilatory depression at 59 concentration pairs (Appendix A).

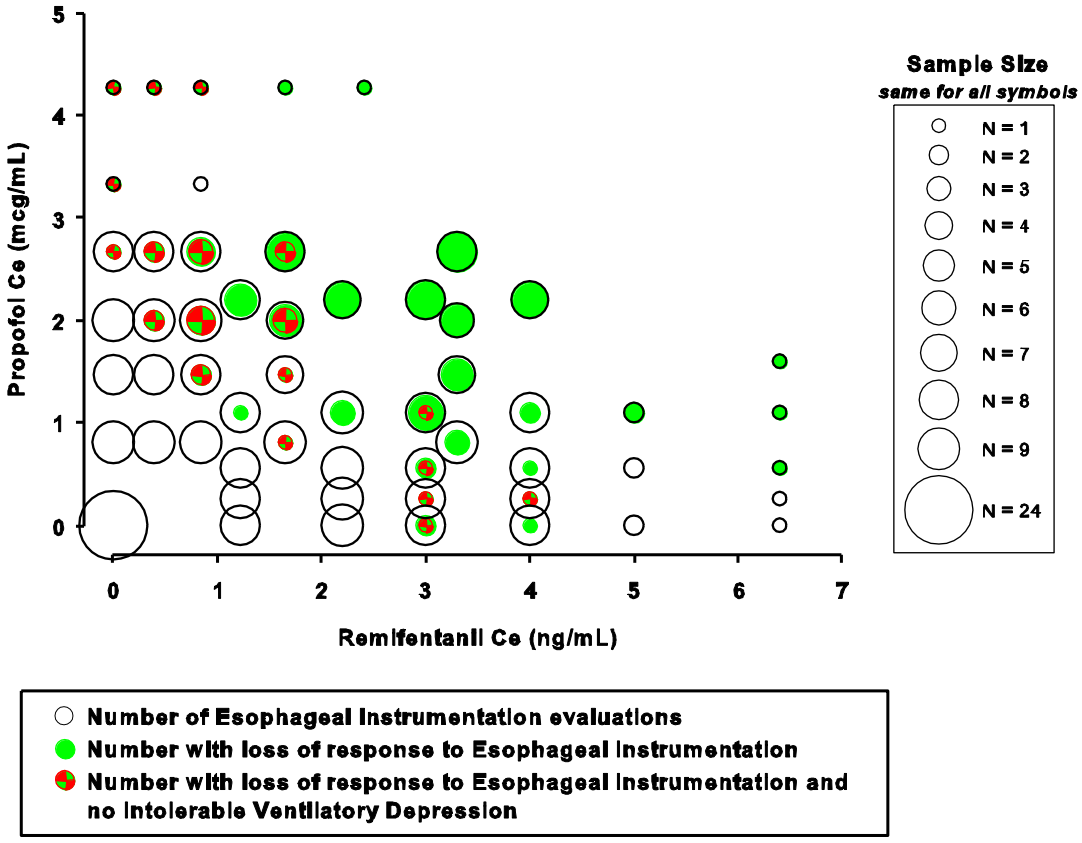
2.4.1 Effect measures

For esophageal instrumentation, some or all of the volunteers in 38 out of the 56 target concentration pairs exhibited no response (105 out of the 367 evaluations). Ten of the 38 concentration pairs consistently blocked the response to esophageal instrumentation (Figure 2.1). Responses at the remaining 28 concentration pairs were mixed (i.e. some volunteers responded, others did not). For example, with propofol at 2.7 $mcg \cdot mL^{-1}$ and remifentanil at 0.8 $ng \cdot mL^{-1}$, 4 volunteers tolerated esophageal instrumentation and 4 did not.

Of the concentration pairs that blocked the response to esophageal instrumentation, 30 assessments at 19 concentration pairs had no intolerable ventilatory depression (Figure 2.1, Panel A). Of those, 4 assessments at 4 concentration pairs between 0.0 and 0.8 $ng \cdot mL^{-1}$ for remifentanil and 3.3 and 4.3 $mcg \cdot mL^{-1}$ for propofol

Figure 2.1: Presentation of raw data (observed responses) at 56 predicted remifentanil-propofol effect-site concentration pairs. Open circle size indicates the total number of esophageal instrumentation (EI) assessments made. Solid green circles represent a subset of those assessments where volunteers had no response to EI. Circles with two colors represent smaller subsets that had a combination of selected responses. In **Panel A**, red and green circles represent a loss of response to EI and no intolerable ventilatory depression (IVD). In **Panel B**, blue and green circles represent a loss of response to EI and no loss of responsiveness (LOR). In **Panel C**, blue and red circles represent a loss of response to EI, no LOR, and no IVD. Circle size represents the number of assessments (see legend) for each circle type (open, solid green, etc.). Ce indicates effect-site concentration. IVD was defined as a respiratory rate of 4 or less breaths per minute.

a) Panel A: Loss of Response to EI and no IVD



b) Panel B: Loss of response to EI and no LOR

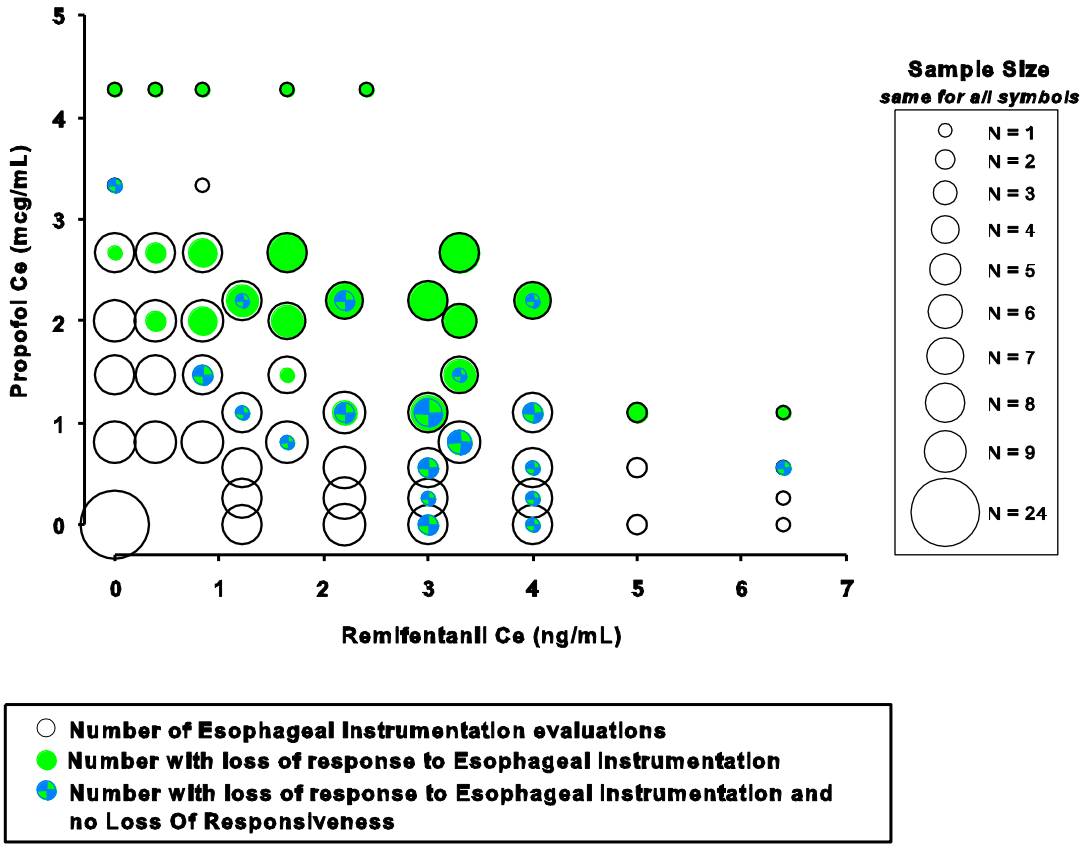


Figure 2.1 continued

c) Panel C: Loss of response to EI and no LOR and no IVD

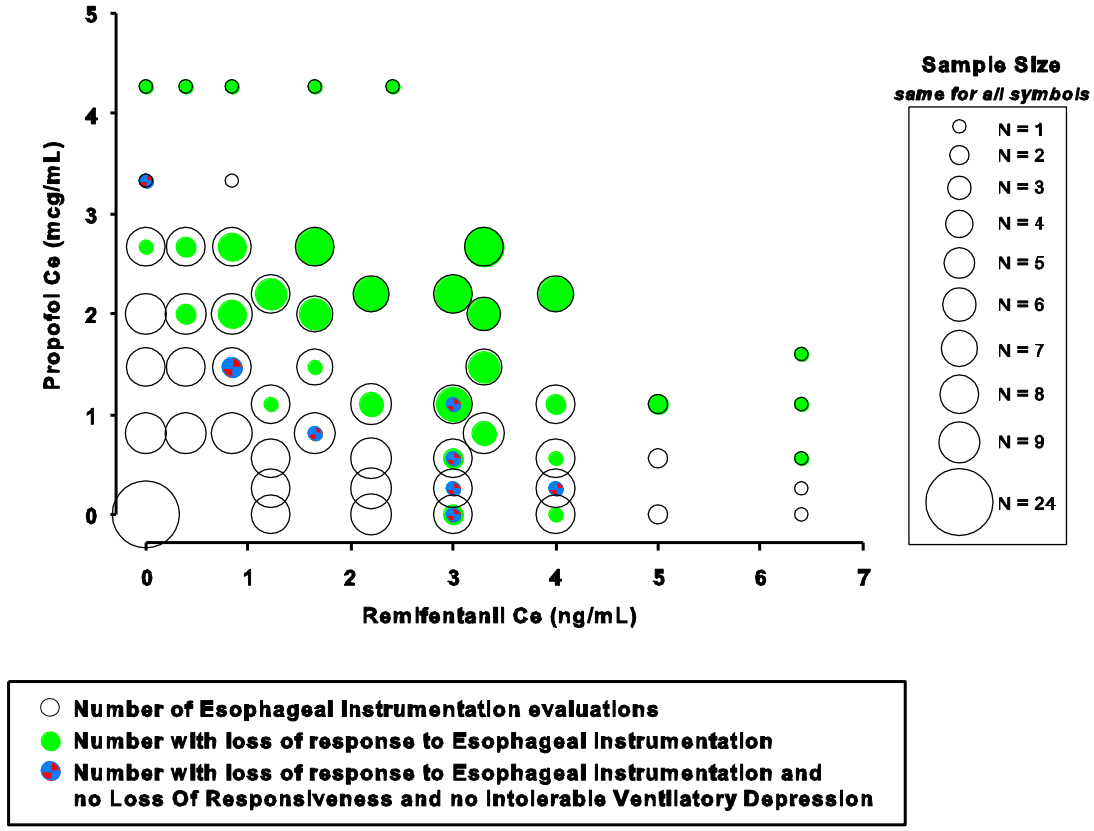


Figure 2.1 continued

consistently had no intolerable ventilatory depression and tolerated esophageal instrumentation. All other pairs had a mixed response; some volunteers tolerated esophageal instrumentation but had intolerable ventilatory depression while others did not. For example, with remifentanil at 1.6 $ng \cdot mL^{-1}$ and propofol at 2.0 $mcg \cdot mL^{-1}$, 5 out of 7 volunteers tolerated esophageal instrumentation and 2 of those 5 (3 of the 7) had no intolerable ventilatory depression.

Of the concentration pairs that blocked the response to esophageal instrumentation, 30 assessments at 19 concentrations pairs (not identical to the 30 above) had no loss of responsiveness (Figure 2.1, Panel B). At 8 of the concentration pairs, 9 volunteers also had no intolerable ventilatory depression and no loss of responsiveness (Figure 2.1, Panel C). For example, with propofol at 1.5 $mcg \cdot mL^{-1}$ and remifentanil at 0.8 $ng \cdot mL^{-1}$, 2 of 8 volunteers tolerated esophageal instrumentation with no intolerable ventilatory depression and no loss of responsiveness, but the other 6 did not tolerate esophageal instrumentation.

2.4.2 Response surface models

With visual inspection of the raw data, it is clear that the development of intolerable ventilatory depression at high propofol, low remifentanil concentrations was beyond the range of target concentrations used in our study design. For model building purposes, 31 data points at higher concentrations taken from previous work in our laboratory as part of a study in similar volunteers conducted by Kern et al.[1] were therefore included in our analysis. These additional data, presented in Appendix B, were collected using the same drugs, drug delivery technique, and approach to assessment of respiratory rate. Four hundred and seven data points were used to construct the model of intolerable ventilatory depression.

Model parameters, coefficients of variation, and goodness-of-fit analysis for loss

of response to esophageal instrumentation and intolerable ventilatory depression are presented in Table 2.2. P values from the Chi squared goodness-of-fit test confirmed the null hypothesis that predicted and observed frequencies were from the same distribution, indicating a good fit for each model. Coefficients of variation ranged from 5 to 58%. More variability (i.e. larger coefficients of variation) was estimated about the alpha (interaction) model parameter. The positive alphas were consistent with a synergistic interaction for all models. The response surface models predicted transitions from responsive to unresponsive over a large range of the tested remifentanil and propofol concentrations (as indicated by the small gamma parameter values).

Observed responses superimposed over response surface models for each effect measure are presented in Figure 2.2A and Figure 2.2C. In both models, predictions are consistent with observations; all volunteers above the 95% isobole are unresponsive, a large majority are unresponsive between the 50 and 95% isoboles, the responses are mixed between the 5 and 50% isoboles, and very few are unresponsive below the 5% isobole.

Isoboles in both models bow toward the origin, indicating a synergistic interaction. The shape of the model of intolerable ventilatory depression and that of the model of esophageal instrumentation were different. Isoboles for intolerable ventilatory depression (Figure 2.2C) bow asymmetrically towards remifentanil, illustrating the large influence of opioids on this effect measure. By contrast, isoboles for esophageal instrumentation (Figure 2.2A) bow symmetrically between remifentanil and propofol.

Agreement between model predictions and observations is presented graphically in Figure 2.2B and Figure 2.2D. For both models, agreement was high at concentration pairs below and above the slope of the response surface, but in the transition from 5 to 95%, the difference between predictions and observations were greater than 0.5 at several of the observations. Using an absolute difference less than 0.5 as a cutoff for

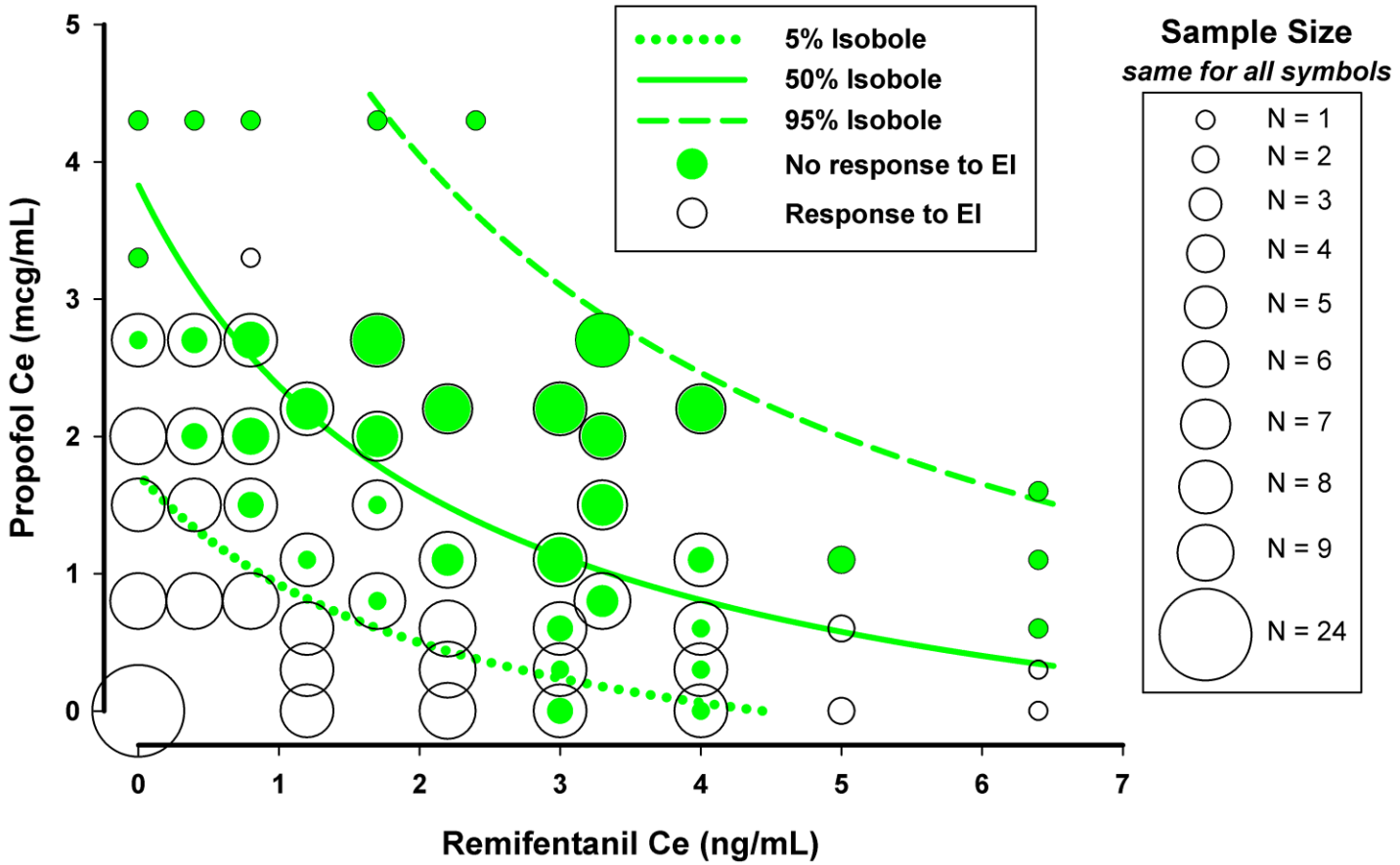
Table 2.2: Interaction model parameters, coefficients of variation, and goodness-of-fit parameters

Stimulus	**$C_{50\ remi}$ (CV)** ng·mL^{-1}	**$C_{50\ prop}$ (CV)** mcg·mL^{-1}	**α (CV)** *(interaction)*	**γ (CV)** *(slope)*	**p,X^2**
LOR*	33.1	2.2	3.6	5.0	
LREI	9.8 (25%)	3.8 (5%)	4.5 (58%)	3.7 (10%)	0.643
IVD	4.1 (24%)	7.0 (26%)	3.0 (38%)	3.2 (25%)	0.929

LOR = Loss of responsiveness (OAA/S = 1), LREI = Loss of response to esophageal instrumentation, and IVD = Intolerable ventilatory depression, CV = coefficients of variation, remi =remifentanil, prop = propofol, C50 = predicted concentration associated with a 50% probability of maximum effect. *Previously reported by Johnson et al.[5]

Figure 2.2: Observed and response surface model predictions for loss of response to esophageal instrumentation (EI) and intolerable ventilatory depression (IVD). Panels A and C present topographical views of raw data and model predictions. In **Panel A**, open circles represent assessments of a response to EI and solid green circles represent a subset of those assessments where there was a loss of response to EI. In **Panel C**, open circles represent assessments of IVD and solid red circles represent a subset of those assessments where there was IVD. The dotted, solid, and dashed lines represent the 5, 50, and 95% iso-effect lines (isoboles) for each model, respectively. Panels B and D present three-dimensional views of the raw data, model predictions, and an assessment of model error. The grid and colored lines represent response surface model predictions with their associated isoboles. Circles represent observed responses. Circles at the bottom of the response surface (0% probability) represent a response to EI (**Panel B**) or no IVD (**Panel D**). Circles at the top (100% probability) represent no response to EI (**Panel B**) or the presence of IVD (**Panel D**). Open circles represent assessments where the difference between predicted and observed response is less than 50% while solid circles represent assessments where the difference is greater than 50%. Circle size represents the number of assessments (see legend) for each circle type (open, solid, etc.). Ce indicates effect-site concentration. IVD was defined as a respiratory rate of 4 or less breaths per minute.

a) Panel A: Esophageal Instrumentation



b) Panel B: Esophageal Instrumentation

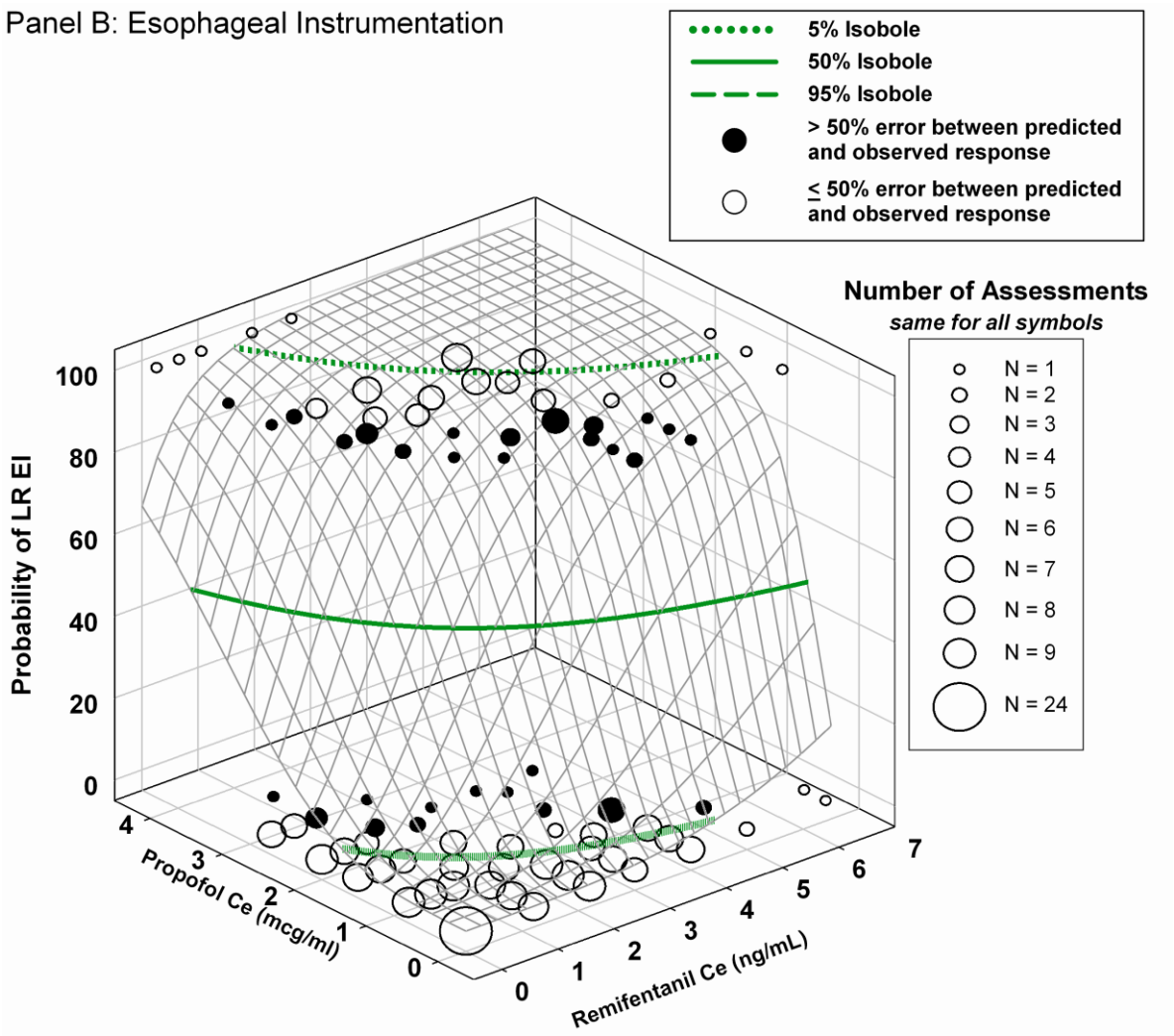


Figure 2.2 continued

c) Panel C: Intolerable Ventilatory Depression

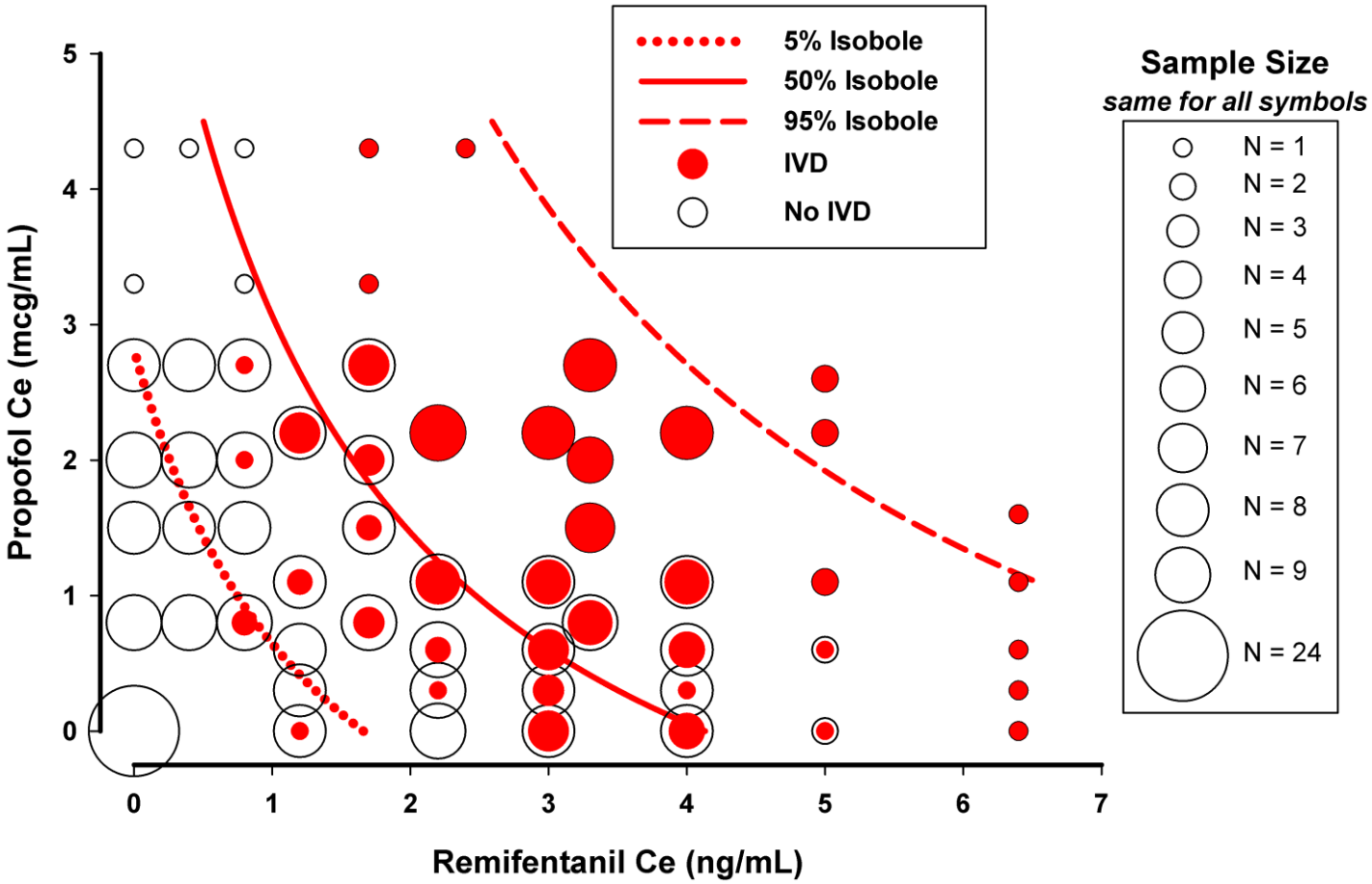


Figure 2.2 continued

d) Panel D: Intolerable Ventilatory Depression

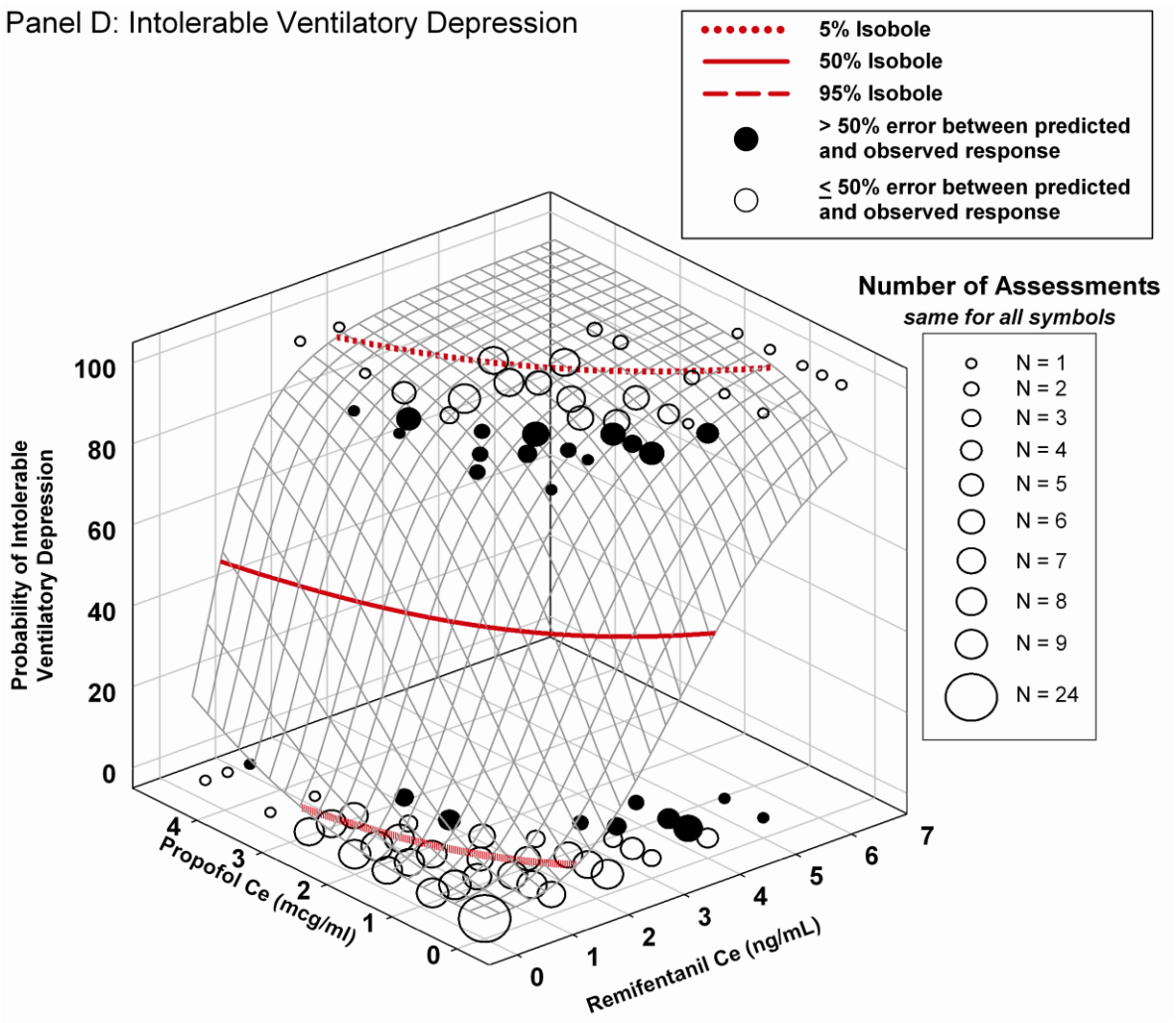


Figure 2.2 continued

model goodness-of-fit, the percentage of model predictions consistent with observed responses was 79% and 81% for the EI (Figure 2.2B) and IVD (Figure 2.2D) models, respectively.

Superimposed topographical plots of the loss of responsiveness, loss of response to esophageal instrumentation, and intolerable ventilatory depression models are presented in Figure 2.3. A comparison of isoboles between models revealed no regions of remifentanil-propofol concentration pairs that would have a high probability (>95%) of no response to EI and a low probability (<5%) of intolerable ventilatory depression and loss of responsiveness. Disregarding loss of responsiveness, there is a region of low remifentanil (0-1.5 $ng \cdot mL^{-1}$) and high propofol (4-6 $mcg \cdot mL^{-1}$) concentrations where there is a high probability (> 80-95%) of loss of response to esophageal instrumentation and a moderate probability (40-70%) of intolerable ventilatory depression.

2.5 Discussion

We explored the effects of various combinations of remifentanil-propofol target concentrations on responsiveness, esophageal instrumentation, and ventilatory depression. We hypothesized that in a high percentage of volunteers, selected concentration pairs would allow esophageal instrumentation yet avoid intolerable ventilatory depression. Our results in part confirmed this hypothesis; we found that low remifentanil (0.8 $ng \cdot mL^{-1}$) and high propofol (2 -3 $mcg \cdot mL^{-1}$) concentration pairs blocked the response to esophageal instrumentation and avoided intolerable ventilatory depression in a majority of volunteers (Figure 2.1). At higher propofol concentrations, the response to esophageal instrumentation was blocked completely with no intolerable ventilatory depression, but the number of assessments was small, making it difficult to conclude that these concentration pairs would consistently lead to the desired response.

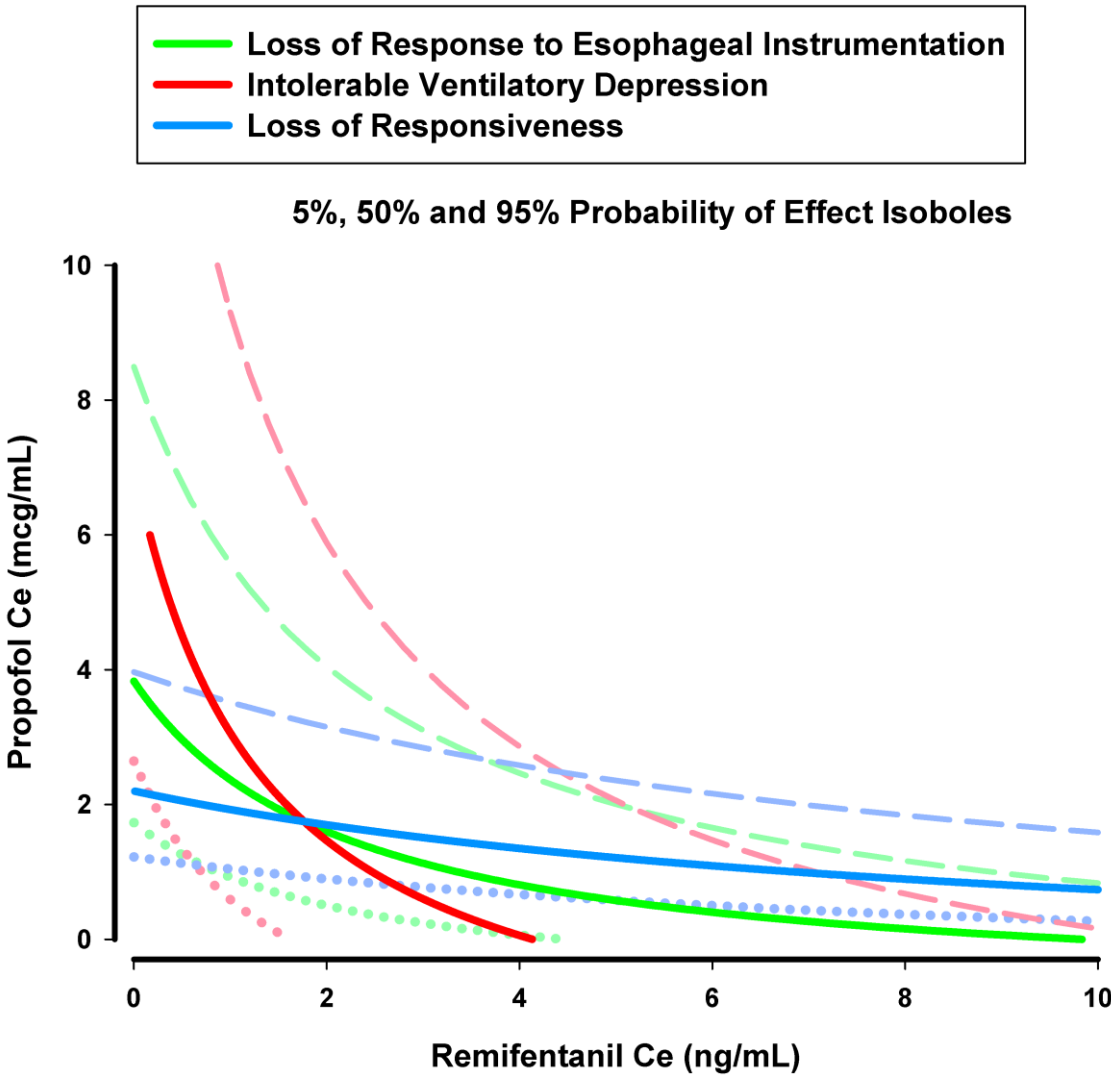


Figure 2.3: Superimposed topographical plots for probability of loss of responsiveness (blue), loss of response to esophageal instrumentation (green), and intolerable ventilatory depression (red) response surface models. Isobole probability is indicated by line style: dotted lines represent 5%, solid lines represent 50% and dashed lines represent 95%. The loss of responsiveness model was created using parameters previously reported by Johnson et al.[5]

2.5.1 Effect measures

By comparison to studies by Kazama and Drover who also explored propofol requirements for esophageal instrumentation, our results are somewhat different; we had to use higher concentrations to achieve conditions that would allow esophageal instrumentation than what these authors have reported. The differences are most likely due to variations in study design. Kazama et al. studied the use of target controlled infusions in patients of various ages undergoing endoscopy [20]. They reported a propofol C_{50} of 2.8 mcg·mL^{-1} to blunt the response to esophageal instrumentation in 17-49 year old patients. Higher concentrations were required to blunt the gag reflex (C_{50} = 3.0 mcg·mL^{-1}). These are both lower than what we reported (C_{50} of 3.8 mcg·mL^{-1}). By design, they considered some movement and coughing NOT to be a response during endoscope placement. By comparison, our criteria to consider movement and heart rate change as responses are perhaps overly stringent and not reflective of clinical practice. Endoscopists may tolerate some level of patient movement or heart rate change to blunt rather than completely block the response to esophageal instrumentation.

Drover et al. have studied the use of target controlled infusion in pediatric patients ages 3-10 years old undergoing endoscopy.[21] Similar to Kazama et al., minimal movement was NOT considered a response to esophageal instrumentation. They reported a propofol C_{50} of 3.7 mcg·mL^{-1}. Drover also explored how a remifentanil infusion would alter propofol requirements for esophageal instrumentation. Using a continuous remifentanil infusion of 0.025 mcg·kg^{-1}·min^{-1}, the propofol requirement decreased to 2.8 mcg·mL^{-1}. For ease of comparison, we simulated this remifentanil infusion in a 55 year old, 75 kg, 175 cm male, which lead to a steady state predicted remifentanil Ce near 0.7 ng·mL^{-1}. This concentration pair is consistent with our findings and very close to the 50% isobole we reported in Figure 2.2. Drover et al. also explored 0.05 and 0.10 mcg·kg^{-1}·min^{-1} remifentanil infusion rates, which, when simulated in the same demographic, lead

to remifentanil Ces of 1.4 and 2.8 $ng \cdot mL^{-1}$, but patients developed significant respiratory depression requiring positive pressure ventilation. They concluded that lower remifentanil infusion rates may be more appropriate for pediatric endoscopies.

In addition to defining the loss of response to esophageal instrumentation, we also sought to characterize the extent of intolerable ventilatory depression and loss of responsiveness over the same set of target remifentanil and propofol concentrations. We found that many of the volunteers tolerated esophageal instrumentation and did not develop intolerable ventilatory depression, but this profile of responses was highly variable. At the same concentration pair, some volunteers would tolerate esophageal instrumentation, others would not; some would have significant ventilatory depression, others would not. The raw data revealed no pattern between volunteers who tolerated esophageal instrumentation and those that had intolerable ventilatory depression. A majority of the volunteers that tolerated esophageal instrumentation without significant ventilatory depression were at target concentration pairs consisting of high propofol, low remifentanil levels (Figure 2.1A). Similarly, we found that many of the volunteers tolerated esophageal instrumentation and did not lose responsiveness, but this profile was also quite variable (Figure 2.1B). By contrast, a majority of the volunteers that tolerated esophageal instrumentation and did not lose responsiveness were at target concentration pairs consisting of high remifentanil, low propofol levels. Finally, there were very few volunteers that tolerated esophageal instrumentation with no intolerable ventilatory depression and no loss of responsiveness.

With regard to intolerable ventilatory depression, we made our evaluations in an un-stimulated state. This was done to facilitate data collection using the capnograph, mimicking the scenario where patients receive anesthetics to blunt the response to a brief, painful stimulus followed by a period of relatively little stimulus, and to explore the impact this dosing approach has on ventilatory function. It is conceivable that

observations of respiratory rate during stimuli such as calling out their name during the OAA/S assessment would increase their ventilatory rate and shift the observed onset of intolerable ventilatory depression to higher concentrations.

We also chose respiratory rate as a measure of ventilatory function because of its familiarity among practitioners and its availability on many physiologic monitors. There are limitations to this measure. For example, we did not account for tidal volume; we acknowledge that minute volume may have been adequate to achieve both oxygenation and ventilation despite a slow respiratory rate. Many volunteers achieved tidal volumes greater than 1000 mL at slow respiratory rates. Furthermore, we did not account for changes in arterial CO_2 on respiratory drive as many other authors have.[22-25] Nevertheless, in the setting of moderate sedation, most clinicians would agree that a ventilatory rate of 4 or less per minute is concerning.

2.5.2 Response surface models

We constructed a response surface model for loss of response to esophageal instrumentation and the presence of intolerable ventilatory depression. Both graphical and statistical approaches indicated that the models fit the observed data well. From a graphical perspective (Figure 2.2), the models appear to capture the transition from responsive to unresponsive well and this was confirmed by the χ^2 analysis and percentage of model predictions consistent with observed responses. We hypothesized that the interaction between these drugs would by synergistic for both effect measures. Our results confirmed this hypothesis as illustrated by the positive alpha values presented in Table 2.2.

To our knowledge, no prior interaction model exists for esophageal instrumentation. Judged in terms of the concentrations required to blunt the response, the stimulus associated with esophageal instrumentation is much less than what we

previously reported for loss of response to laryngoscopy but similar to reports by Bouillon et al. (Table 2.2). For laryngoscopy, we reported remifentanil and propofol C_{50}'s for loss of response to laryngoscopy of 48.9 ng·mL^{-1} and 5.6 mcg·mL^{-1} respectively[1] and Bouillon et al. reported 9.0 ng·mL^{-1} and 5.6 mcg·mL^{-1} respectively.[2] With regard to intolerable ventilatory depression, prior work by Nieuwenhuijs et al. explored the onset of respiratory depression at remifentanil-propofol concentrations ranging from 0.0 to 2.0 ng·mL^{-1} and 0.0 to 2.0 mcg·mL^{-1} respectively.[23] They used a 50% decrease from baseline minute ventilation as their effect measure (i.e. presence or absence of respiratory depression). They constructed a response surface model from their data using a nonlinear pharmacodynamic model structure. Although the effect measures and model constructs were different than ours, the C_{50}'s reported were similar considering the range of drugs they tested (4.2 versus 3.3 ng·mL^{-1} for remifentanil and 6.8 versus 15.8 mcg·mL^{-1} for propofol).

To further explore the behavior of propofol in combination with remifentanil, we compared model predictions from three response surfaces: the two presented in this study and a previously reported response surface for loss of responsiveness.[5] In attempting to orient oneself to the clinical meaning of response surfaces, a simple "take home" message is that target concentrations of approximately 2 ng·mL^{-1} of remifentanil and 2 mcg·mL^{-1} of propofol produce about a 50% probability of no response to esophageal instrumentation, no response to verbal and tactile stimuli, and intolerable ventilatory depression. Similarly, target Ces of 1 ng·mL^{-1} of remifentanil and 1 mcg·mL^{-1} of propofol have a low probability (i.e. 5%) and concentrations above 3 ng·mL^{-1} for remifentanil and 3 mcg·mL^{-1} have a high probability (i.e. 95%) (Figure 2.3) of producing those end points.

As illustrated in Figure 2.3, model predictions from each model had considerable overlap. This was consistent with our observations; there was no set of concentration

pairs that consistently provided conditions for esophageal instrumentation yet avoided intolerable ventilatory depression and loss of responsiveness.

In all models, the zone of transition from responsiveness to unresponsiveness (between the 5 and 95% isoboles) covered a wide range of remifentanil and propofol effect-site concentrations. In fact, some of the C_{50}'s are outside the range of predicted concentrations we used during data collection. This is a limitation of our study design. We designed our study with the intent of making assessments over a range of concentrations that were below, at, and above the concentrations necessary to produce a loss of response to esophageal instrumentation or intolerable ventilatory depression. In a majority of our observations, volunteers were either responsive or within the transition zone from responsive to unresponsive. Few of our observations were made where responses were completely blocked. With relatively little data at higher concentrations, our best fit models may have generated parameter sets that were skewed to higher concentrations due to the larger amount of response data at lower concentrations.

With the Greco model structure, when data are well distributed about the C_{50}, the fit is reasonable. When the C_{50} is outside the range of concentrations evaluated, it is extrapolated; in this scenario, small changes in the data can result in large changes in the C_{50}, particularly when the interaction is synergistic. Model predictions will fit the data well at concentrations where observations were made, but can inflate to clinically unrealistic levels for just one drug (i.e. propofol in the intolerable ventilatory depression model). When this occurs, the alpha (interaction) term must also increase to ensure that the model characterizes the data rich portions of the response surface. Caution should be used when interpreting the magnitude of the alpha parameter when C_{50} estimates lie well outside the range of drugs tested.

In summary, we explored the feasibility of blocking the response to esophageal instrumentation in volunteers at various target effect-site concentration pairs of

remifentanil and propofol. In general, our results suggest that although it is possible to identify target concentration pairs that produce significant sedation and analgesia while preserving responsiveness and adequate ventilation, rendering a patient completely unresponsive to esophageal instrumentation requires target concentration pairs that produce a clinical state beyond moderate sedation. In comparison to other similar work and typical clinical practice, the criteria we used to define a loss of response to esophageal instrumentation were perhaps too strict. Our results suggest that in order to stay within the boundaries of moderate sedation, it may be necessary to accept some discomfort and blunt rather than block the response to esophageal instrumentation in order to always avoid intolerable ventilatory depression. Alternatively, it may also be necessary to accept brief unresponsiveness while instrumenting the esophagus. An important clinical feature in this setting is the ability to prompt patients to breathe. Clinicians may tolerate a loss of responsiveness as long as patients continue to breathe; however, in the presence of intolerable ventilatory depression, clinicians are likely to find a prolonged loss of responsiveness and the inability to prompt a patient to breathe unacceptable. In conclusion, our results represent a preliminary finding in healthy volunteers. Further work is warranted to validate these models in patients undergoing moderate to deep sedation for procedures that require esophageal instrumentation.

2.6 Appendix A: Target Effect-site Concentration Sets and Observed Responses.

Table 2.3: Target effect-site concentration sets and observed responses

Remifentanil Group							Propofol Group						
		Primary Infusion	Secondary Infusion	Effect Measures					Secondary Infusion	Primary Infusion	Effect Measures		
Set	N	Remi ($ng \cdot mL^{-1}$)	Prop ($mcg \cdot mL^{-1}$)	LREI	LOR	IVD	Set	N	Remi ($ng \cdot mL^{-1}$)	Prop ($mcg \cdot mL^{-1}$)	LREI	LOR	IVD
0	12	0.0	0.0	0/12	0/12	0/12	**0**	12	0.0	0.0	0/12	0/12	0/12
1	9	0.0	0.8	0/9	0/9	0/9	**1**	8	1.2	0.0	0/8	0/8	1/8
1	9	0.4	0.8	0/9	0/9	0/9	**1**	8	1.2	0.3	0/8	0/8	0/8
1	9	0.8	0.8	0/9	0/9	2/9	**1**	8	1.2	0.6	0/8	0/8	0/8
1	9	1.6	0.8	1/9	0/9	3/9	**1**	8	1.2	1.1	1/8	0/8	2/8
1	9	3.3	0.8	3/9	0/9	6/9	**1**	8	1.2	2.2	5/8	6/8	5/8
2	8	0.0	1.5	0/8	0/8	0/8	**2**	8	2.2	0.0	0/9	0/9	0/9
2	8	0.4	1.5	0/8	2/8	0/8	**2**	8	2.2	0.3	0/9	0/9	1/9
2	8	0.8	1.5	2/8	0/8	0/8	**2**	8	2.2	0.6	0/9	0/9	2/9
2	8	1.6	1.5	1/7	3/8	2/8	**2**	8	2.2	1.1	3/9	2/9	6/9
2	8	3.3	1.5	5/7	5/7	7/7	**2**	8	2.2	2.2	6/7	6/8	9/9
3	9	0.0	2.0	0/9	1/9	0/9	**3**	8	3.0	0.0	2/8	0/8	5/8
3	9	0.4	2.0	2/9	5/9	0/9	**3**	8	3.0	0.3	1/8	0/8	3/8
3	9	0.8	2.0	4/9	7/9	1/9	**3**	8	3.0	0.6	2/8	0/8	5/8
3	9	1.6	2.0	5/7	7/8	3/7	**3**	8	3.0	1.1	6/8	2/8	6/8
3	9	3.3	2.0	5/6	7/7	6/6	**3**	8	3.0	2.2	7/8	7/8	8/8
4	8	0.0	2.7	1/8	5/8	0/8	**4**	8	4.0	0.0	1/8	0/8	4/8
4	8	0.4	2.7	2/8	8/8	0/8	**4**	8	4.0	0.3	1/8	0/8	1/8
4	8	0.8	2.7	4/8	8/8	1/8	**4**	8	4.0	0.6	1/8	0/8	4/8
4	8	1.6	2.7	7/8	8/8	5/8	**4**	8	4.0	1.1	2/8	1/8	6/8
4	8	3.3	2.7	8/8	8/8	8/8	**4**	8	4.0	2.2	6/7	5/7	8/8
5	1	0.0	3.3	1/1	0/1	0/1	**5**	2	5.0	0.0	0/2	0/2	1/2
5	1	0.8	3.3	0/1	1/1	0/1	**5**	2	5.0	0.6	0/2	0/2	1/2
5	1	1.6	3.3	-	1/1	1/1	**5**	2	5.0	1.1	2/2	2/2	2/2
5	1	3.3	3.3	-	1/1	-	**5**	2	5.0	2.2	-	-	2/2
5	1	3.9	3.3	-	1/1	-	**5**	2	5.0	2.6	-	-	2/2

Table 2.3 continued

Remifentanil Group							Propofol Group						
		Primary Infusion	Secondary Infusion	Effect Measures					Secondary Infusion	Primary Infusion	Effect Measures		
Set	N	Remi ($ng \cdot mL^{-1}$)	Prop ($mcg \cdot mL^{-1}$)	LREI	LOR	IVD	Set	N	Remi ($ng \cdot mL^{-1}$)	Prop ($mcg \cdot mL^{-1}$)	LREI	LOR	IVD
6	1	0.0	4.3	1/1	1/1	0/1	**6**	2	6.4	0.0	0/1	0/1	1/1
6	1	0.4	4.3	1/1	1/1	0/1	**6**	2	6.4	0.3	0/1	0/1	1/1
6	1	0.8	4.3	1/1	1/1	0/1	**6**	2	6.4	0.6	1/1	0/1	1/1
6	1	1.6	4.3	1/1	1/1	1/1	**6**	2	6.4	1.1	1/1	1/1	1/1
6	1	2.4	4.3	1/1	1/1	1/1	**6**	2	6.4	1.6	1/1	-	1/1
total	192			56/182	83/188	47/184		192			49/185	32/185	89/192

Remi = Remifentanil, Prop = Propofol, N is the number of subjects assigned to each set based on the study design. Effect measures: LOR = Loss of responsiveness (OAA/S = 1), LREI = Loss of response to esophageal instrumentation, and IVD = Intolerable ventilatory depression defined as a respiratory rate of 4 breaths per minute or less. Dashes (-) = unable to complete evaluation of effect measure. The numerator represents the number of subjects at maximum effect and the denominator represents the total number of subjects assessed at that concentration pair. Subjects were randomly assigned to three sets in a two-step approach. Subjects were first randomized to either the remifentanil or the propofol group. Each subject was further randomized to receive three of the six possible sets of infusions within their group. In the propofol group, we incorrectly dosed one volunteer, which caused there to be nine subjects in set two instead of two subjects in set six.

2.7 Appendix B: Target Effect-site Concentrations and Observed Responses for Intolerable Ventilatory Depression from Prior Work

Table 2.4: Target effect-site concentrations and observed responses for intolerable ventilatory depression from prior work (data unpublished).[1]

	Secondary Infusion	Primary Infusion	Effect Measures
Set	**Remi** ($ng \cdot mL^{-1}$)	**Prop** ($mcg \cdot mL^{-1}$)	**IVD**
1	0.0	5.0	4/8
1	0.0	7.5	6/8
1	0.0	10.0	6/8
2	1.0	5.0	1/3
2	1.0	7.5	1/2
3	5.0	3.0	0/1
3	5.0	5.0	0/1

Remi = remifentanil, Prop = propofol, IVD = intolerable ventilatory depression defined as a respiratory rate of 4 or less breaths per minute.

2.8 References

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CHAPTER 3

A SIMULATION STUDY OF COMMON PROPOFOL AND PROPOFOL-OPIOID DOSING REGIMENS FOR UPPER ENDOSCOPY: IMPLICATIONS ON THE TIME COURSE OF RECOVERY

3.1 Abstract

3.1.1 Background

Using models of respiratory compromise, loss of response to esophageal instrumentation and loss of responsiveness, we explored through simulation published dosing schemes for endoscopy using propofol alone and in combination with selected opioids. We hypothesized that models would predict adequate conditions for esophageal instrumentation and once drug administration is terminated, rapid return of responsiveness and minimal respiratory compromise.

3.1.2 Methods

Four published dosing regimens of propofol alone or in combination with opioids were used to predict the probability of loss of response to esophageal instrumentation for a 10-min procedure and the probability of respiratory compromise and return of responsiveness once the procedure had ended.

3.1.3 Results

Propofol alone provided a low probability (9-20%) and propofol-opioid techniques provided a moderate probability (15-58%) of loss of response to esophageal

instrumentation. Once the procedure ended, all techniques provided a high likelihood of rapid return of responsiveness (<3 min). Propofol-opioid techniques required more time than propofol alone to achieve a high probability of no respiratory compromise (7 versus 4 min).

3.1.4 Conclusions

Propofol alone would likely lead to inadequate conditions for esophageal instrumentation but would provide a rapid return to responsiveness and low probability of respiratory compromise once the procedure ended. The addition of remifentanil or fentanyl improved conditions for esophageal instrumentation and had an equally rapid return to responsiveness. The time required to achieve a low probability of respiratory compromise was briefly prolonged; this is likely inconsequential given that patients are responsive and can be prompted to breathe.

3.2 Introduction

Propofol alone and in combination with selected opioids are used by clinicians with no formal training in anesthesia to provide moderate or deep sedation for procedures associated with mild to moderately painful stimuli such as cardiac catheterizations,[1] upper endoscopies,[2-4] and colonoscopies.[5] This is of particular clinical interest and controversy[6,7†] because doses used to blunt responses to moderately painful stimuli can be associated with loss of responsiveness,[8-10] ventilatory depression[9,11,12] and/or airway obstruction.

Prior work in our laboratory on healthy unstimulated volunteers explored the presence or absence of intolerable ventilatory depression, defined as a respiratory rate

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† AANA-ASA Joint Statement Regarding Propofol Administration, April 14, 2004. Available at: http://www.aana.com/resources2/professionalpractice/Documents/PPM%20PS%20Joint%20AANA-ASA%20Propofol.pdf. Accessed January 17, 2012

of ≤4 breaths per minute, over a wide range of propofol-remifentanil concentration pairs administered in a laboratory setting. From this data, a propofol-remifentanil interaction model of intolerable ventilatory depression was built. While conducting this study, it was clear that intolerable ventilatory depression was not the only adverse respiratory effect that developed. In many instances, volunteers developed partial to complete airway obstruction at higher drug concentrations.

To build upon our interaction model for intolerable ventilatory depression, the first aim of this study was to construct a propofol-remifentanil interaction model that accounted for both airway obstruction and intolerable ventilatory depression. We named the combined effect ***respiratory compromise***. We hypothesized that the interaction between propofol and remifentanil for respiratory compromise would be synergistic.

Using the same volunteers, we also explored the loss of response to esophageal instrumentation, defined as no response to placing a surrogate of an endoscope (42F blunt end bougie) 40 cm into the esophagus. Non-responsiveness was defined as no gag, no change in heart rate or blood pressure greater than 20% from baseline, and no voluntary or involuntary movement. When comparing our model results with other similar modeling and dosing studies for endoscopy,[8,9,12] the criteria we used to define loss of response to esophageal instrumentation were perhaps overly stringent and not reflective of clinical practice. Endoscopists may tolerate some level of patient movement, gag response, and heart rate or blood pressure change rather than expect to block completely the response to esophageal instrumentation in order to avoid intolerable ventilatory depression. Thus a second aim of our study was to revise our loss of response to esophageal instrumentation model by redefining the response criteria to better reflect clinical practice. We hypothesized that the revised model would predict adequate conditions at lower propofol-remifentanil target concentrations and that the interaction would be synergistic.

A third aim of our study was to explore through simulation the behavior of published dosing schemes for endoscopy in terms of the probability of loss of response to esophageal instrumentation during a brief (10-min) procedure and the probabilities of respiratory compromise and loss of responsiveness in an unstimulated state following the procedure. We hypothesized that simulations of these dosing regimens would predict a 50 to 95% probability of loss of response to esophageal instrumentation and a rapid decline in the probabilities of respiratory compromise and loss of responsiveness once drug administration ended.

3.3 Materials and Methods

Previously collected data were used in this analysis; details regarding volunteer recruitment, study design, and physiologic monitoring have been previously reported.[13] In brief, the University of Utah Internal Review Board (Salt Lake City, Utah, USA) approved the study. After receiving informed, written consent, twenty-four volunteers were enrolled and received escalating target controlled infusions of propofol and remifentanil covering a range of effect-site concentrations (Ces) for each drug (propofol 0 to 4.3 $mcg \cdot mL^{-1}$ and remifentanil 0 to 6.4 $ng \cdot mL^{-1}$). Volunteers were randomly assigned to receive three of 12 possible sets of target concentrations (360 evaluations at 60 unique target concentration pairs plus 24 baseline). Each set consisted of five target concentration pairs (Appendix). Measures of inspired and expired airway flow and tidal volumes were recorded using a pneumotachometer (Novametrix, Louisville, KY) and chest and abdominal wall excursion were recorded using inductive plethysmography (Respitrace, Ambulatory Monitoring Inc., Ardsley, NY) at each target concentration pair.

3.3.1 Effect measures

Assessments of intolerable ventilatory depression and airway obstruction were made in the fourth minute after reaching predicted target Ces. We previously reported

the presence or absence of intolerable ventilatory depression (respiratory rate of ≤4 breaths per minute) at each target concentration pair.[13] The presence of airway obstruction was defined as partial or complete. Partial airway obstruction was defined as a 30 second average inspired tidal volume <3 $ml \cdot kg^{-1}$ AND >2 breaths in the same time period. Complete airway obstruction was defined as the absence of airway flow detected by the pneumotachometer in the presence of a respiratory effort detected by the plethysmograph. Respiratory compromise was defined as the presence of intolerable ventilatory depression and/or airway obstruction.

Revised assessments of esophageal instrumentation were made at the same set of Ces as described for respiratory compromise. No response was defined as no voluntary movement when placing the bougie and no request by the volunteer (by raising their hand) that placement of the bougie stop. Involuntary movement, gag response, and changes in heart rate or blood pressure were not considered responses.

3.3.2 Response surface models

Response surface models for respiratory compromise and loss of response to esophageal instrumentation were constructed by fitting binary effect data (presence or absence of effect) to a Greco model construct[14] adjusted for categorical data[15] using a naïve pooled technique[16] and modeling software (MATLAB R2008b, The MathWorks, Inc., Natick, MA). Model parameters and their coefficients of variation were estimated as previously described.[13] There were insufficient data points collected from individual subjects to construct post-hoc individual models.

Model fits were evaluated using a Chi-square (χ^2) goodness-of-fit test. Response/no response data were divided into probability bins with at least five no response data points in each bin. The expected frequency of no response for each bin (P_i) was calculated by multiplying the mean predicted probability by the total number of

observations in the bin. Observed frequency of no response (O_i) was the number of observations where no response occurred. The χ^2 test statistic was computed using equation 3.1:

$$\chi^2 = \sum_{i=1}^{k} \frac{(O_i - P_i)}{P_i} \qquad 3.1$$

k is the number of bins. The null hypothesis was that the expected (based on the model's prediction of probability of no response) and observed frequencies were from the same distribution and was rejected if the χ^2 test statistic exceeded the χ^2 critical value at a significance level of 5% with k-5 degrees of freedom (four parameters used to compute expected frequency are estimated from the data).

Two graphical approaches were used to assess model fits. The first plot presented the observed responses and a topographical rendering of model predictions created by plotting the 5%, 50%, and 95% iso-effect lines (isoboles). Isoboles represent all predicted propofol-remifentanil Ce combinations that produce the same probability of observing a modeled effect. This format was used to illustrate the number of volunteers that developed a loss of response alongside model predictions of the same effect measure. The second plot presented the observed responses on a three-dimensional rendering (response surface) of model predictions. This format was used to illustrate the differences between model predictions (ranging from 0 to 1) and observed responses (either 0 or 1). An assessment of how well model predictions fit the observations was made by calculating the percentage of predictions that agreed with observations. Agreement was defined as an absolute difference ≤0.5.

3.3.3 Identification of published endoscopy dosing regimens

Keyword searches were performed in PubMed to identify published dosing regimens for upper endoscopy. Only those dosing schemes that administered propofol, remifentanil and/or fentanyl were considered. Any studies using additional local or topical agents were excluded. All searches included the keyword propofol in combination with one or more of the following: dosing, endoscopic retrograde cholangiopancreatography, endoscopic ultrasound, endoscopist-directed propofol sedation, endoscopy, esophagogastroduodenoscopy, nurse administered propofol sedation, protocol, and sedation.

3.3.4 Simulations of published dosing regimens for endoscopy

A series of simulations were conducted to explore the duration of drug effects using published dosing regimens for endoscopy. Of particular interest was the ability of the dosing regimens to provide analgesia for esophageal instrumentation and the time to recovery (respiratory compromise and loss of responsiveness in an unstimulated state) once the procedure ended.

Simulations consisted of an induction period and a 10-min maintenance period followed by a 10-min washout. Ces were estimated for remifentanil, propofol and fentanyl using published pharmacokinetic models.[17-19] For purposes of using propofol-remifentanil models of drug effects, fentanyl was converted to remifentanil equivalents using a remifentanil:fentanyl equivalency ratio of 1:1.2.[20,21]

Simulated drug Ces from each dosing regimen were then used to predict the probability of drug effects over time using the response surface models described above for respiratory compromise and loss of response to esophageal instrumentation and a previously reported response surface model for loss of responsiveness[22] (Table 3.1). Low, moderate, and high probabilities of drug effect were defined as <25%, 25-75% and

Table 3.1: New, revised, and published propofol-remifentanil pharmacodynamic interaction model parameters for selected drug effects.

Effect	**$C_{50\ remi}$ (CV)** ng·mL^{-1}	**$C_{50\ prop}$ (CV)** mcg·mL^{-1}	**α (CV)** *(interaction)*	**γ(CV)** *(slope)*	**p,χ^2**
RC	6.7 (22%)	4.3 (26%)	9.7 (49%)	2.0 (14%)	0.724
LREI (revised)	9.6 (25%)	4.1 (8%)	7.7 (49%)	2.7 (11%)	0.708
LOR[22]	33.1	2.2	3.6	5.0	–

CV = coefficient of variation; remi =remifentanil, prop = propofol; C50 = predicted concentration associated with a 50% probability of effect; χ^2=Chi-square goodness-of-fit, RC = respiratory compromise; LREI = loss of response to esophageal instrumentation; LOR = loss of responsiveness.

>75% respectively. Once the simulated 10-min procedure ended, the time required for drug effects to dissipate were estimated using the time to reach a high probability of no respiratory compromise and no loss of responsiveness (<5% probability).

3.4 Results

Data were obtained from all 24 subjects. The Appendix presents the observed responses for each effect measure. Of the possible 384 assessments at 61 possible concentration pairs, 376 assessments for intolerable ventilatory depression, 247 assessments for airway obstruction and 370 assessments for esophageal instrumentation were made at 59, 48 and 59 concentration pairs respectively. Twenty assessment periods were completely or partially aborted at higher target concentrations; seventeen because blood pressure and/or heart rate changed more than 20% from baseline and three due to inadequate oxygenation. This included eight intolerable ventilatory depression, eleven airway obstruction, three respiratory compromise and 14 esophageal instrumentation assessments. Results from an additional eight assessments were not used because of recording difficulties with the pneumotachometer. 118 assessments of airway obstruction could not be made because volunteers were experiencing intolerable ventilatory depression.

3.4.1 Effect measures

Airway obstruction was observed in 27 of the 61 target concentration pairs (59 of 247 assessments) and consistently in ten (11 of 11 assessments). Airway obstruction occurred more often at high propofol Ces. Intolerable ventilatory depression was observed in 41 of the 61 target concentration pairs (137 of 376 assessments) and consistently in 17 (59 of 59 assessments). Intolerable ventilatory depression occurred more often at high remifentanil Ces. Combining airway obstruction and intolerable ventilatory depression, respiratory compromise was present in 54 of the target

concentration pairs (189 of 377 assessments). Volunteers in 25 of the 54 concentration pairs (86 of 86 assessments) consistently developed respiratory compromise (Figure 3.1A). Responses in the remaining 29 concentration pairs were mixed (i.e. some volunteers developed respiratory compromise others did not). For example, with propofol at 2.0 $mcg \cdot mL^{-1}$ and remifentanil at 0.8 $ng \cdot mL^{-1}$, 7 volunteers developed respiratory compromise and two did not.

Loss of response to esophageal instrumentation was observed in 48 of the 61 target concentration pairs (135 of 370 assessments). Volunteers in 19 of the 48 concentration pairs (51 of 51 assessments) consistently had a loss of response to esophageal instrumentation (Figure 3.1B). Responses at the remaining 29 concentration pairs were mixed (i.e. some volunteers responded, others did not). For example, with propofol at 2.7 $mcg \cdot mL^{-1}$ and remifentanil at 0.8 $ng \cdot mL^{-1}$, 5 volunteers tolerated esophageal instrumentation and 3 did not.

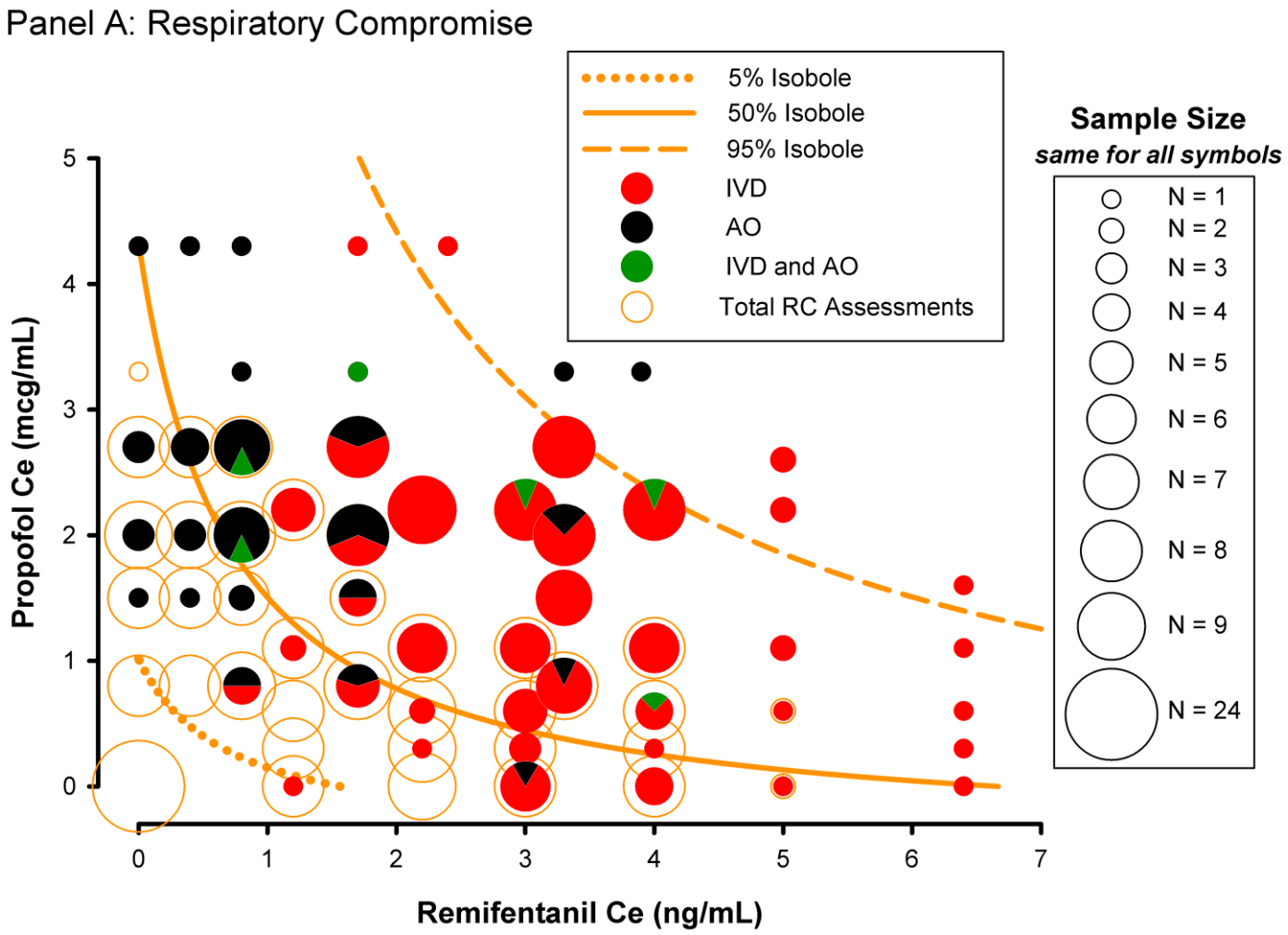
3.4.2 Response surface models

Model parameters, coefficients of variation, and the p-value from the Chi-square goodness-of-fit test are presented in Table 3.1. The positive alpha (interaction term) values indicate a synergistic relationship between remifentanil and propofol for respiratory compromise and loss of response to esophageal instrumentation. The small gamma value indicates a large range of concentrations covering the transition from responsive to unresponsive. Coefficients of variation indicated low parameter variability (<30%) except for the alpha parameters (49% for both the respiratory compromise and loss of response to esophageal instrumentation models). The Chi-square goodness-of-fit tests indicate good model fits to the raw data.

Observed responses and topographical representation of model predictions are presented in Figure 3.1A for respiratory compromise and Figure 3.1B for loss of

Figure 3.1: Observed responses and model predictions for respiratory compromise (RC) and loss of response to esophageal instrumentation (EI). **Panels A and B:** Topographical plot of raw data and model predictions. Open circle size indicates the number of RC and loss of response to EI assessments made at the corresponding drug effect-site concentration (Ce) pairs respectively. Filled circle size indicates the number of subjects with RC and loss of response to EI. RC data is further characterized using pie charts to indicate the source of RC: either intolerable ventilatory depression (IVD, red) or airway obstruction (AO, black) or both (green). **Panels C and D:** Response surface plot of model prediction and model error. Model predictions are presented as a mesh surface. Dotted, solid, and dashed lines represent drug concentration pairs resulting in a 5%, 50% and 95% probability of effect (RC in orange and loss of response to EI in green). Model error is presented as open (error ≤0.5) and filled (error >0.5) circles. Circle size indicates the number of observations and corresponding effect at each concentration pair (0 = no RC or no loss of response to EI, 1 = RC or loss of response to EI).

a)


Panel A: Respiratory Compromise
5% Isobole
50% Isobole
95% Isobole
IVD
AO
IVD and AO
Total RC Assessments
Sample Size
same for all symbols
N = 1
N = 2
N = 3
N = 4
N = 5
N = 6
N = 7
N = 8
N = 9
N = 24
Propofol Ce (mcg/mL)
Remifentanil Ce (ng/mL)
0
1
2
3
4
5
6
7

b)

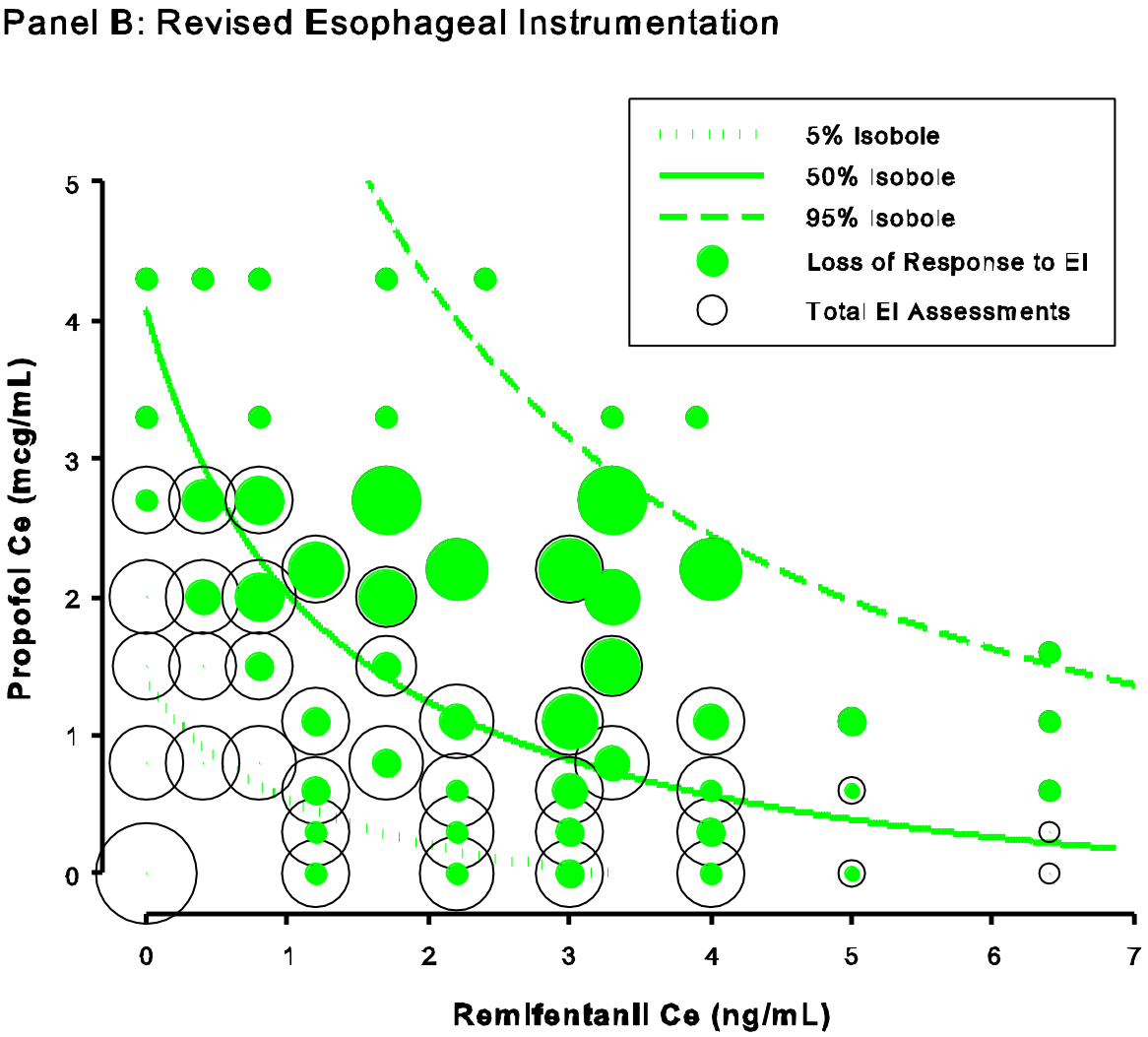


Figure 3.1 continued

c)

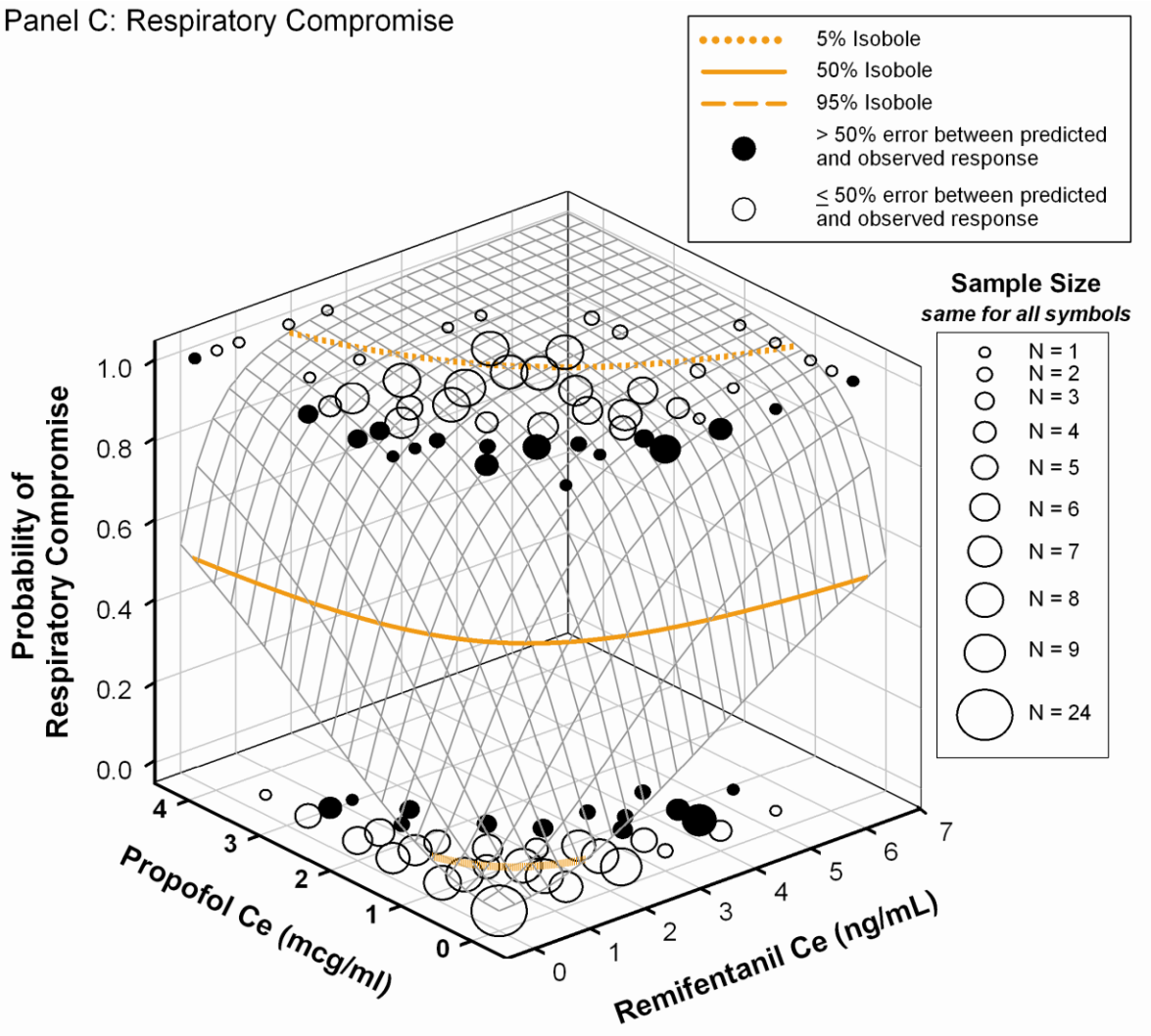


Figure 3.1 continued

d)

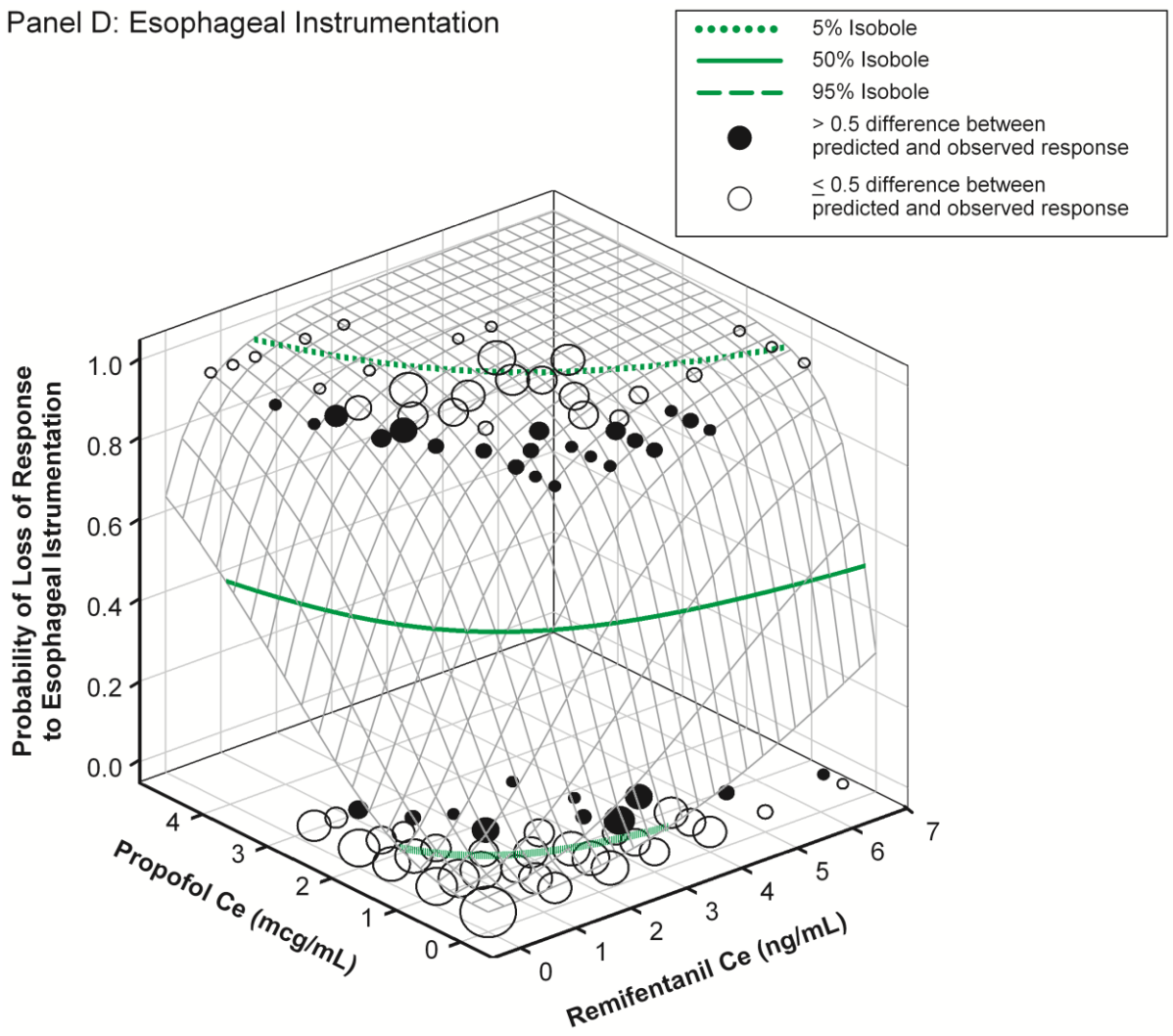


Figure 3.1 continued

response to esophageal instrumentation. Model predictions were consistent with observations. The observed frequency of respiratory compromise and loss of response to esophageal instrumentation below the 5% isobole was 2.5% and 6.7% respectively and 100% for both above the 90% isobole. Along the 50% isobole, approximately half the assessments at each target concentration pair developed respiratory compromise or loss of response to esophageal instrumentation. Most assessments between the 50% and 95% isoboles had respiratory compromise and loss of response to esophageal instrumentation while most between 5% and 50% did not.

Observed responses and prediction errors are presented in Figure 3.1C and Figure 3.1D. For respiratory compromise, 79% of the model predictions and for loss of response to esophageal instrumentation, 81% of the model predictions agreed with observed responses using an absolute difference of ≤0.5.

One previously published propofol-remifentanil interaction model for loss of responsiveness is also presented in Table 3.1.[22] Loss of responsiveness was defined as an Observer's Assessment of Alertness/Sedation score of 1.[23] Volunteers experienced verbal and tactile stimuli during these assessments.

3.4.3 Identification of published endoscopy/colonoscopy dosing regimens

Ten published manuscripts were identified using search criteria for endoscopy and propofol alone or in combination with an opioid. They were characterized according to drugs used: four describing techniques with propofol alone, three for propofol in combination with fentanyl using various bolus and infusion strategies for propofol, and one using target controlled infusion of propofol and remifentanil. Four dosing schemes were selected for simulation purposes and are presented in Table 3.2: (1) intermittent boluses of propofol alone,[24] (2) loading bolus of fentanyl with intermittent boluses of propofol,[25] (3) a loading bolus of fentanyl followed by a propofol bolus and infusion

Table 3.2: Selected published propofol and propofol – opioid dosing regimens for upper endoscopy for a 55 year old, 75 kg, 175 cm male.

Author	Technique	Published Recommendation	Simulated Dosing Regimen
Technique #1: Cohen et al., 2007[24]*	Propofol Boluses	Initial bolus of 10-60 mg. Additional 10-20 mg boluses as needed with a minimum of 20 to 30 seconds between doses	Initial bolus of 35 mg followed by 15 mg boluses 0.5, 3.5, 5.5, 8 and 10.5 minutes later
Technique #2: Cohen et al., 2003[25]	Propofol Boluses &	Initial bolus of 5-10 mg. Additional 5-15 mg boluses as needed with a minimum of 30 seconds between doses	Initial bolus of 7.5 mg followed by 10 mg boluses 0.5, 2, 4.5, 7, 9.5 and 12 minutes later
	Fentanyl Bolus	Initial bolus of 75 mcg	Initial bolus of 75 mcg
Technique #3: Pambianco et al., 2008[4,26]	Propofol Bolus and Infusion & Fentanyl Bolus	Loading dose of 0.5 mg·kg^{-1}·(maintenance infusion rate)·75^{-1} started 3 minutes after fentanyl bolus and administered over 3 minutes followed by a maintenance infusion of 25-75 mcg·kg^{-1}·min^{-1} that is titrated to effect Initial bolus of 50-100 mcg 3 minutes prior to administration of propofol	Three minutes after fentanyl bolus, a loading dose of 8.3 mg·min^{-1} for 3 minutes followed by a 10 minute infusion at 50 mcg·kg^{-1}·min^{-1} Initial bolus of 75 mcg
Technique #4: Gambus et al., 2011[27]	Propofol TCI & Remifentanil TCI	2.8 to 1.8 mcg·mL^{-1} 0 to 1.5 ng·mL^{-1}	Ce target of 1.8 mcg·mL^{-1} Ce target 1.5 ng·mL^{-1}

*Dosing recommendation reported by the American Gastroenterological Association Institute and cited by the American Society for Gastrointestinal Endoscopy. TCI=Target Controlled Infusion. Ce=effect-site concentration.

administered by SEDASYS (Ethicon Endo-Surgery, Inc., Cincinnati, OH),[4,26] and target controlled infusions of propofol and remifentanil.[27]

3.4.4 Simulations of published dosing regimens for endoscopy

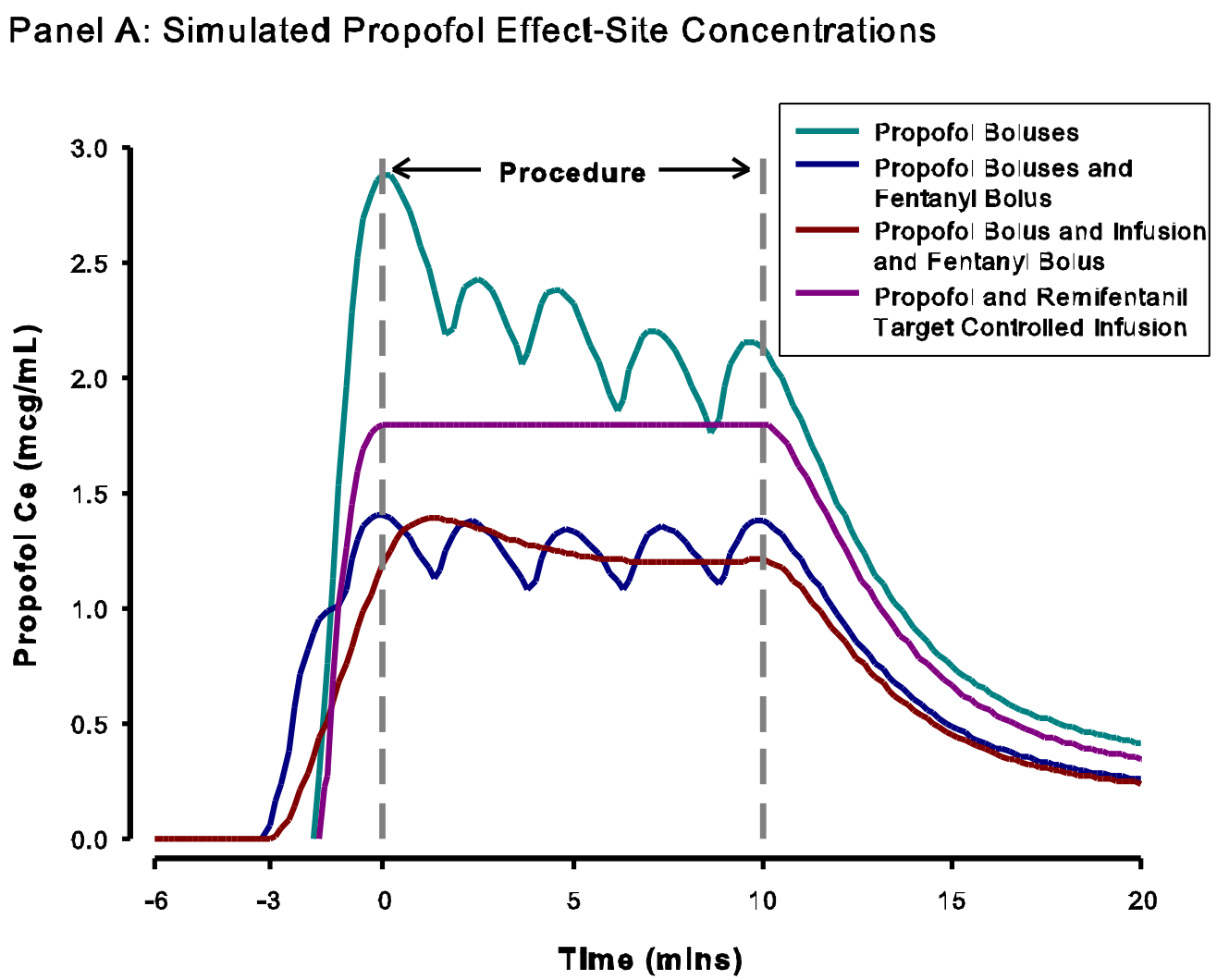
Published dosing recommendations were used to simulate a 10-min upper endoscopy procedure. Published recommendations were converted to dosing regimens (Table 3.2) assuming a 75 kg, 175 cm, 55-year-old male patient. Predicted Ces for propofol, fentanyl (in remifentanil equivalents), and remifentanil for each dosing scheme are presented in Figure 3.2. During the 10-min procedure, estimated propofol concentrations ranged from 1.2 to 3.0 $mcg \cdot mL^{-1}$ and remifentanil concentrations ranged from 0.7 to 1.5 $ng \cdot mL^{-1}$. Predictions of time to recovery for respiratory compromise and loss of responsiveness are presented in Figure 3.2D. and predictions of loss of response to esophageal instrumentation throughout the 10-min procedure are presented in Figure 3.3.

3.4.4.1 Technique #1: For the intermittent propofol boluses, the resultant propofol concentrations during the 10 min procedure ranged from 2 to 3 $mcg \cdot mL^{-1}$ and then dissipated to near 0.5 $mcg \cdot mL^{-1}$ over the next 10 min. This led to a low probability of respiratory compromise and a moderate probability of loss of responsiveness at the end of the procedure that both quickly dissipated. This technique led to a low probability of loss of response to esophageal instrumentation during the 10-min procedure that dissipated within 3 min from the end of the procedure.

3.4.4.2 Technique #2: For the fentanyl bolus followed by intermittent propofol boluses, fentanyl reached a peak of about 1.2 $ng \cdot mL^{-1}$ (in remifentanil equivalents) within 5 min of starting induction and then slowly dissipated to near 0.8 $ng \cdot mL^{-1}$ at 10 min. The accompanying propofol concentrations ranged between 1 and 2 $mcg \cdot mL^{-1}$ and dissipated to less than 0.5 $mcg \cdot mL^{-1}$ over the next 10 min. This led to a moderate

Figure 3.2: Predicted propofol, fentanyl (in remifentanil equivalents), and remifentanil effect-site concentrations (Ce) for selected published dosing regimens for endoscopy (**Panels A and B**). Time 0 corresponds to the peak propofol Ce for techniques #1 and #2, the start of the propofol infusion for technique #3, and achievement of the propofol target for technique #4. **Panel C** presents a topographical plot of propofol versus remifentanil concentrations for each dosing regimen. Arrows indicate the time course of the dosing; dotted and solid orange lines represent drug concentration pairs that produce 5% and 50% probabilities of respiratory compromise. **Panel D** shows the time to recovery using a topographical plot of propofol versus remifentanil concentrations during the 10-min washout period for each dosing regimen. Arrows indicate the time course of the dosing; closed circles represent the Ces at the end of the procedure, and dotted blue and orange lines represent drug concentration pairs that produce 5% probabilities of loss of responsiveness and respiratory compromise. Numbers represent time (in minutes) to recovery, defined as a probability of effect <5%, and are placed next to the corresponding washout curve and isobole.

a)


Panel A: Simulated Propofol Effect-Site Concentrations
Propofol Boluses
Propofol Boluses and Fentanyl Bolus
Propofol Bolus and Infusion and Fentanyl Bolus
Propofol and Remifentanil Target Controlled Infusion
Procedure
Propofol Ce (mcg/mL)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-6
-3
0
5
10
15
20
Time (mins)

b)

Panel B: Simulated Remifentanil Effect-Site Concentrations

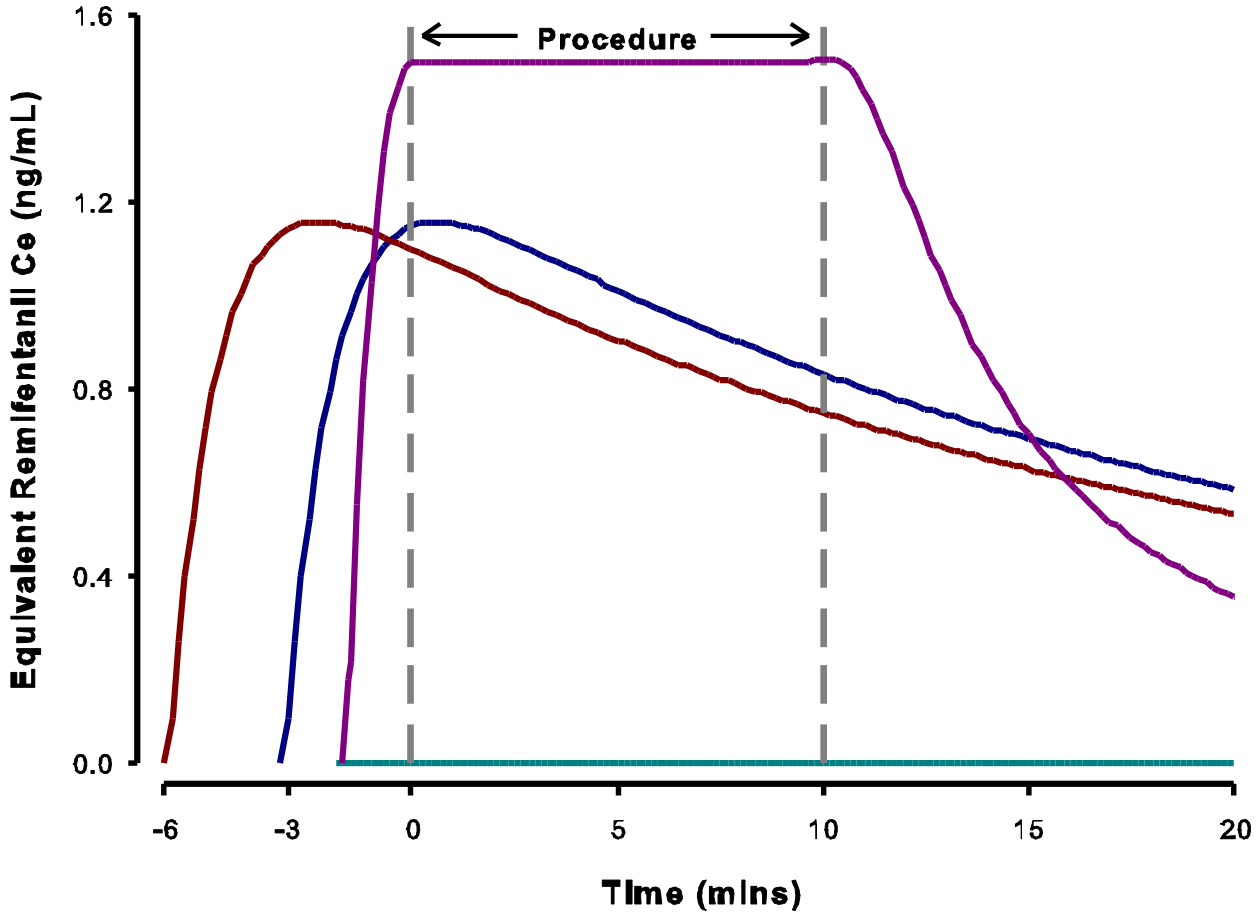


Figure 3.2 continued

c)

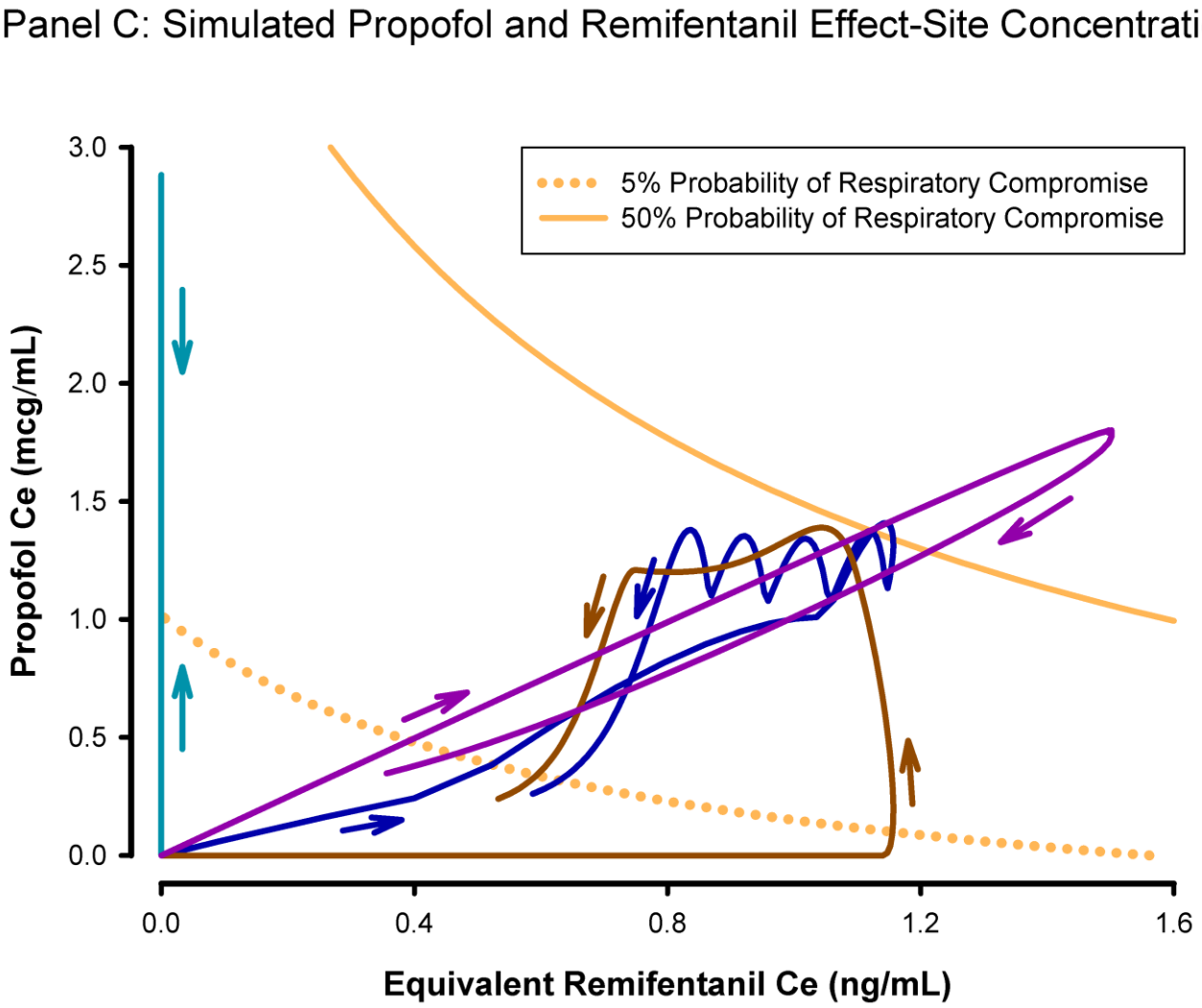


Figure 3.2 continued

d)

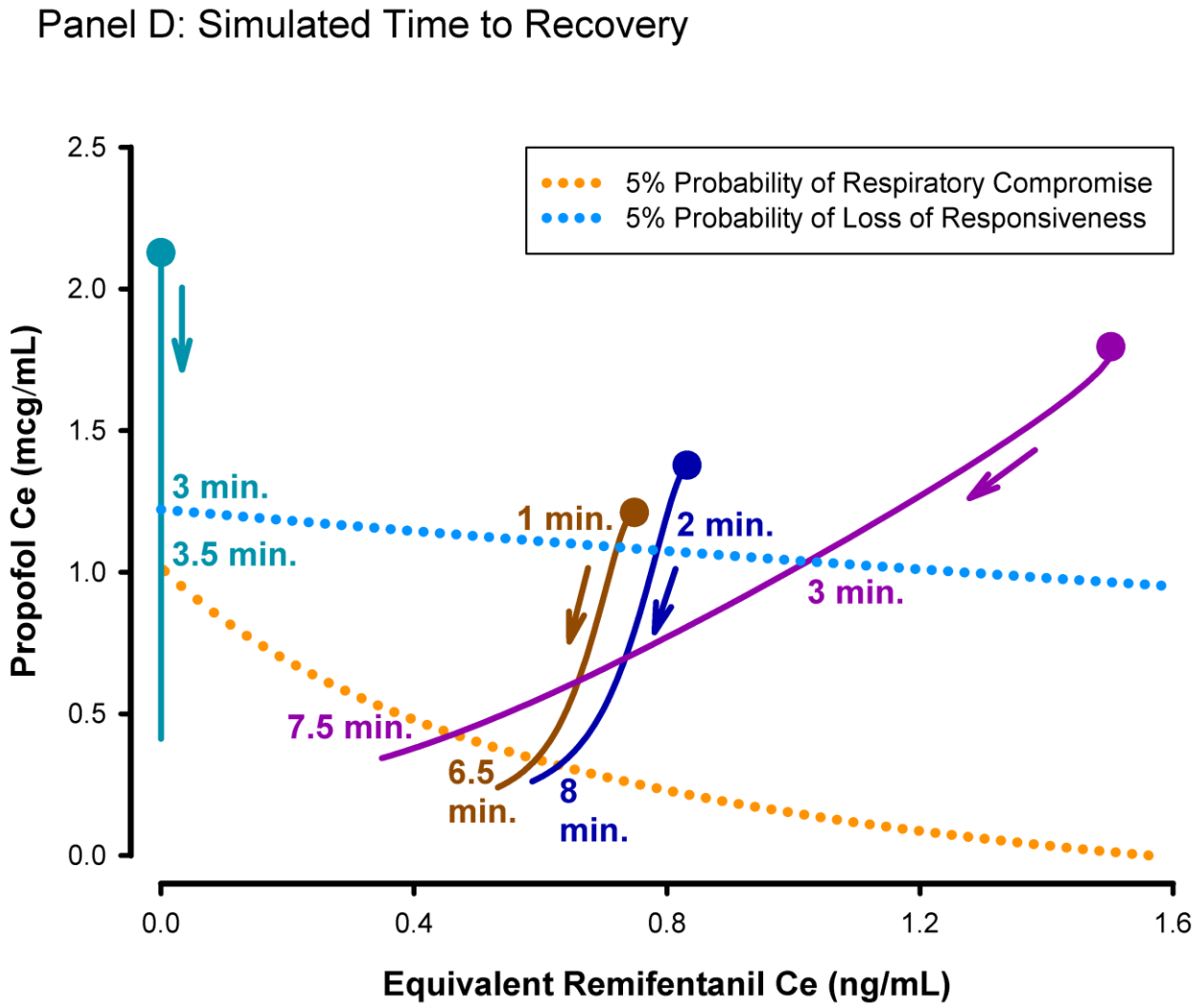


Figure 3.2 continued

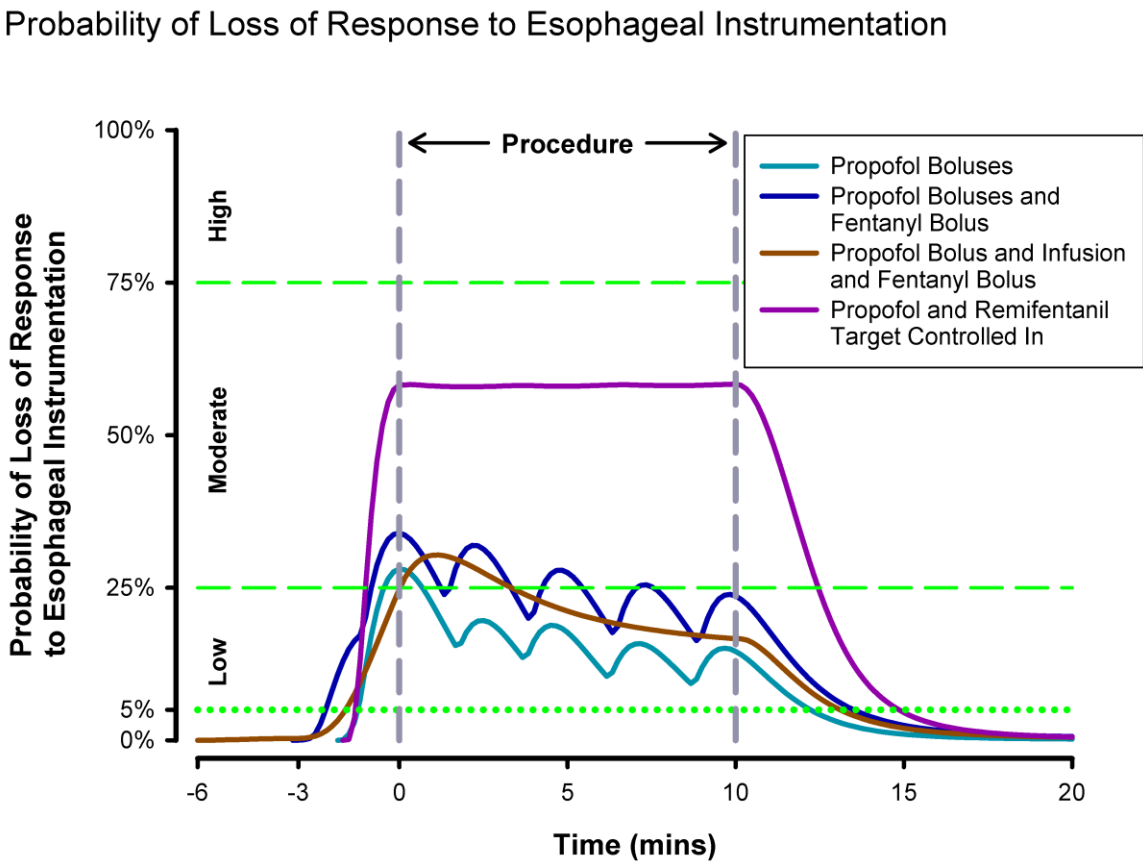


Figure 3.3: Simulations of loss of response to esophageal instrumentation over time for selected published dosing regimens for upper endoscopy (solid lines). Simulations were designed to provide sedation and analgesia for a 10-min procedure (gray vertical lines). Horizontal dashed lines represent the boundary between low and moderate (25%) and moderate and high (75%) probabilities of effect. The horizontal dotted line represents the boundary for high probability of recovery (<5%).

probability of respiratory compromise and a low probability of loss of responsiveness at the end of the procedure. Respiratory compromise dissipated within 8 min while loss of responsiveness dissipated in less than 2. This technique led to a moderate probability of loss of response to esophageal instrumentation during the 10-min procedure that dissipated within 4 min.

3.4.4.3 Technique #3: For the fentanyl bolus 3 min prior to the start of a propofol bolus followed by infusion, fentanyl had a concentration profile similar to that of Technique #2 with the difference that it reached its peak near the start of the propofol bolus. Propofol concentrations ranged between 1.4 and 2 $mcg \cdot mL^{-1}$ and then dissipated to less than 0.5 $mcg \cdot mL^{-1}$ within 5 min following the procedure. This led to a moderate probability of respiratory compromise and a low probability of loss of responsiveness at the end of the 10-min procedure. Respiratory compromise dissipated within 8 min while loss of responsiveness dissipated in less than 2. This technique led to a moderate probability of loss of response to esophageal instrumentation for 8 min followed by a low probability for the rest of the procedure and dissipated within 4 min.

3.4.4.4 Technique #4: For the target controlled infusions, propofol was maintained at 1.8 $mcg \cdot mL^{-1}$ and remifentanil at 1.5 $ng \cdot mL^{-1}$ for 10 min. This led to a moderate probability of respiratory compromise and loss of responsiveness at the end of the procedure that required 8 and 3 min to dissipate, respectively. This technique also led to a moderate probability of loss of response to esophageal instrumentation during the procedure that dissipated within 5 min of terminating the infusions.

3.5 Discussion

Predicting the likelihood, magnitude and duration of adverse effects such as ventilatory depression, airway obstruction and/or loss of responsiveness is important in formulating rational dosing regimens for procedural sedation. In a prior study, we

explored the feasibility of completely blocking the response to esophageal instrumentation in volunteers at various target remifentanil and propofol Ce pairs. Similar to what other authors have reported, we found that rendering a volunteer completely unresponsive to esophageal instrumentation often required doses that were associated with loss of responsiveness, intolerable ventilatory depression, or both.[9,10,25] In clinical practice, patient movement and/or discomfort for a brief duration rather than completely blocking the response to esophageal instrumentation may be acceptable in order to avoid unwanted side effects from these drugs.

In this present study, we modified our previously reported interaction model of intolerable ventilatory depression to include a measure of airway obstruction and called the combined effect respiratory compromise. We also modified our interaction model of loss of response to esophageal instrumentation by changing the criteria used to define a "response" to esophageal instrumentation. In this revised model, we categorized heart rate or blood pressure changes, non-purposeful movement, and gag response to esophageal instrumentation as "unresponsive" to be more consistent with other published work[8,9,12] and better reflect clinical practice during endoscopy.

3.5.1 Effect measures

By combining measures of partial or complete airway obstruction with the intolerable ventilatory depression data, volunteers were found to have respiratory compromise at more of the concentration pairs studied. As expected, airway obstruction primarily occurred at high propofol concentrations and intolerable ventilatory depression primarily occurred at high remifentanil concentrations.

When interpreting this data, some important limitations merit discussion. First, all measures of loss of responsiveness, airway obstruction and intolerable ventilatory depression were made with volunteers in an unstimulated state. It is well known that

stimulation shifts the concentration-effect relationship of anesthetics to the right (i.e. higher concentrations are needed to achieve the same effect).[28] Thus, in the presence of procedural stimulation, the number of volunteers that we observed with either loss of responsiveness and/or respiratory compromise would likely decrease. Second, it is likely that once an endoscope is in place, much of the partial or complete airway obstruction would resolve because the endoscope would stent the airway open.[12] Furthermore, an increase in body habitus may lead to more prevalent airway obstruction than what we observed. Third, our measures of partial airway obstruction were rather simplistic. More sophisticated techniques exist.[29-35] It is possible that our criteria for partial airway obstruction (tidal volume <3 $mL \cdot kg^{-1}$) did not accurately capture clinically significant partial airway obstruction. Fourth, the time course of airway obstruction or intolerable ventilatory depression necessary to produce clinically significant hypoxia or hypercarbia is not established; nevertheless, we believe that a respiratory rate ≤4 breaths per minute or a 30-second average tidal volume <3 $mL \cdot kg^{-1}$ would potentially lead to worrisome hypoxia and/or hypercarbia. Fifth, debilitated patients will likely require less propofol and remifentanil to achieve the same airway and respiratory effects.

By changing our criteria for loss of response to esophageal instrumentation, more assessments were considered “unresponsive” than in our original model. In our prior work,[13] volunteers were unresponsive in 105 out of 367 assessments,. With our revised criteria, 135 were unresponsive. For example, with propofol at 2.7 $mcg \cdot mL^{-1}$ and remifentanil at 0.8 $ng \cdot mL^{-1}$ and using the original response criteria, 4 volunteers tolerated esophageal instrumentation and 4 did not. With the revised criteria, 5 volunteers tolerated esophageal instrumentation and 3 did not.

One potentially important nuance to consider when interpreting these results is the difference in anesthetic requirements between placing an endoscope versus tolerating one already in place. Our anecdotal experience was that during placement of

the bougie, some volunteers exhibited a gag response or involuntary movement that resolved once it was in place. Hence, less propofol or propofol with an opioid may be required to keep patients analgesic and sedated during endoscopy once the scope is in place. This concept is confirmed by other authors who observed that endoscope insertion is the most stimulating portion of the procedure.[9,12]

3.5.2 Response surface models

We constructed a response surface model for respiratory compromise and loss of response to esophageal instrumentation. Graphical and statistical approaches indicated that the models fit the observed data well. From a graphical perspective (Figure 3.1C and D), the models captured the transition from no effect to effect well. This was confirmed by the χ^2 analysis and percentage of model predictions that agreed with observed responses. Our results confirmed our hypothesis that the interaction between propofol and remifentanil would be synergistic for both effect measures as illustrated by the positive alpha values presented in Table 3.1.

The respiratory compromise model had a propofol C_{50} of 4.3 mcg·mL^{-1} compared to our previously reported 7.0 mcg·mL^{-1} for intolerable ventilatory depression and is due to the additional airway obstruction data along the propofol axis. In the region of low remifentanil Ces (i.e. <1 ng·mL^{-1}), as propofol Ces increase from 0, any worrisome ventilation is preliminarily likely due to airway obstruction and can be resolved with a head tilt/chin lift and/or insertion of an oral airway. However, as propofol Ces approach 7.0 mcg·mL^{-1}, intolerable ventilatory depression is increasingly present, requiring prompting to breathe or manual ventilations to maintain adequate ventilation.

In contrast, the respiratory compromise model had a remifentanil C_{50} of 6.7 ng·mL^{-1} compared to our previously reported 4.1 ng·mL^{-1} for intolerable ventilatory depression. The increase in remifentanil C_{50} is likely a function of a few more volunteers

developing respiratory compromise due to airway obstruction at higher remifentanil concentrations (i.e. near 3 $ng \cdot mL^{-1}$) and the mathematical limitations of the Greco model structure.[14,36] Specifically, the Greco model is an adaptation of the model proposed by Berenbaum for two non-interacting drugs[37] and assumes each drug can be independently modeled using the Hill equation (sigmoid-Emax model).[14] This assumption imposes mathematical constraints on what type of behavior can be modeled, a limitation that has been described by other authors as insufficiently flexible.[36,38] Specifically, the interaction (alpha) and slope (gamma) are held constant for all drug combination ratios. In reality, each drug ratio can itself be considered a unique drug and could potentially have different alpha and gamma values from its neighbors. Additionally, assuming a sigmoid shape imposes an inflection point on the fit, which could lead to poor model fit in some data sets. Various models and techniques have been introduced by other authors to correct for these limitations.[36,38,39]

The revised loss of response to esophageal instrumentation model is somewhat similar to our previously reported model. The C_{50}'s and gamma terms are similar (propofol C_{50}: original 9.8 versus revised 9.6 $mcg \cdot mL^{-1}$, remifentanil C_{50}: original 3.8 versus revised 4.1 $ng \cdot mL^{-1}$, and gamma: original 3.7 versus revised 2.7) but the alpha term is larger in the revised model (original 4.5 versus revised 7.7). Although the C_{50}'s are similar, the larger alpha in the revised model indicates a more significant drug synergy, meaning less of either drug is required to achieve the same effect. In graphical terms, the iso-effect lines (isoboles) have more of a bow towards the origin with the larger alpha.

For both models, the gamma value ranges from 2 to 3. These relatively small values indicate that the range between the 5% and 95% probability isoboles will be large. A wider range indicates more uncertainty of the concentration at which a given subject will transition from no effect to effect, with the typical patient transitioning near

the 50% isobole.

3.5.3 Simulations of published dosing regimens for endoscopy

With regard to a rapid recovery, the propofol only technique had the fastest recovery (i.e. both no loss of responsiveness and no respiratory compromise within 3-4 min) once the procedure was completed. Nevertheless, it only achieved a low probability of loss of response to esophageal instrumentation during all but the very beginning of the procedure (Figure 3.3).

An important clinical implication of these simulations is that should patients require prompting to breathe to avoid ventilatory depression, techniques that minimize loss of responsiveness may be more desirable because patients can respond to the prompting. This may be especially important when dosing with propofol alone; given that propofol has minimal analgesic effect, clinicians may be tempted to administer more propofol and over sedate patients to compensate for the lack of analgesia.[24]

Simulations of the propofol-opioid techniques did lead to moderate probabilities of respiratory compromise and loss of responsiveness at the end of the procedure, but they also provided a moderate probability of loss of response to esophageal instrumentation. Once drug administration was terminated, the time to return of responsiveness was faster for some of these techniques than it was for propofol alone (Figure 3.2D). More time was required for the respiratory compromise effect to dissipate with the propofol-opioid techniques (7-9 min), but a majority of this time would be with a patient in a responsive state and likely be receptive to prompting to breathe or open their airway.

By way of comparison, authors have published observations using propofol in combination with opioids for endoscopy and colonoscopy. For example, in a trial where 496 patients received a fentanyl bolus followed by a computer administered feedback-

controlled propofol infusion (SEDASYS), Pambianco et al.[26] found that over 95% of the patients experienced mild to moderate sedation during brief procedures (on average <4 min for upper gastrointestinal endoscopy and <14 min for colonoscopy) and a rapid recovery. There was a very low incidence of deeper than intended sedation and adverse respiratory events. They reported an area under the desaturation curve as a surrogate measure of the risk of hypoxic injury. Propofol combined with fentanyl led to a lower on average area under the curve than conventional dosing with midazolam, meperidine, and fentanyl (on average, 23 %·seconds versus 88 %·seconds). Although these results are not directly comparable, simulations presented in Figure 3.2C predicted only brief periods of a moderate probability of respiratory compromise.

Some additional limitations deserve special emphasis. First, our models assume steady state conditions. This assumption is violated whenever drug concentrations are rapidly changing (e.g., such as after a bolus is injected). The respiratory depression associated with bolus doses of ventilatory depressants is greater than when the same drugs are administered by infusion to similar target concentrations.[40,41] Thus, the simulations involving bolus drug administration are likely to be associated with more respiratory compromise than our models predict. Second, simulation predictions are based on population pharmacokinetic models associated with substantial variability. For example, using target controlled infusions, median absolute performance errors for propofol only and remifentanil only of 25%[42] and 22%[43] have been reported, respectively. The median performance error of propofol in the presence of remifentanil has been reported as 49%.[43] Third, some of the published dosing regimens did not provide weight adjusted dosing. When conducting our simulations, we assumed a patient weight of 75 kg. Predictions would be different for simulations using a patient weight of 45 or 100 kg. Fourth, when implementing dosing recommendations, some degree of interpretation was required to formulate a dosing regimen; time intervals

between doses and infusion rates were published as ranges. We chose dosing intervals based on a published regimen[44] but as with any simulation, we may have inappropriately interpreted the dosing regimens. Fifth, although the models we used to predict propofol and remifentanil concentrations do account for age, our pharmacodynamic models do not. As reported by Kazama et al. and Hammer et al., age is an important covariate when considering doses of propofol for endoscopy.[8,9]

Finally, although there are obvious limitations to the volunteer setting, particularly the problem of lack of stimulation, the volunteer paradigm is a necessary first step towards building models that can then be perfected and eventually validated in patients. In patients, it is not practically feasible to target the numerous concentration pairs necessary to build a response surface; these volunteer studies typically require an entire day for each subject. Furthermore, it is unethical to intentionally anesthetize or sedate a patient inadequately. In the volunteer setting, using noninvasive stimulation techniques, it is acceptable to produce inadequate anesthesia or sedation intentionally.

In summary, we modified two previously reported propofol-remifentanil interaction models of loss of response to esophageal instrumentation and intolerable ventilatory depression. Revised models fit observed responses well. We used them and an additional model to make predictions regarding the temporal profile of recovery for sedation and respiratory endpoints using published dosing regimens for propofol alone and in combination with an opioid for upper endoscopy. Simulations of propofol-opioid techniques led to a moderate probability of conditions that allow esophageal instrumentation whereas propofol only techniques led to a low probability. Once the procedure was terminated, techniques that used a fentanyl bolus just prior to the procedure and propofol throughout the procedure provided the highest likelihood of rapid return of responsiveness.

3.6 Appendix: Target Effect-site Concentrations and Respiratory and Esophageal Instrumentation Outcomes

Table 3.3: Target effect-site concentrations and respiratory and esophageal instrumentation outcomes

Remifentanil Group								Propofol Group							
				Effect Measures								Effect Measures			
Set	**n**	**Remi ($ng \cdot mL^{-1}$)**	**Prop ($mcg \cdot mL^{-1}$)**	**IVD**	**AO**	**RC**	**LREI (revised)**	**Set**	**n**	**Remi ($ng \cdot mL^{-1}$)**	**Prop ($mcg \cdot mL^{-1}$)**	**IVD**	**AO**	**RC**	**LREI (revised)**
0	12	0.0	0.0	0/12	0/12	0/12	0/12	**0**	12	0.0	0.0	0/12	0/12	0/12	0/12
1	9	0.0	0.8	0/9	0/8	0/8	0/9	**1**	8	1.2	0.0	1/8	0/7	1/8	1/8
1	9	0.4	0.8	0/9	0/8	0/8	0/9	**1**	8	1.2	0.3	0/8	0/8	0/8	1/8
1	9	0.8	0.8	2/9	2/7	4/9	0/9	**1**	8	1.2	0.6	0/8	0/8	0/8	2/8
1	9	1.6	0.8	3/9	2/6	5/9	2/9	**1**	8	1.2	1.1	2/8	0/6	2/8	2/8
1	9	3.3	0.8	6/9	1/3	7/9	3/9	**1**	8	1.2	2.2	5/8	0/3	5/8	6/8
2	8	0.0	1.5	0/8	1/8	1/8	0/8	**2**	8	2.2	0.0	0/9	0/9	0/9	1/9
2	8	0.4	1.5	0/8	1/8	1/8	0/8	**2**	8	2.2	0.3	1/9	0/8	1/9	1/9
2	8	0.8	1.5	0/8	2/7	2/7	2/8	**2**	8	2.2	0.6	2/9	0/7	2/9	1/9
2	8	1.6	1.5	2/8	2/5	4/7	2/7	**2**	8	2.2	1.1	6/9	0/3	6/9	3/9
2	8	3.3	1.5	7/7	–	7/7	6/7	**2**	8	2.2	2.2	9/9	–	9/9	7/7
3	9	0.0	2.0	0/9	3/9	3/9	0/9	**3**	8	3.0	0.0	5/8	1/3	6/8	2/8
3	9	0.4	2.0	0/9	3/9	3/9	3/9	**3**	8	3.0	0.3	3/8	0/5	3/8	2/8
3	9	0.8	2.0	1/9	7/9	7/9	5/9	**3**	8	3.0	0.6	5/8	0/3	5/8	3/8
3	9	1.6	2.0	3/7	5/5	8/8	6/7	**3**	8	3.0	1.1	6/8	0/2	6/8	6/8
3	9	3.3	2.0	6/6	2/2	8/8	6/6	**3**	8	3.0	2.2	8/8	1/1	8/8	7/8
4	8	0.0	2.7	0/8	3/8	3/8	1/8	**4**	8	4.0	0.0	4/8	0/4	4/8	1/8
4	8	0.4	2.7	0/8	4/8	4/8	4/8	**4**	8	4.0	0.3	1/8	0/7	1/8	2/8
4	8	0.8	2.7	1/8	7/8	7/8	5/8	**4**	8	4.0	0.6	4/8	1/5	4/8	1/8
4	8	1.6	2.7	5/8	3/3	8/8	8/8	**4**	8	4.0	1.1	6/8	0/2	6/8	3/8
4	8	3.3	2.7	8/8	–	8/8	8/8	**4**	8	4.0	2.2	8/8	1/1	8/8	7/7
5	1	0.0	3.3	0/1	0/1	0/1	1/1	**5**	2	5.0	0.0	1/2	0/1	1/2	0/2
5	1	0.8	3.3	0/1	1/1	1/1	1/1	**5**	2	5.0	0.6	1/2	0/1	1/2	0/2
5	1	1.6	3.3	1/1	1/1	1/1	1/1	**5**	2	5.0	1.1	2/2	–	2/2	2/2
5	1	3.3	3.3	–	1/1	1/1	1/1	**5**	2	5.0	2.2	2/2	–	2/2	–
5	1	3.9	3.3	–	1/1	1/1	1/1	**5**	2	5.0	2.6	2/2	–	2/2	–

Table 3.3 continued

Remifentanil Group								Propofol Group							
				Effect Measures								Effect Measures			
Set	**n**	**Remi ($ng \cdot mL^{-1}$)**	**Prop ($mcg \cdot mL^{-1}$)**	**IVD**	**AO**	**RC**	**LREI (revised)**	**Set**	**n**	**Remi ($ng \cdot mL^{-1}$)**	**Prop ($mcg \cdot mL^{-1}$)**	**IVD**	**AO**	**RC**	**LREI (revised)**
6	1	0.0	4.3	0/1	1/1	1/1	1/1	**6**	2	6.4	0.0	1/1	–	1/1	0/1
6	1	0.4	4.3	0/1	1/1	1/1	1/1	**6**	2	6.4	0.3	1/1	–	1/1	0/1
6	1	0.8	4.3	0/1	1/1	1/1	1/1	**6**	2	6.4	0.6	1/1	–	1/1	1/1
6	1	1.6	4.3	1/1	–	1/1	1/1	**6**	2	6.4	1.1	1/1	–	1/1	1/1
6	1	2.4	4.3	1/1	–	1/1	1/1	**6**	2	6.4	1.6	1/1	–	1/1	1/1
total	**192**			**47/184**	**55/141**	**99/185**	**71/185**		**192**			**89/192**	**4/106**	**90/192**	**64/185**

Remi = Remifentanil, Prop = Propofol, N is the number of subjects assigned to each set based on the study design. Effect measures: IVD = Intolerable ventilatory depression defined as a respiratory of ≤4 breaths per minute, AO = Airway obstruction defined as a 30 second average tidal volume <3 ml/kg AND respiratory rate >2 breaths in the same time period OR absence of airway flow in the presence of respiratory effort, RC = Respiratory compromise defined as the presence of IVD and/or AO, LREI = Loss of response to esophageal instrumentation. Dashes (–) = unable to complete evaluation of effect measure. The denominator is the total number of subjects assessed at that concentration pair for the corresponding effect. The numerator is the number of subjects at maximum effect. Totals for each effect are provided at the bottom. After being randomized to either the remifentanil or the propofol group, each subject was further randomized to receive three of the six possible sets of infusion targets within their group. One subject was incorrectly dosed in the propofol group, which caused there to be nine subjects in set two instead of two subjects in set six.

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CHAPTER 4

DEVELOPMENT OF PROPOFOL-REMIFENTANIL DOSING MULTIOBJECTIVE OPTIMIZATION ALGORITHM FOR MODERATELY PAINFUL PROCEDURES REQUIRING ESOPHAGEAL INSTRUMENTATION

4.1 Abstract

4.1.1 Introduction

Anesthesia for upper endoscopy balances drug requirements with patient safety. The ideal dosing scheme provides adequate analgesia and sedation while avoiding loss of responsiveness (LOR), respiratory depression (RD), and airway obstruction (AO). Clinicians often accept some LOR, RD, and/or AO to achieve their overall therapeutic goals. We hypothesized that optimization techniques applied to response surface drug interaction models can identify dosing regimens that minimize LOR, RD, and AO yet provides satisfactory conditions for upper endoscopy.

4.1.2 Methods

Six experts in procedural sedation were asked to achieve a consensus on the allowable duration of LOR, RD, and AO during a 10-min upper endoscopy procedure using propofol and remifentanil. Objective functions were developed that used this expert opinion to identify an optimal dosing regimen for propofol and remifentanil. Using previously developed propofol-remifentanil interaction models of LOR, RD, respiratory compromise (RC) and loss of response to esophageal instrumentation (LREI), the

objective functions were evaluated using 3840 different propofol-remifentanil dosing regimens. Each dosing regimen varied in terms of the propofol and remifentanil bolus sizes and infusion rates.

4.1.3 Results

Ideal times and acceptable ranges were obtained from experts. A lexicographic goal programming optimization algorithm was developed. An optimal dosing recommendation was identified for a simulated 55 year-old, 75 kg, 175 cm male undergoing an anticipated 10-min upper endoscopy and consisted of a propofol bolus of 0.8 mg/kg and infusion rate of 40 mcg/kg/min and a remifentanil bolus of 0.2 mcg/kg and an infusion rate of 0.05 mcg/kg/min. This optimal dosing regimen produced peak Ces of ~3 mg/mL of propofol and ~1 ng/mL of remifentanil during placement. When the procedure ended, Ces were ~1.3 mcg/mL for propofol and ~1.3 ng/mL for remifentanil.

4.1.4 Discussion

Our hypothesis was confirmed. Optimization techniques identified a remifentanil propofol dosing regimen that minimizes the duration of LOR, RD and AO and, according to expert opinion and models of drug effect, provides conditions that will permit upper endoscopy procedures. This dosing regimen merits clinical validation in patients undergoing brief endoscopic procedures.

4.2 Introduction

Sedatives or analgesics are administered to alleviate patient discomfort and provide optimal conditions for esophagogastroduodenoscopy. Use of anesthetics also introduces risks of adverse respiratory effects such as airway obstruction and respiratory depression. Those administering sedatives and analgesics must balance patient comfort and procedure needs against the risk of these adverse effects.

Propofol and, to a lesser extent, propofol in combination with opioids have been used by clinicians with no formal training in anesthesiology for procedures associated with mild to moderate stimulation. Nonanesthesiologists have presented an impressive number of cases (646,080) with low rates of adverse effects (0.1% mask ventilation, 0.002% endotracheal intubation, 0.0006% death).[1] Prior work in our laboratory explored through simulation several published dosing regimens for propofol alone and in combination with selected opioids for upper endoscopic procedures.[2] Drug interaction models were used to predict the probability over time of creating conditions that would allow esophageal instrumentation while avoiding airway obstruction, loss of responsiveness, and ventilatory depression. In that preliminary analysis, we found that the probability of adverse events (prolonged airway obstruction, ventilatory depression, or loss of responsiveness) was low for the simulated 10-min procedure. Published dosing techniques primarily used low dose opioids mixed with moderate doses of propofol. However, given the wide range of combination possibilities, it is potentially feasible that other combinations of propofol mixed with an opioid may have better probability profiles for these adverse effects.

In this study, we utilized control theory to explore a wide range of opioid-propofol combinations to meet the needs of an upper endoscopic procedure. In this effort, we built an optimization algorithm that accounted for the duration of loss of responsiveness, ventilatory depression, and airway obstruction along with the need to provide conditions where patients would tolerate esophageal instrumentation. We solicited expert opinion to prioritize clinical endpoints (i.e. time needed to place an endoscope in the duodenum vs. duration of loss of responsiveness) and identify goal times for each clinical endpoint (i.e. what is an acceptable duration of loss of responsiveness). Analysis of patient data identified target probabilities for clinical endpoints (i.e. what probability of loss of response to esophageal instrumentation must be obtained).

The aim of this study was to use the optimization algorithm to identify an ideal propofol-remifentanil dosing regimen for upper endoscopy procedures from a wide range of possibilities. We hypothesized that a dosing regimen existed that would adequately meet these clinical objectives.

4.3 Methods

To test our hypothesis, propofol-remifentanil dosing regimens were simulated and an optimization algorithm was developed to identify an optimal propofol-remifentanil dosing regimen based on patient age, weight, height and gender. The optimization process accounted for (i) the pharmacokinetic behavior of each drug, (ii) the pharmacodynamic interaction between propofol and remifentanil, (iii) the analgesic and sedative requirements for esophageal instrumentation and (iv) the respiratory and sedative effects of propofol and remifentanil.

4.3.1 Objective functions

Objective functions were defined for six clinical endpoints: *time until esophagus can be instrumented*, *time needed to maintain no response while endoscope is placed in the duodenum*, *time with no response while the procedure is performed*, and once the procedure has ended, *time to ventilatory depression recovery*, *time to airway obstruction recovery*, and *time to return of responsiveness*.

"*Time until esophagus can be instrumented*" represents how long a clinician must wait to start the procedure once drug administration has begun. For the purposes of this study, the procedure could start once the probability of loss of response to esophageal instrumentation was greater than or equal to 70%. This probability was obtained from data collected in 110 ultrasonographic endoscopy patients[3] and was defined as the probability at which 85% of patients tolerated esophageal instrumentation (Figure 4.1). This objective function returned the time elapsed from the start of drug administration to

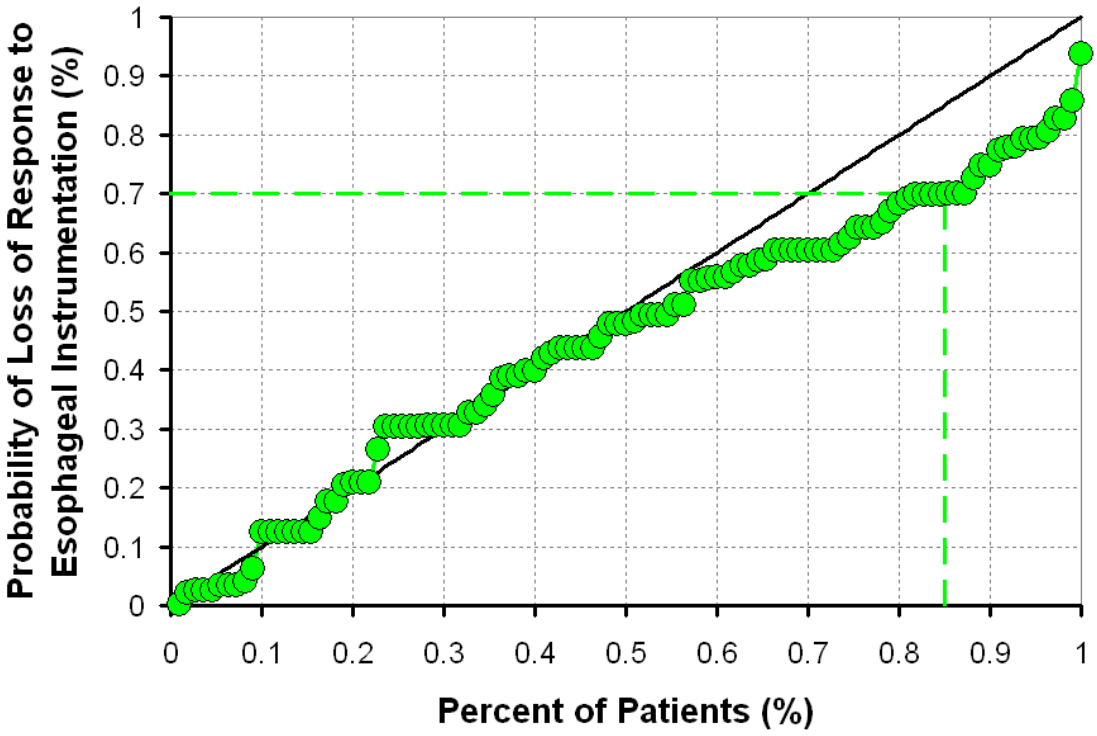


Figure 4.1: An evaluation of the loss of response to esophageal instrumentation model in 110 ultrasonographic endoscopy patients. For each patient, the probability at which they tolerated esophageal instrumentation is calculated (green circles). Probabilities are sorted and plotted against percent of total patients. The line of identify (black line) indicates pairs where model predictions and observed responses are equal. The point where 85% of patients tolerated esophageal instrumentation was selected as the target for the ready for esophageal instrumentation objective and corresponded to a 70% probability of loss of response to esophageal instrumentation (dashed green).

the first time the probability of loss of response to esophageal instrumentation was greater than or equal to 70%. If this probability was never reached, the objective function returned infinity.

Anecdotal observations from previous work and corroborated by other researchers indicated that placing an endoscope was the most stimulating part of upper endoscopies.[2,4,5] Once the endoscope had been placed, drug requirement decreased. For this study, the initial elevated phase is termed "*time needed to maintain no response while endoscope is placed in the duodenum*" and the dosing provided for the balance of the procedure is termed "*time with no response while the procedure is performed*" or simply "maintenance dosing".

The "*time needed to maintain no response while endoscope is placed in the duodenum*" objective returned the total elapsed time from when the probability of loss of response to esophageal instrumentation first reached 70% to when it first dropped below the upper limit for maintenance dosing, which is defined in the next paragraph. If the probability never exceeded 70% or did but never fell below the upper limit for maintenance, the objective function returned infinity.

Gambus, et al. report in their findings in 110 ultrasonographic endoscopy patients that optimal sedation was achieved in unstimulated patients at Ce pairs ranging from 2.8 mcg/mL propofol and 0 ng/mL remifentanil to 1.8 mcg/mL and 1.5 ng/mL.[3] When converted to probabilities of loss of response to esophageal instrumentation, these correspond to probabilities of 26% and 58% respectively. "*Time with no response while the procedure is performed*" was the total time the probability of loss of response to esophageal instrumentation was greater than or equal to 26% and less than or equal to 58% during the procedure. If the predicted probability of loss of response to esophageal instrumentation never entered this targeted region, the objective function returned infinity.

Our models for intolerable ventilatory depression, respiratory compromise and loss of responsiveness were collected in unstimulated, healthy volunteers and, as suggested in previous work, are best applied to patients recovering from a procedure.[2] We also postulate that respiratory depression and airway obstruction are more worrisome when the subject is unresponsive and therefore unable to respond to prompts to breathe. Therefore, "*time to ventilatory depression recovery*" is the time to reach a probability of intolerable ventilatory depression < 5% or return of responsiveness (loss of responsiveness < 5%), whichever occurs first, once the procedure has ended. If both probabilities were less than 5% before the procedure ended, the objective function returned zero.

The respiratory compromise model is comprised of both airway obstruction and intolerable ventilatory depression data. We do not know of a model for airway obstruction alone. However, intolerable ventilatory depression and airway obstruction predominantly occur in different regions of drug combinations. Airway obstruction tends to occur at low remifentanil Ces while intolerable ventilatory depression tends to occur at high remifentanil concentrations. Therefore, the predicted probability of respiratory compromise tends to be for intolerable ventilatory depression in one region and airway obstruction in the other. The probability of airway obstruction was approximated as the difference between the probabilities of respiratory compromise and intolerable ventilatory depression. Any negative values were set equal to zero. The "*time to airway obstruction recovery*" was the shorter of either time to reach a <5% probability of airway obstruction or time to return of responsiveness following the end of the procedure. If both probabilities were less than 5% before the procedure ended, the objective function returned zero.

The "*time to return of responsiveness*" objective was the elapsed time from when the procedure ended to when the probability of loss of responsiveness dropped below

5%. If the probability of loss of responsiveness was below 5% before the end of the procedure, the objective function returned zero.

Priorities, ideal times and acceptable ranges for each objective were obtained from experts in sedation, analgesia and airway management using the Delphi technique.[6] A questionnaire was distributed to six board certified anesthesiologists (Appendix) repeatedly until an acceptable concordance was reached for objective priority. Concordance was defined as a Kendall W statistic of 0.75 or greater. Once concordance was reached, questioning continued until agreement was obtained on ideal objective times and acceptable ranges. Agreement was defined as experts all agreeing with the median times from the previous round.

To control for variance in each objective, times were transformed to dimensionless parameters with identical ideal scores (0) and ranges (-1 to 1), in a two-step process. First, times for each objective were normalized as shown in equation 4.1.

$$F_j^{Norm}(x) = \frac{F_j(x)}{F_j^o} - 1 \qquad 4.1$$

$F_j^{Norm}(x)$ is a normalized, dimensionless parameters with a lower limit of -1 and no upper limit. $F_j(x)$ is the objective function time for the j^{th} objective while F_j^o is the corresponding ideal time (assuming $F_j^o \neq 0$). When the objective function time $F_j(x)$ and ideal time F_j^o are equal, F_j^{Norm} is zero.

Second, objective times were scaled to express percent deviation from ideal. The difference between actual objective function time and ideal time was divided by the corresponding acceptable range (equation 4.2), determined by the value F_j^{Norm}. $F_j^{trans}(x)$ is the final objective score and is the percent deviation of the objective time within the ideal range. $F_j^{o,max}$ and $F_j^{o,min}$ are the maximum and minimum values of the acceptable range,

respectively. An objective time equal to the minimum or maximum acceptable value was transformed to a score of -1 or +1, respectively, while an objective time equal to the ideal time was transformed to zero. Negative values indicated a less than ideal score while positive values indicated greater than ideal scores (Figure 4.2). As an example, if the ideal time for an objective was 1 min and minimum and maximum acceptable times were 0.25 and 3, then objective times of 0.5, 1, and 2 would be transformed to scores of -67%, 0% and 50% respectively.

$$F_j^{trans}(x) = \begin{cases} \dfrac{F_j(x) - F_j^o}{F_j^{o,\max} - F_j^o} & if \quad F_j^{Norm}(x) > 0, \\ 0 & if \quad F_j^{Norm}(x) = 0, \\ -\dfrac{F_j(x) - F_j^o}{F_j^{o,\min} - F_j^o} & if \quad F_j^{Norm}(x) < 0 \end{cases} \qquad 4.2$$

4.3.2 Optimization model

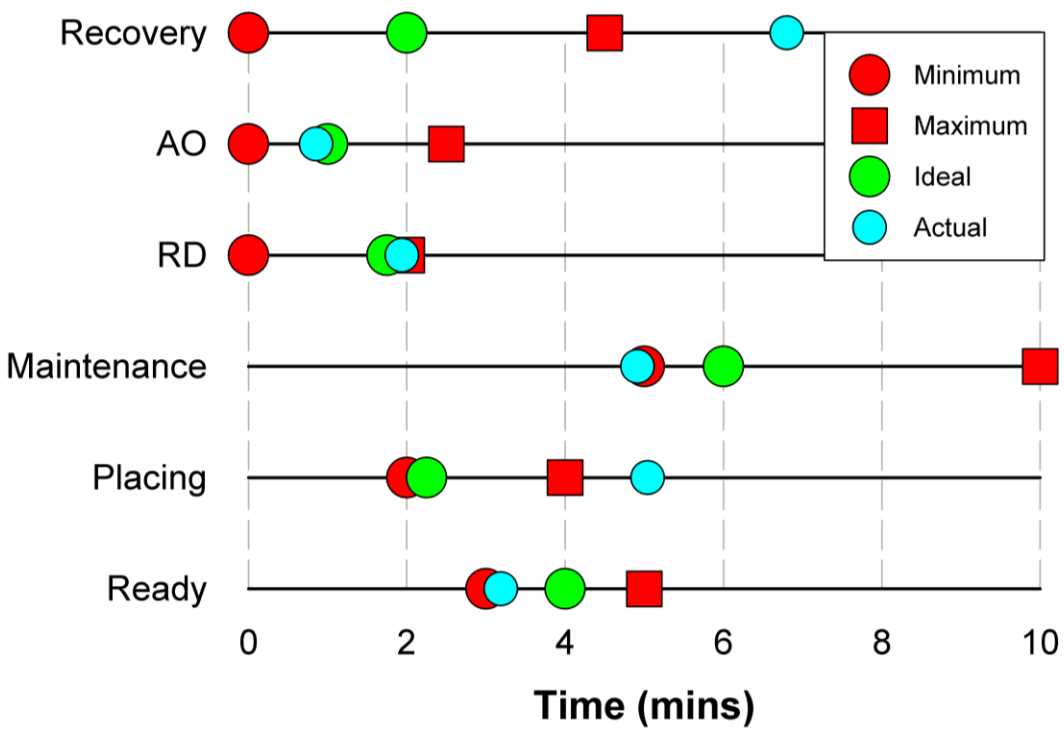
This study used the lexicographic goal programming method to identify an optimal dosing regimen from a set of simulated dosing regimens (x).[7] This process minimizes the total deviation (δ_j) of all objective functions (F_j(x)) from defined goals (b_j) as shown in equation 4.3. The subscript j is used to indicate the objective.

$$\min_{x \in X} \sum_{j=1}^{k} \left| \delta_j \right| \qquad \text{subject to } F_j(x) + \delta_j = b_j, \quad j = 1,2,\ldots,k. \qquad 4.3$$

The minimization is conducted iteratively and optimizes multiple objectives in order of their assigned priorities i = 1 to n, with the optimization only considering those simulations that are within some tolerance δ_j from the ideal solution $F_j(x_j^*)$. The optimal

Figure 4.2: Graphical representation of objective times **(Panel A)** and transformed objective scores **(Panel B)**. Time in minutes is represented on the horizontal axis while the vertical axis represents the six objectives. Ready = ready for esophageal instrumentation. Placing = placing endoscope. Maintenance = maintenance dosing. RD = respiratory depression. AO = airway obstruction. Recovery = return of responsiveness. Red circles and squares represent the minimum and maximum values considered acceptable for each objective, respectively. Green circles represent the ideal time obtained from experts using the Delphi technique. Cyan circles represent actual objective times for a simulated dosing regimen. Transformed objective scores have identical acceptable ranges (-1 to 1) and ideal scores (0), removing potential biases introduced by an objective's magnitude or range.

a)


Recovery
AO
RD
Maintenance
Placing
Ready
Minimum
Maximum
Ideal
Actual
0
2
4
6
8
10
Time (mins)

b)

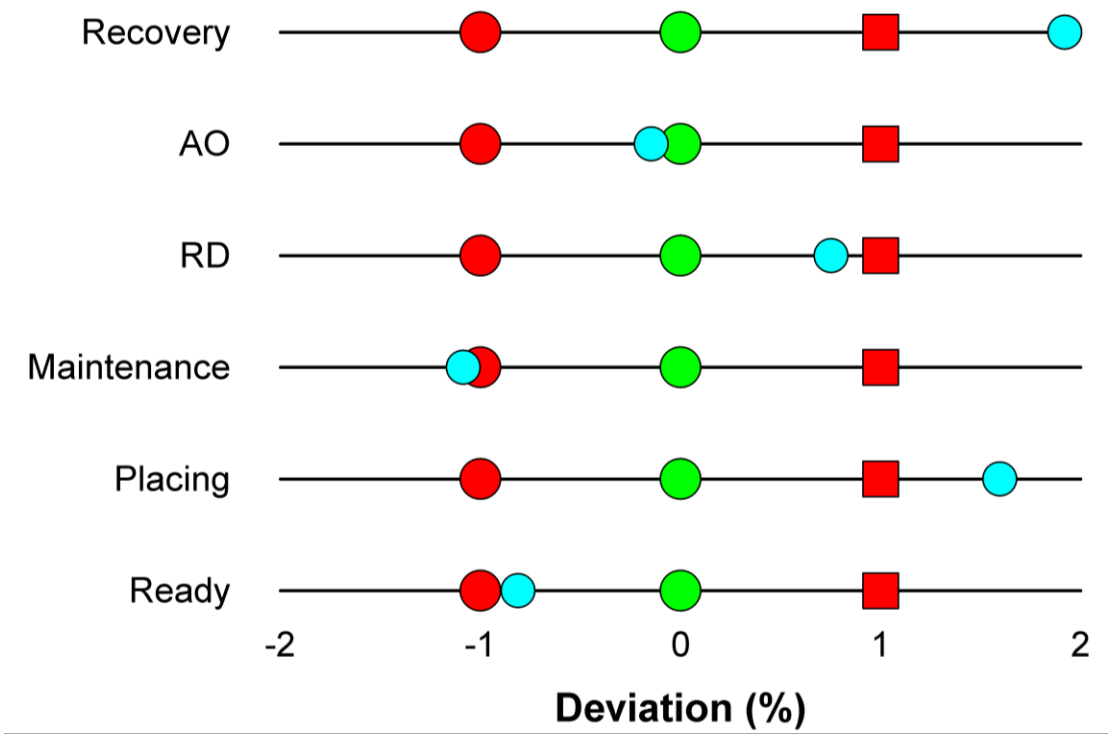


Figure 4.2 continued

dosing regimen is identified as the remaining simulation with the minimum total deviation. The general equation is shown as equation 4.4.

$$\min_{x \in X} F_i(x)$$
$$\text{subject to } F_j(x) \le F_j\left(x_j^*\right) + \delta_j, \quad j = 1,2,\ldots,i, \quad i > 1. \tag{4.4}$$

The tolerance can be a fixed amount or a percentage, and can be the same for all objectives or can be a function of objective priority. For this study, δ_j will be a value multiplied by objective priority. The value was determined by increasing from 0 in increments of 0.05 until at least one simulation was within the tolerance of all objectives.

All solutions containing at least one objective score of infinity were eliminated from the simulated set. Additionally, any simulation with a probability of loss of response to esophageal instrumentation less than 25% at the end of the procedure was also eliminated for not providing adequate sedation and analgesia for the entire procedure.

The first time an objective was included, a minimum solution was identified from the remaining set of simulations. The next iteration found a compromise solution between it and all other objectives. In all remaining iterations, only simulations with an objective score within a specified tolerance of the compromise solution were considered. The tolerance around the compromise solution for each objective was proportional to objective priority and took the form (δ_j = objective priority * value). After seven iterations, the optimal dosing regimen was identified as the simulation with the minimum total score in the remaining set. Following is a description of the iterative optimization process.

First iteration: The first iteration identified the simulation with the minimum absolute deviation from ideal for the objective with a priority of one ($F_1(x)$). We will call this solution A.

Second iteration: A compromise solution for $F_1(x)$ was identified by adding the

absolute change in objective scores for $F_1(x)$ from solution A to the absolute value of the objective scores for $F_2(x)$. The new optimal solution was identified as the simulation with the lowest summed score. We will call this solution B.

Third iteration: This round identified a compromise solution for $F_2(x)$. The absolute change in objective scores for $F_1(x)$ and $F_2(x)$ from solution B was calculated and summed with the absolute objective scores for $F_3(x)$. In addition, a constraint was added that only simulations with an objective score for $F_1(x)$ within $\pm\delta_1$ of solution B were considered. The new optimal solution was identified as the simulation with the lowest summed score. We will call this solution C.

Fourth iteration: This iteration identified a compromise solution for $F_3(x)$. The absolute changes in objective scores for $F_1(x)$ from solution B and $F_2(x)$ and $F_3(x)$ from solution C were added to the absolute objective scores for $F_4(x)$. An additional constraint that only solutions with objective scores for $F_2(x)$ within $\pm\delta_2$ of solution C was added to the constraint of $\pm\delta_1$ of solution B's score for $F_1(x)$. The simulation with the lowest total score was identified as the new optimal solution, which we will call solution D.

Fifth iteration: A compromise solution for $F_4(x)$ was identified in this iteration. The absolute differences between objective scores for $F_1(x)$ and solution B, $F_2(x)$ and solution C and $F_3(x)$ and $F_4(x)$ and solution D were added to the absolute objective scores for $F_5(x)$. In addition to constraining the results to those simulations with objective scores within $\pm\delta_1$ of solution B's score for $F_1(x)$ and $\pm\delta_2$ of solution C's score for $F_2(x)$, scores for $F_3(x)$ were constrained to $\pm\delta_3$ of solution D's score. The simulation with the lowest total score was identified as the new compromise solution, which we will call solution E.

Sixth iteration: This round identified a compromise solution for $F_5(x)$. The

absolute differences in objective scores for $F_1(x)$, $F_2(x)$, and $F_3(x)$ were computed as has been described and added to the absolute difference between the scores for $F_4(x)$ and $F_5(x)$ and solution E. The absolute objective scores for $F_6(x)$ were added to the totals. The final compromise solution was identified as the minimum total score that was also within $\pm\delta_1$ of solution B's score for $F_1(x)$, $\pm\delta_2$ of solution C's score for $F_2(x)$, $\pm\delta_3$ of solution D's score for $F_3(x)$ and $\pm\delta_4$ of solution E's score for $F_4(x)$. This solution is referred to as F.

Seventh iteration: identifying optimal solution: The final score for each simulation was computed by adding the absolute differences in objective scores for $F_1(x)$, $F_2(x)$, $F_3(x)$ and $F_4(x)$ as has been described to the absolute difference between scores for $F_5(x)$ and $F_6(x)$ and solution F. After eliminating all simulations that were not within $\pm\delta_1$ of solution B's score for $F_1(x)$, $\pm\delta_2$ of solution C's score for $F_2(x)$, $\pm\delta_3$ of solution D's scores for $F_3(x)$, $\pm\delta_4$ of solution E's score for $F_4(x)$ and $\pm\delta_5$ of solution F's score for $F_5(x)$, the remaining simulation with the minimum score was identified as the best compromise solution for the demographic simulated.

4.3.3 Recommended dosing regimens

Dosing simulations assumed a 10-min upper endoscopic procedure in a spontaneously breathing 55 year-old, 75 kg, 175 cm male. Simulations were performed using custom pharmacokinetic and pharmacodynamic modeling software. (MATLAB R2008b; MathWorks, Inc., Natick, MA) using published pharmacokinetic models for propofol and remifentanil and a 10 second time step.[8,9]

Dosing simulations consisted of a propofol bolus (0-1.4 mg/kg) administered over 3 min beginning at t = -3 min and a remifentanil bolus (0-1 mcg/kg) administered over 1 min starting at t = -1 min. At t = 0 min, parallel but independent fixed-rate infusions of

propofol (0-150 mg/kg/min) and remifentanil (0-0.2 mcg/kg/min) were started and run for the duration of the procedure. All possible combinations of bolus sizes and infusion rates were simulated using the increments indicated in Table 4.1. Probabilities of no response to esophageal instrumentation, loss of responsiveness, intolerable ventilatory depression and respiratory compromise were computed for each time step using published remifentanil propofol interaction models.[2,10,11]

4.4 Results

4.4.1 Objective functions

Six board-certified anesthesiologists from the University of Utah Department of Anesthesiology with an average of twelve years of experience participated in our survey. Consensus on objective priority was reached in three rounds and agreement on ideal objective times and ranges was obtained in the fourth round. Priorities and times are listed in Table 4.2. Times for "*time to ready for esophageal instrumentation"* were increased by 2 min to coincide with the start of the remifentanil bolus. Minimum times for "*time to ventilatory depression recovery"*, "*time to airway obstruction recovery"*, and "*time to return of responsiveness*" were changed to zero under the assumption no effect during recovery would also be acceptable. Ideal times and ranges were successfully used to convert objective times in minutes to a unit-less number representing percent deviation from ideal time for each objective.

4.4.2 Optimization model

Objectives in order by priority are 1) *time to ventilatory depression recovery* (respiratory depression), 2) *time to airway obstruction recovery* (airway obstruction), 3) *time until esophagus can be instrumented* (ready for esophageal instrumentation), 4) *time to return of responsiveness* (return of responsiveness), 5) *time needed to maintain*

Table 4.1: Dosing bolus and infusion rate ranges simulated for each patient demographic. Step sizes indicate the interval within the corresponding range. Simulations will be run for all 3,840 possible combinations of bolus and infusion rate.

	Bolus		Infusion	
	Range	**Step Size**	**Range**	**Step Size**
Remifentanil	0 – 1 mcg/kg	0.2	0 – 0.2 mcg/kg/min	0.05
Propofol	0 – 1.4 mg/kg	0.2	0 -150 mg/kg/min	10

Table 4.2: Ideal objective times, ranges, and priorities obtained from experts in anesthesiology for the six optimization objectives following four rounds of questioning.

	Ideal	Min	Max	Priority
Time to ready for esophageal instrumentation	4*	3*	5*	3
Placing endoscope	2.25	2	4	5
Maintenance dosing	6	5	10	6
Respiratory depression	1.75	0†	2	1
Airway obstruction	1	0‡	2.5	2
Return of responsiveness	2	0‡	4.5	4

* Times presented have had 2 min added to them to adjust for administering the propofol bolus over 3 min. † Time has been reduced from 0.5 to 0.
‡ Time has been reduced from 1 to 0

no response while endoscope is placed in the duodenum (placing endoscope) and 6) *time with no response while the procedure is performed* (maintenance dosing).

Tolerance took the form (δ_j = objective priority * value). The value identified in this study was 0.2. Some steps in the iteration were modified once final objective priority was known. In the fourth iteration, objective scores for $F_4(x)$ (return of responsiveness) were added instead of absolute objective scores. The fifth iteration used the difference between the objective scores for $F_4(x)$ and solution D instead of the absolute difference. The sixth iteration subtracted objective scores for $F_6(x)$ instead of adding the absolute objective scores.

4.4.3 Recommended dosing regimens

A total of 3,840 dosing regimens were simulated from the possible dosing combinations shown in Table 4.1. Probabilities of no response to esophageal instrumentation, loss of responsiveness, intolerable ventilatory depression and respiratory compromise were computed and objective scores calculated. As was expected, no simulated dosing regimen optimally satisfied all objectives (objective scores = 0). In addition, only 17 of the simulated dosing regimens had every objective score within the acceptable range (objective scores between -1 and 1). The dosing combinations for these 17 simulations are shown in Table 4.3 and the corresponding probabilities of loss of response to esophageal instrumentation are shown in Figure 4.3.

An optimal dosing recommendation was identified for the simulated 55 year old, 75 kg, 175 cm male undergoing an anticipated 10-min upper endoscopy. It consisted of a 0.8 mg/kg bolus of propofol administered over 3 min starting at t = -3 min and a 0.2 mcg/kg bolus of remifentanil administered over 1 min starting at t = -1 min. At t = 0 min, infusions of 40 mg/kg/min of propofol and 0.05 mcg/kg/min of remifentanil were started. The resulting Ces of propofol and remifentanil are shown in Figure 4.4 along with

Table 4.3: Dosing regimens that produce objective scores within the ideal ranges for all six objective scores when run on a 55 year-old, 75 kg, 175 cm male demographic assuming a 10-min procedure length. The propofol bolus is administered over a 3 min period beginning at t=-3 min. The remifentanil bolus is given over a 1 min time period beginning at t=-1 min. Both infusions are started at t=0 min and run for 10 min.

Bolus		**Infusion**	
Prop (mg/kg)	**Remi** (mcg/kg)	**Prop** (mg/kg/min)	**Remi** (mcg/kg/min)
0.2	1	10	0.15
0.2	1	10	0.20
0.2	1	20	0.10
0.2	1	20	0.15
0.2	1	30	0.10
0.2	1	40	0.05
0.2	1	70	0
0.4	0.6	0	0.20
0.4	0.6	10	0.15
0.4	0.6	20	0.10
0.4	0.6	40	0.05
0.4	0.6	50	0.05
0.6	0.2	0	0.20
0.6	0.4	40	0.05
0.6	0.4	50	0.05
0.8	0.2	40	0.05
1.4	0	30	0.05

Prop = propofol. Remi = remifentanil.

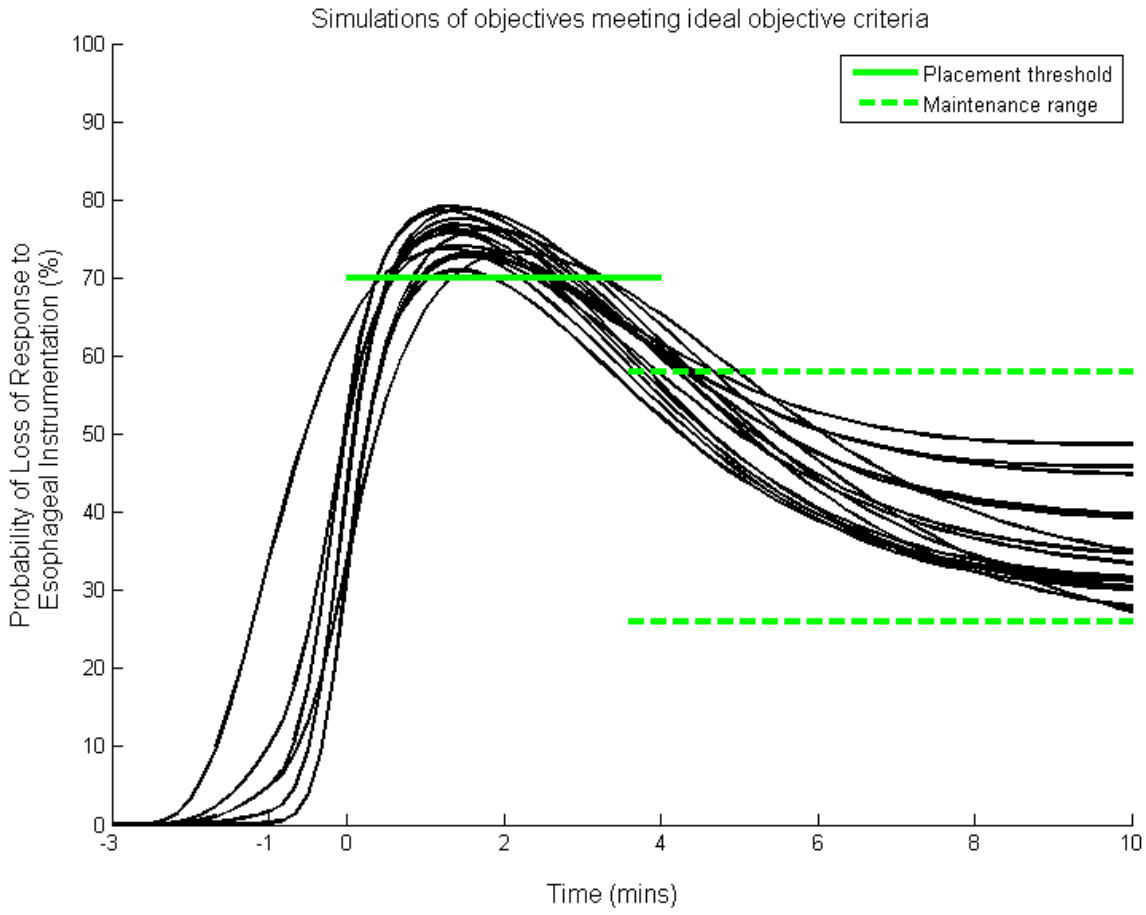


Figure 4.3: Of the 3,840 dosing combinations simulated, only 17 had every objective score within the minimum and maximum ideal range. Shown are the probabilities of loss of response to esophageal instrumentation for these 17 (solid black) along with a solid green line showing the target for ready for placement as well as dashed green lines showing the range for maintenance dosing.

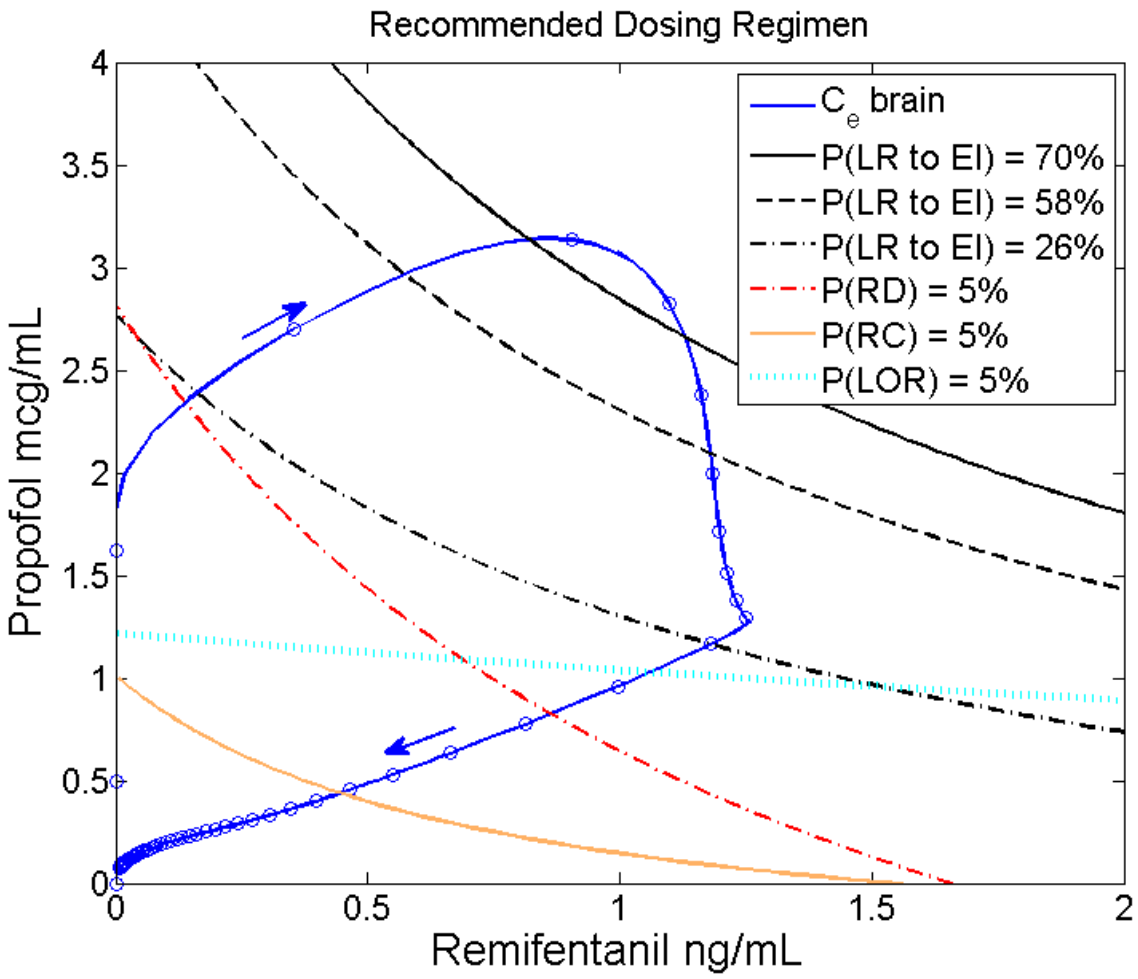


Figure 4.4: Dosing scheme recommended for a 55 year-old, 75 kg, 175 cm male presenting for an anticipated 10-min upper endoscopy (solid blue). The X-axis displays remifentanil effect site concentrations while the Y-axis displays propofol effect-site concentrations. The other lines on the plot represent drug iso-effect isoboles and indicate the propofol-remifentanil drug combinations that would be expected to produce the same probability of effect. Open blue circles represent time in minutes while blue arrows indicate the direction of time. In terms of optimization objective functions in order of occurrence, the dosing must first reach at least a 70% probability of loss of response to esophageal instrumentation (P(LR to EI) = 70%, dashed black). It then must drop within the maintenance dosing range (solid black) and remain there until the end of the procedure (sharp elbow around Propofol = 1.3 mcg/mL, remifentanil = 1.3 ng/mL). It then must drop below a 5% probability of loss of response to esophageal instrumentation (P(LOR) = 5%, dotted cyan), 5% probability of respiratory depression (dash-dot red), or 5% probability of airway obstruction (not shown). Because there is no model for airway obstruction, it was approximated as the actual probability of respiratory compromise (P(RC), orange) minus the actual probability of respiratory depression.

topographical representations of the pharmacodynamic targets. The final total objective score was 0.5.

A typical patient in this demographic would be ready for esophageal instrumentation in 3.8 min (ideal = 4). The dosing regimen would provide 2.9 min of elevated drug levels while the scope is placed in the duodenum (ideal = 2.25) and 6.5 min (ideal = 6) of maintenance dosing. Once the procedure had ended, return of responsiveness would occur within 1.3 min (ideal = 2), at which point respiratory compromise and respiratory depression would no longer be worrisome. This optimal dosing regimen produced peak Ces of ~3 mg/mL of propofol and ~1 ng/mL of remifentanil during placement. When the procedure ended, Ces were ~1.3 mcg/mL for propofol and ~1.3 ng/mL for remifentanil.

4.5 Discussion

When selecting drugs to administer for a procedure, care must be taken to consider the drug effects – good and bad – as well as the drug interactions for these effects. While propofol and remifentanil can offer rapid onset of effect, ease of titration to effect and rapid recovery times, a limitation to their safe use is lack of experience with or knowledge of their interaction profile. Previous work has explored the effects of propofol-remifentanil combinations for loss of response to esophageal instrumentation, loss of responsiveness, respiratory depression and respiratory compromise. This current work seeks to combine effect models with optimization techniques to identify an optimal propofol-remifentanil dosing regimen for mild to moderately painful procedures requiring esophageal instrumentation.

4.5.1 Objective functions

The dosing strategy used in this study administered the loading bolus of propofol over a 3 min time period. This was done to provide dosing consistent with the propofol

packet insert. However, it also increased the time required to reach a 70% probability of loss of response to esophageal instrumentation, making it unlikely an optimal solution would reach this probability in less than 3 min. To compensate, the times were increased by 2 min, coinciding with the start of the remifentanil bolus instead of the propofol bolus. Minimum times for "*time to ventilatory depression recovery"*, "*time to airway obstruction recovery"*, and "*time to return of responsiveness*" were reduced to 0 to allow dosing regimens with objective scores of 0 (no effect during recovery) to also be considered.

A change in objective priority will influence the results obtained from the optimization model. Experts placed the highest priorities on minimizing respiratory depression and airway obstruction. Because models for these effects only apply to unstimulated subjects, objective scores for respiratory depression and airway obstruction corresponded to recovery once the procedure had ended. The application of these models in this way corresponded to optimizing propofol and remifentanil Ces at the end of the procedure. Additionally, these effects were considered worrisome only if the subject was unresponsive and, except for high remifentanil dosing regimens (remifentanil Ces > 1.5 ng/mL), maintenance dosing produced probabilities of loss of responsiveness in excess of 5%. The lowest probability of respiratory depression and <5% probability of loss of responsiveness corresponded to Ces of ~1 mcg/mL for propofol and ~1.5 ng/mL for remifentanil (Figure 4.4). Therefore, optimal dosing regimens recommend loading boluses and infusion rates predicted to come closest to this point once drug administration is terminated for the specific demographic.

It was also noted that ideal objective times influenced the final dosing recommendation. For example, time to ready for esophageal instrumentation, the third priority in this implementation, principally determined the sizes of the loading boluses. Shorter times required higher propofol boluses, but also resulted in a larger overshoot of the targeted 70% probability of loss of response to esophageal instrumentation. This

produced longer times for the placing endoscope objective and lower total time for the maintenance dosing objective. This objective is not critical to patient safety and the start of drug administration could be adjusted so the patient is ready for esophageal instrumentation at the clinician's discretion. Therefore, it may be best to optimize all other criteria and have the final solution dictate when the subject is ready for esophageal instrumentation.

Some limitations must be also addressed. First, pharmacokinetic and pharmacodynamic models are population-based models and represent what may be expected in a typical person. Large variability is associated with these models and actual drug needs may be more or less than what is recommended. Next, priorities and objective criteria were obtained using the Delphi technique. The responses may be different if a different set of panelists were queried, or if the panel was made up of clinicians instead of anesthesiologists. Also, it is possible we have misspecified or left out an objective. However, we were limited to the pharmacodynamic models available for propofol-remifentanil combinations. Finally, it is possible that some aspects cannot be quantified, making it impossible to include in an objective function.

4.5.2 Optimization model

The lexicographic goal programming technique allows detailed *a priori* articulation of preferences. Compromise between objectives is necessary independent of the dosing regimen used and all drug effects are not equal. This technique provides a methodology whereby objective priorities are considered, ranges of deviation from ideal can be specified, and flexibility exists within the construct to allow for identification of a compromise solution.

However, it must be understood that these recommendations are based on population models and suffer from the same limitations mentioned for objective

functions. They are meant to assist in the selection of doses prior to sedating and not as absolutes to be fed into an automated dosing system. There is no mechanism for real-time patient feedback so careful observation of a patient by a dedicated person is still necessary.

In our approach, we defined dosing regimens using fixed intervals for boluses and infusion rates. While these were selected to ensure the simulated dosing regimens covered the full range of drug effects, it is possible this approach excluded a more optimal dosing regimen. However, intervals were selected in increments that allowed them to be easily administered by a clinician and accounted for the limited resolution in both syringes and infusion pump rates.

4.5.3 Recommended dosing regimens

An ideal dosing would provide rapid loss of response to esophageal instrumentation, mild sedation, and no risk of respiratory depression and airway obstruction. However, previous work has shown this condition is not likely to exist in a majority of patients.[2,11] Instead, compromises between effects must be made. In this work we present a multiobjective optimization function that evaluates the tradeoffs between the effects mentioned for procedures requiring esophageal instrumentation and provides an *a priori* dosing regimen recommendation for a specific patient demographic.

The optimization model recommended an optimal dosing regimen for a 55 year-old, 75 kg, 175 cm male. In comparison to propofol-fentanyl (in remifentanil equivalents) simulations conducted for this same demographic in previous work, endoscope placement occurs at higher propofol Ces (~3 mcg/mL compared to ~1.3 mcg/mL) while the procedure ends at higher remifentanil Ces (~1.3 ng/mL compared to ~0.8 ng/mL).[2] However, previous simulations administered drugs based on time and did not target probabilities of loss of response to esophageal instrumentation, resulting in peak

probabilities between 20-30%. The optimized dosing strategy targets a peak probability of 70% and necessarily reaches higher propofol Ces to do so. In addition, previous simulations administered fentanyl as a single bolus at the beginning of the procedure. Fentanyl is longer-acting than remifentanil and no additional fentanyl was needed for the 10-min procedure simulated. Fentanyl Ces were therefore decreasing during the procedure. In contrast, additional remifentanil is needed and is administered with a fixed-rate infusion throughout the procedure, causing remifentanil Ces to increase.

The optimal dosing regimen identified is not the best solution for any single objective. However, it does incorporate compromises between all objectives and does recommend a dosing regimen that would produce objective times within the acceptable ranges obtained from our expert panel in the typical 55 year-old, 75 kg, 175 cm male patient. When compared to previous work, the simulated optimal dosing regimen produces peak probabilities of loss of response to esophageal instrumentation in a region where a high number of volunteers had no response to esophageal instrumentation but a high probability of loss of responsiveness. Predicted Ces at the end of the simulated procedure corresponded to a region where a high number of unstimulated volunteers did not have respiratory depression or respiratory compromise.

While our results confirmed our hypothesis, it is possible other solutions exist. In this study, drug administration was limited to propofol or propofol in combination with remifentanil. This was principally because of their rapid pharmacokinetics and ease of titration to effect. In addition, previous research on propofol and propofol in combination with remifentanil during upper endoscopy had been conducted and pharmacodynamic models of their interaction for needed drug effects existed.

Besides choice of drugs, the dosing strategy used was simplistic. In this preliminary look at dose optimization, this was intentional but it is possible a different dosing strategy would lead to a more optimal recommendation. However, the strategy

used has several benefits. First, its simplicity makes it easy to implement. A fixed-rate infusion of drug provides more stable sedation and analgesia for the duration of the procedure than current intermittent bolusing techniques. Stimulation in upper endoscopies is intermittent and transient. Waiting until a patient responds to a stimulation to administer additional drug often means peak drug effects are occurring when there is no more need. In addition, steady drug administration allows the natural buildup of carbon dioxide to stimulate respiratory drive. Rapid changes in drug level may produce periods of respiratory depression before carbon dioxide levels reach levels that stimulate respiration. However, incorporation of “negative boluses”, or periods where drug infusion is paused, could potentially allow larger boluses to be given up front without causing prolonged overshoot as well as more rapid drop in Ces once the endoscope is placed.

The objective function scores developed in this study provide a means of quantifying and evaluating the performance of propofol-remifentanil dosing regimens for procedures requiring esophageal instrumentation independent of the dosing strategy used. Dosing regimens that come closest to ideal times achieve lower scores. In this way, the optimization algorithm presented may also prove useful in evaluating various dosing strategies and identifying and optimal technique.

In summary, an optimal dosing regimen was identified from a set of simulated dosing regimens that, according to expert opinion and models of drug effect, provides conditions that will permit upper endoscopy procedures. Dosing recommendations in a 55 year old, 75 kg, 175 cm male for a simulated 10-min upper endoscopic procedure were consistent with our previous work. Future work is needed to validate recommended dosing regimens in patients undergoing brief procedures requiring esophageal instrumentation.

4.6 Appendix: Questionnaire

Background:
We would like to identify the optimal sedation and analgesia conditions for upper endoscopic procedures when using **propofol or propofol in combination with remifentanil**. The ideal dosing regimen provides optimal working conditions for the endoscopist while preserving patient safety and comfort. We are seeking expert consensus to define ideal conditions.

Please provide answers for the **current procedure** (10 minute upper endoscopy)

Definitions:
Unresponsive: Does not respond to "shake and shout"
Respiratory depression: Four or less breaths per minute (bpm). This state is corrected by prompting the patient to breathe or manual ventilations
Airway Obstruction: Either complete or partial airway obstruction (AO). This state is corrected with a chin lift or oral airway
Unresponsive to placement of an endoscope: No gag reflex or response to placement of an endoscope

Instructions: You will be asked to provide the ideal time and acceptable range of times (section I) and priority (section II) for each objective presented.

When formulating your responses, please consider patient safety, patient satisfaction, and procedural demands. The comment section provides you an opportunity to explain to other participants if your answer is different from the mean/median response. Comments you make will be available for other experts to review during the subsequent round.

I. Ideal Times and Acceptable Ranges

Instructions: Please specify both an **ideal** time AND an acceptable **range** of times (with resolution to half a minute) for each objective presented below. (e.g. ideal time of 1.5 mins, range of 1 – 3 mins).

Case Stem: You will provide sedation and analgesia to a healthy 55 year old, 75 kg (165 lbs), 170 cm (5' 7") male undergoing an upper endoscopy. Assume the procedure will last 10 minutes.

1. Once drug administration has begun, how many minutes should it take before the patient tolerates esophageal instrumentation?
***Ideal*:** _____ minutes
***Acceptable range*:** min _____ – max _____ minutes

2. How many minutes are needed to place a scope in the duodenum?
***Ideal*:** _____ minutes
***Acceptable range*:** min _____ – max _____ minutes

3. Once the scope has been placed, how many minutes of maintenance dosing are needed? Assume drug administration starts at 0 mins and the procedure ends (scope out) at 10 mins.
(balance of the procedure is 10 mins – ideal time for #1 – ideal time for #2)
***Ideal*:** _____ minutes
***Acceptable range*:** min _____ – max _____ minutes

4. How many minutes will you allow the patient to be in a state where they require prompting to breathe or manual ventilations to correct respiratory depression?
(*assume all vital signs start at normal levels*)
***Ideal*:** _____ minutes
***Acceptable range*:** min _____ – max _____ minutes

5. How many minutes will you allow the patient to be in a state where they require a chin lift or oral airway to correct airway obstruction?
(*assume all vital signs start at normal levels*)?
***Ideal*:** _____ minutes
***Acceptable range*:** min _____ – max _____ minutes

6. Once the procedure has ended, how long should it take for the patient to return to responsiveness?
(*responds to name spoken in a normal tone without any tactile, painful or noxious stimulation*)
***Ideal*:** _____ minutes
***Acceptable range*:** min _____ – max _____ minutes

II. Objective Priority

Instructions: Prioritize each of the 6 objectives from 1 (most important) to 6 (least important).
Each objective must be assigned a priority. Each priority can only be used once.

_____ Time to ready for esophageal instrumentation

_____ Time needed to place scope in duodenum

_____ Providing maintenance dosing for the balance of the procedure

_____ Duration of time requiring corrective action for respiratory depression

_____ Duration of time requiring corrective action for airway obstruction

____ Time to return of responsiveness

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CHAPTER 5

DISCUSSION

This dissertation was undertaken to determine if a dosing combination exists that provides adequate sedation and analgesia for esophageal instrumentation while minimizing the risk of adverse effects. Work conducted for each aim has contributed to the field and provided pieces needed to answer to this question.

5.1 Summary

5.1.1 Pharmacodynamic models of drug effect

Pharmacodynamic models of drug effect for esophageal instrumentation, intolerable ventilatory depression and respiratory compromise were not available prior to this work. Therefore, novel techniques were developed to capture and process this data, in particular, the use of respiratory rate and tidal volume to determine clinically significant respiratory depression and airway obstruction.

Response to esophageal instrumentation could be blocked at low remifentanil (0.8 $ng \cdot mL^{-1}$) and high propofol (2-3 $mcg \cdot mL^{-1}$) concentration pairs. Procedures ending at these same concentrations also avoided intolerable ventilatory depression. Response to esophageal instrumentation could be blocked while avoiding loss of responsiveness for high remifentanil low propofol combinations, but would not be recommended due to the increased risk of intolerable ventilatory depression.

A revised model of loss of response to esophageal instrumentation was created when comparison of our preliminary model was found to be overly stringent. Model fit

improved after relaxing the classification of response to only those with purposeful movement. This infers that clinicians are willing to tolerate some level of patient discomfort and blunt rather than completely block the response to esophageal instrumentation.

Limitations associated with interpreting models are that for loss of responsiveness, respiratory depression and respiratory compromise, data were collected in unstimulated volunteers. Because procedures requiring esophageal instrumentation are stimulating, the models cannot be applied to stimulated patients. They do, however, apply to periods when there is no stimulation such as when the procedure has ended. In addition, all models were generated from data collected in young, healthy volunteers and do not have covariates for age, etc.

Stimulation provided by the procedure would likely minimize the occurrence of loss of responsiveness, intolerable ventilatory depression and respiratory compromise during a procedure. In addition, intolerable ventilatory depression and respiratory compromise are only worrisome when a subject in unresponsive to prompting to breathe.

5.1.2 Evaluation of common dosing strategies

A review of published dosing regiments found the most common dosing combination referenced was propofol and fentanyl. The most frequently referred to dosing technique was a loading bolus of propofol and fentanyl followed by intermittent boluses of propofol titrated to effect. Only one published recommendation for propofol and remifentanil was identified but used target controlled infusions, a technique not approved in the United States.

Through simulation it was shown that propofol only techniques would lead to longer time of unresponsiveness following the procedure but quicker recovery times for

respiratory compromise. Combined techniques had a quicker return of responsiveness yet longer time of respiratory compromise. An important clinical implication of these simulations is that should patients require prompting to breathe to avoid ventilatory depression, techniques that minimize loss of responsiveness may be more desirable because patients can respond to the prompting.

A limitation of interpreting these simulations is that dosing recommendations were published as ranges. Some degree of interpretation was needed when designing the simulations and the dosing may be misspecified.

5.1.3 Identification of optimal drug combination and dosing

An optimal dosing recommendation was identified for a simulated 55 year-old, 75 kg, 175 cm male undergoing an anticipated 10-min upper endoscopy and consisted of a propofol bolus of 0.8 mg/kg and infusion rate of 40 mcg/kg/min and a remifentanil bolus of 0.2 mcg/kg and an infusion rate of 0.05 mcg/kg/min. This optimal dosing regimen produced peak Ces of ~3 mg/mL of propofol and ~1 ng/mL of remifentanil during placement. When the procedure ended, Ces were ~1.3 mcg/mL for propofol and ~1.3 ng/mL for remifentanil. One difference of note between the recommended dose and those simulated in aim 2 was that opioid concentration is increasing throughout the procedure while in aim 2 it was decreasing. This is a result of using a remifentanil infusion instead of a single loading bolus of fentanyl.

This optimization approach was based on a priori articulation of preferences and population-based pharmacokinetic models. Conditions in an actual patient may vary widely from these predictions. Also, a simplified drug dosing strategy has been implemented to minimize the number of optimization parameters. A more complex strategy may provide a more optimal dosing recommendation. Finally, the optimization is a function of the objectives as defined and is therefore susceptible to any error they

contain. Important objective functions may be missing and unnecessary objectives may have been added.

In summary, propofol-remifentanil pharmacodynamic effect models for loss of response to esophageal instrumentation, respiratory depression and respiratory compromise were built. When overlaid with each other, a prospective target region of high probability of loss of response to esophageal instrumentation and low probability of intolerable ventilatory depression was identified. Research into common dosing regimens discovered intermittent bolus dosing techniques of propofol-fentanyl were commonly used. For simplicity in optimizing, this technique was converted to a loading bolus of propofol and remifentanil followed by fixed rate infusions. An optimal dosing regimen was identified from a set of simulated dosing regimens that, according to expert opinion and models of drug effect, provides conditions that will permit upper endoscopy procedures.

5.2 Future Work

Dosing recommendations from this dissertation could be improved. First, models of loss of responsiveness, respiratory depression and respiratory compromise should be validated. Additionally, models created in stimulated patients would provide insight to the probability of these adverse effects occurring during a procedure.

Validation of the priorities, ideal times and ranges is necessary to add confidence to the optimization targets. A dosing strategy that incorporated more variations in drug administration (e.g. ability to pause infusion, administer additional boluses) may be better at reaching ideal times. Finally, dosing recommendations should be validated in patients undergoing brief procedures requiring esophageal instrumentation.