A Simulation Study of Common Propofol and Propofol-Opioid Dosing Regimens for Upper Endoscopy

Implications on the Time Course of Recovery

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ABSTRACT

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

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.

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 (less than 3 min). Propofol-opioid techniques required more time than propofol alone to achieve a high probability of no respiratory compromise (7 *vs.* 4 min).

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.

What We Already Know about This Topic

- The target effect-site propofol and remifentanil concentrations needed to render a volunteer completely unresponsive to esophageal instrumentation are often associated with loss of responsiveness, intolerable ventilatory depression, or both

What This Article Tells Us That Is New

- Simulation of effect-site propofol and either fentanyl or remifentanil concentrations produced by published dosing schemes for endoscopy with a modified propofol-remifentanil interaction model predicted a moderate probability of not only conditions that allow esophageal instrumentation but also respiratory compromise and loss of responsiveness at the end of the procedure

PROPOFOL alone and in combination with selected opioids is 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]

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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.

Previous work in our laboratory on healthy unstimulated volunteers explored the presence or absence of intolerable ventilatory depression, defined as a respiratory rate of ≤4 breaths/min, over a wide range of propofol-remifentanil concentration pairs administered in a laboratory setting. From these 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. Nonresponsiveness 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 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 decreased 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 after the procedure. We hypothesized that simulations of these dosing regimens would predict a 50–95% 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.

‖ 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.

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) approved the study. After receiving informed, written consent, 24 volunteers were enrolled and received escalating target-controlled infusions of propofol and remifentanil covering a range of effect-site concentrations (C_es) for each drug (propofol 0–4.3 mcg/ml and remifentanil 0–6.4 ng/ml). Volunteers were randomly assigned to receive 3 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.

Effect Measures

Assessments of intolerable ventilatory depression and airway obstruction were made in the fourth minute after reaching predicted target C_es. We previously reported the presence or absence of intolerable ventilatory depression (respiratory rate of ≤4 breaths per min) 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-s average inspired tidal volume less than 3 ml/kg and more than two 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 C_es as 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.

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 categoric data[15] using a naïve pooled technique[16] and modeling software

Table 1. New, Revised, and Published Propofol-Remifentanil Pharmacodynamic Interaction Model Parameters for Selected Drug Effects

Effect	$C_{50\ remi}$ (CV) ng/ml	$C_{50\ prop}$ (CV) mcg/ml	α (CV) (Interaction)	γ(CV) *(Slope)*	*P*, chi-square
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	–

C_{50} = predicted concentration associated with a 50% probability of effect; chi-square = chi-square goodnees-of-fit; CV = coefficient of variation; LOR = loss of responsiveness; LREI = loss of response to esophageal instrumentation; prop = propofol; RC = respiratory compromise; remi = remifentanil.

(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 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 chi-square test statistic was computed using equation 1:

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

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 chi-square test statistic exceeded the chi-square 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 graphic approaches were used to assess model fits. The first plot presented the observed responses and a topographic rendering of model predictions created by plotting the 5%, 50%, and 95% isoeffect lines (isoboles). Isoboles represent all predicted propofol-remifentanil C_e combinations that produce the same probability of observing a modeled effect. This format was used to illustrate the number of volunteers who 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.

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.

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. C_es 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 C_es from each dosing regimen were then used to predict the probability of drug effects over time using the response surface models for respiratory compromise and loss of response to esophageal instrumentation and a previously reported response surface model for loss of responsiveness[22] (table 1). Low, moderate, and high probabilities of drug effect were defined as less than 25%, 25–75%, and more than 75%, respectively. Once the simulated 10-min procedure ended, the time required for drug effects to dissipate was estimated using the time to reach a high probability of no respiratory compromise and no loss of responsiveness (less than 5% probability).

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; 17 because blood pressure and/or heart rate changed more than 20% from baseline and 3 due to inadequate oxygenation. This included 8 intolerable ventilatory depression, 11 airway obstruction, 3 respiratory compromise, and 14 esophageal instrumentation assessments. Results from an additional eight assessments were not used because of recording difficulties with the pneumotachometer. One hundred eighteen assessments of airway obstruction could not be made because volunteers were experiencing intolerable ventilatory depression.

Effect Measures

Airway obstruction was observed in 27 of the 61 target concentration pairs (59 of 247 assessments) and consistently in 10 (11 of 11 assessments). Airway obstruction occurred more often at high-propofol C_es. 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 C_es. 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 (fig. 1A). Responses in the remaining 29 concentration pairs were mixed (*i.e.*, some volunteers developed respiratory compromise whereas others did not). For example, with propofol at 2.0 mcg/ml and remifentanil at 0.8 ng/ml, seven 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 (fig. 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/ml and remifentanil at 0.8 ng/ml, five volunteers tolerated esophageal instrumentation and three did not.

Response Surface Models

Model parameters, coefficients of variation, and the *P* value from the chi-square goodness-of-fit test are presented in table 1. The positive α (interaction term) values indicate a synergistic relationship between remifentanil and propofol for respiratory compromise and loss of response to esophageal instrumentation. The small γ value indicates a large range of concentrations covering the transition from responsive to unresponsive. However, the value for γ may be a reflection of both interindividual variability for C_{50} and an individual's γ. Coefficients of variation indicated low parameter variability (less than 30%) except for the α 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 1A for respiratory compromise and figure 1B for loss of response to esophageal instrumentation. Model predictions were consistent with observations. The observed frequency of respiratory compromise and loss of response to esophageal instrumentation less than 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 whereas most between 5% and 50% did not.

Observed responses and prediction errors are presented in figures 1C and 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 $\leq$0.5.

One previously published propofol-remifentanil interaction model for loss of responsiveness is also presented in table 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.

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 infusions of propofol and remifentanil. Four dosing schemes were selected for simulation purposes and are presented in table 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 administered by SEDASYS (Ethicon Endo-Surgery, Inc, Cincinnati, OH),[4,26] and target-controlled infusions of propofol and remifentanil.[27]

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 2) assuming a 75-kg, 175-cm, 55-yr-old male patient. Predicted C_es for propofol, fentanyl (in remifentanil equivalents), and remifentanil for each dosing scheme are presented in figure 2. During the 10-min procedure,

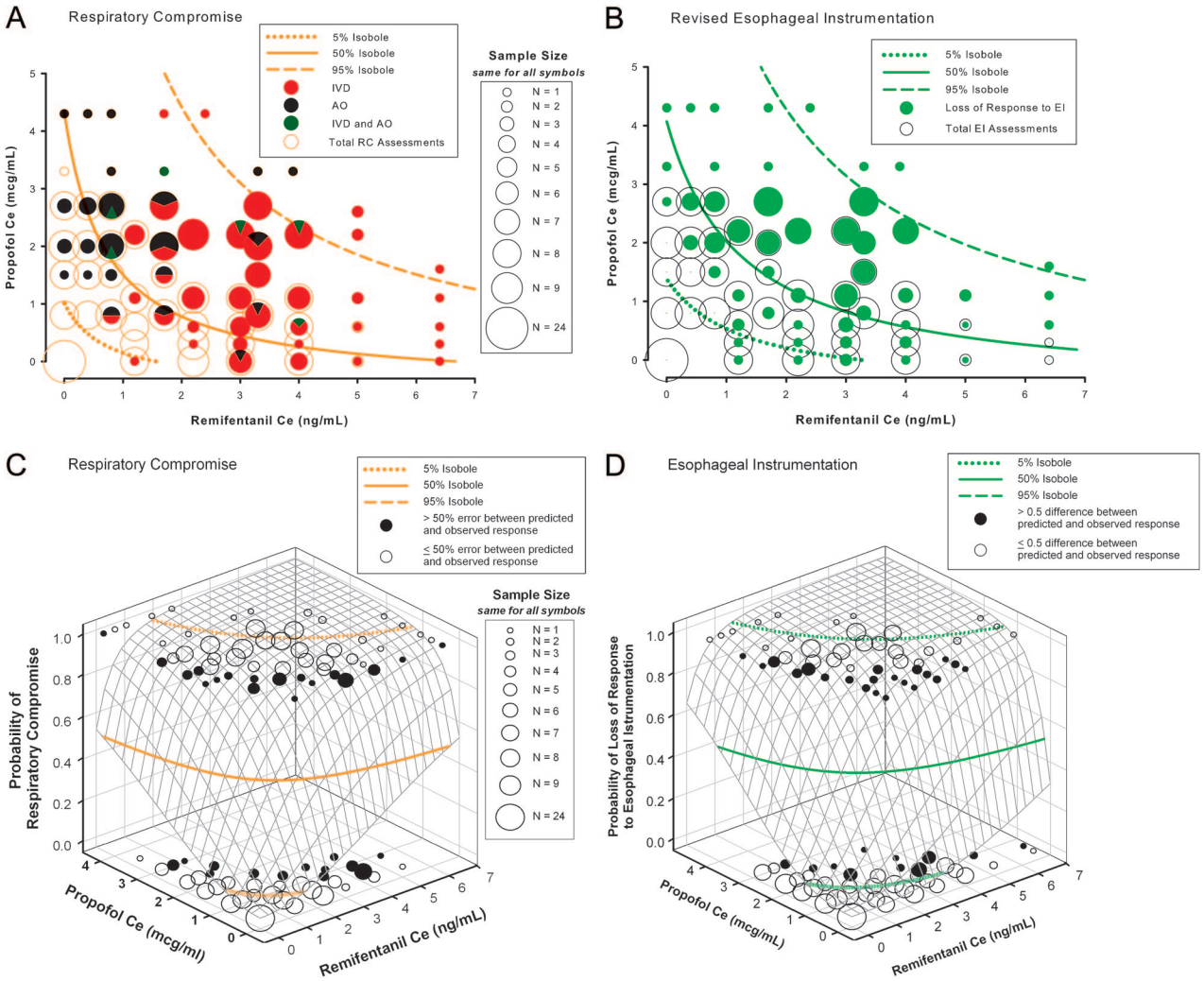

Fig. 1. Observed responses and model predictions for respiratory compromise (RC) and loss of response to esophageal instrumentation (EI). (*A* and *B*) Topographic plot of raw data and model predictions. *Open circle* size indicates the number of RC and loss of response to EI assessments made at the corresponding drug effect-site concentration (C_e) pairs, respectively. *Filled circle* size indicates the number of subjects with RC and loss of response to EI. RC data are 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*). (*C* and *D*) Response surface plot of model prediction and model error. Model predictions are presented as a mesh surface. *Dotted (bottom)*, *solid (middle)*, and *dashed (top) 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 more than 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).

estimated propofol concentrations ranged from 1.2 to 3.0 mcg/ml and remifentanil concentrations ranged from 0.7 to 1.5 ng/ml. Predictions of time to recovery for respiratory compromise and loss of responsiveness are presented in figure 2D and predictions of loss of response to esophageal instrumentation throughout the 10-min procedure are presented in figure 3.

Technique 1. For the intermittent propofol boluses, the resultant propofol concentrations during the 10-min procedure ranged from 2 to 3 mcg/ml and then dissipated to near 0.5 mcg/ml 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.

Technique 2. For the fentanyl bolus followed by intermittent propofol boluses, fentanyl reached a peak of approximately 1.2 ng/ml (in remifentanil equivalents) within 5 min of starting induction and then slowly dissipated to near 0.8 ng/ml at 10 min. The accompanying propofol concentrations ranged between 1 and 2 mcg/ml and dissipated to less than 0.5 mcg/ml over the next 10 min. This led to a moderate probability of respiratory compromise and a low probability of loss of responsiveness at the end of the procedure. Respira-

Table 2. Selected Published Propofol and Propofol-Opioid Dosing Regimens for Upper Endoscopy for a 55-Yr-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 20-30 s between doses	Initial bolus of 35 mg followed by 15 mg boluses 0.5, 3.5, 5.5, 8, and 10.5 min 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 s between doses	Initial bolus of 7.5 mg followed by 10 mg boluses 0.5, 2, 4.5, 7, 9.5, and 12 min 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	Loading dose of 0.5 mg/kg × (maintenance infusion rate)/75 started 3 min after fentanyl bolus and administered over 3 min followed by a maintenance infusion of 25–75 mcg · kg^{-1} · min^{-1} that is titrated to effect	Three min after fentanyl bolus, a loading dose of 8.3 mg/min for 3 min followed by a 10-min infusion at 50 mcg · kg^{-1} · min^{-1}
	Fentanyl bolus	Initial bolus of 50–100 mcg 3 min before administration of propofol	Initial bolus of 75 mcg
Technique 4: Gambus *et al.*, 2011[27]	Propofol TCI	2.8-1.8 mcg/ml	C_e target of 1.8 mcg/ml
	Remifentanil TCI	0-1.5 ng/ml	C_e target 1.5 ng/ml

* Dosing recommendation reported by the American Gastroenterological Association Institute and cited by the American Society for Gastrointestinal Endoscopy.

C_e = effect-site concentration; TCI = target-controlled infusion.

tory compromise dissipated within 8 min whereas 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.

Technique 3. For the fentanyl bolus 3 min before 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/ml and then dissipated to less than 0.5 mcg/ml 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, whereas loss of responsiveness dissipated in less than 2 min. 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.

Technique 4. For the target-controlled infusions, propofol was maintained at 1.8 mcg/ml and remifentanil at 1.5 ng/ml 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, respectively, to dissipate. 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.

Discussion

Predicting the likelihood of ventilatory depression, airway obstruction, and/or loss of responsiveness is important in formulating rational dosing regimens for procedural sedation. In this study, we modified our previously reported interaction model of intolerable ventilatory depression to include a measure of airway obstruction and called it 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. We categorized heart rate or blood pressure changes, nonpurposeful 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.

Effect Measures

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

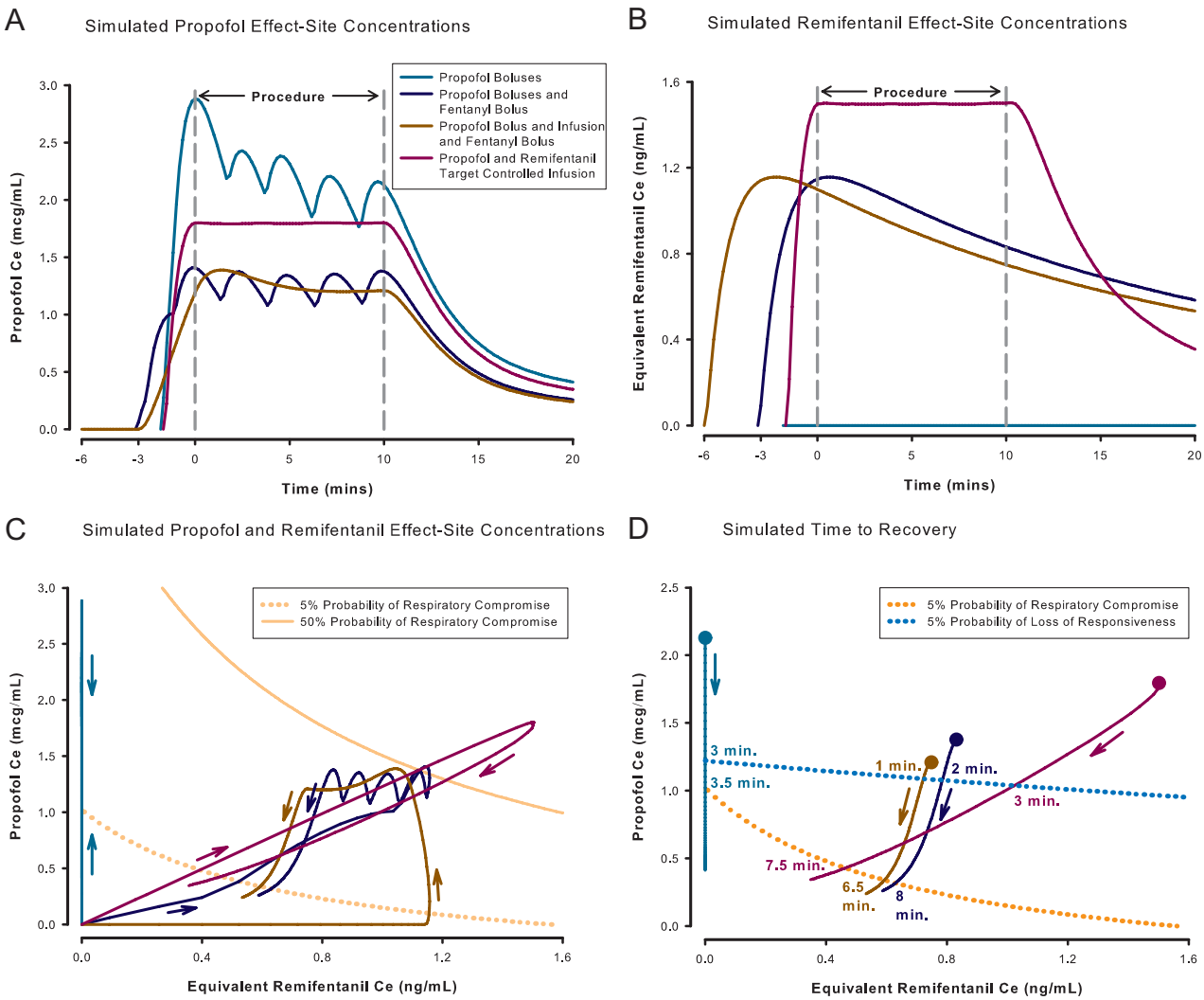

Fig. 2. Predicted propofol, fentanyl (in remifentanil equivalents), and remifentanil effect-site concentrations (C_es) for selected published dosing regimens for endoscopy (*A* and *B*). Time 0 corresponds to the peak propofol C_e for techniques 1 and 2, the start of the propofol infusion for technique 3, and achievement of the propofol target for technique 4. (*C*) A topographic 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. (*D*) Time to recovery using a topographic 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 C_es 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 less than 5%, and are placed next to the corresponding washout curve and isobole.

tolerable ventilatory depression primarily occurred at high remifentanil concentrations.

When interpreting these data, some limitations merit discussion. First, measures of loss of responsiveness, airway obstruction, and intolerable ventilatory depression were made in unstimulated volunteers. 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, with an endoscope in place, much of the partial or complete airway obstruction would likely resolve because the endoscope would stent the airway open.[12] Third, our measures of partial airway obstruction were rather simplistic. More sophisticated techniques exist.[28–34] It is possible that our criteria for partial airway obstruction 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 hypercapnia is not established; nevertheless, we believe that a respiratory rate ≤4 breaths/min or a 30-s average tidal volume less than 3 ml/kg would potentially lead to worrisome hypoxia and/or hypercapnia. Fifth, debilitated patients will likely require less propofol and remifentanil to achieve the same airway and respiratory effects.

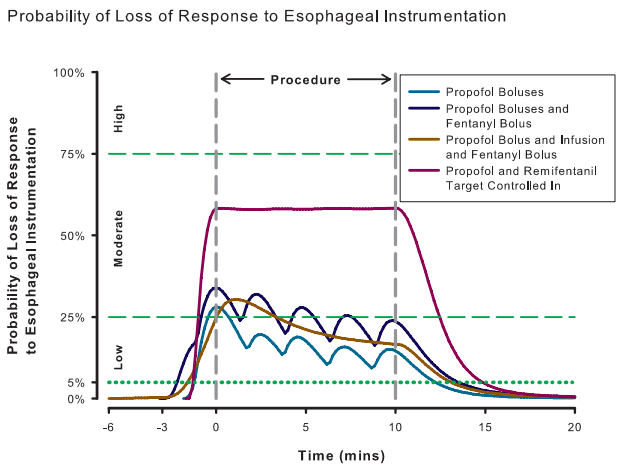

Fig. 3. Simulations of loss of response to esophageal instrumentation over time for selected published dosing regimens for upper endoscopy (*solid lines*). Simulations were designed to provide sedation and analgesia for a 10-min procedure (*gray vertical lines*). *Horizontal dashed lines* represent the 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 (less than 5%).

With our revised criteria for loss of response to esophageal instrumentation, volunteers were unresponsive in 135 of 367 assessments (previously 105).[13] For example, with propofol at 2.7 mcg/ml and remifentanil at 0.8 ng/ml, five volunteers tolerated esophageal instrumentation and three did not (previously four and four).

Similar to what other authors have reported, 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.[9,12] Hence, less drug may be required to keep patients analgesic and sedated during endoscopy once the scope is in place.

Response Surface Models

Graphic and statistical approaches indicated that models for respiratory compromise and loss of response to esophageal instrumentation fit observed data well. Figures 1C and D demonstrate that models captured the transition from no effect to effect well. This was confirmed by the chi-square analysis and percentage of model predictions that agreed with observed responses.

The respiratory compromise model had a propofol C_{50} of 4.3 mcg/ml compared with our previously reported 7.0 mcg/ml for intolerable ventilatory depression: this difference is a function of the additional airway obstruction data. In the region of low remifentanil C_es (*i.e.*, <1 ng/ml), as propofol C_es increase from 0, respiratory compromise is likely due to airway obstruction and can typically be resolved with a head tilt/chin lift and/or insertion of an oral airway. As propofol C_es approaches 7.0 mcg/ml, 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 compared with our previously reported 4.1 ng/ml 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/ml) and the mathematical limitations of the Greco model structure.[14,35] The Greco model is an adaptation of the model proposed by Berenbaum for two noninteracting drugs[36] and assumes each drug can be independently modeled using the Hill equation (sigmoid-Emax model).[14] This assumption imposes mathematical constraints that have been described by other authors as insufficiently flexible.[35,37] Specifically, the interaction (α) and slope (γ) 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 α and γ values from its neighbors. In addition, 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 to correct for these limitations.[35,37,38]

The revised loss of response to esophageal instrumentation model has propofol and remifentanil C_{50}s and γ (9.6, 4.1, and 2.7, respectively) similar to our previously reported model (9.8, 3.8, and 3.7, respectively) but the α term is larger in the revised model (revised 7.7 *vs.* 4.5). The larger α indicates a more significant drug synergy, meaning less of either drug is required to achieve the same effect. In graphic terms, the isoeffect lines (isoboles) have more bow toward the origin.

For both models, the γ 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. This uncertainty may be a function of both interindividual and intraindividual variability.

Simulations of Published Dosing Regimens for Endoscopy

The propofol-only technique recovered from both loss of responsiveness and 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 (fig. 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. 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 oversedate patients to compensate.[24]

Simulations of propofol-opioid techniques provided a moderate probability of loss of response to esophageal instru-

mentation. Once drug administration was terminated, the time to return of responsiveness was faster for some of these techniques than it was for propofol alone (fig. 2D). More time was required to recover from respiratory compromise with the propofol-opioid techniques (7–9 min), but most of this time would be with patients in a responsive state wherein they are likely to be capable of following prompts to breathe or open their airway.

By way of comparison, authors have published observations using propofol in combination with opioids for endoscopy and colonoscopy. In a trial where 496 patients received a fentanyl bolus followed by a computer-administered feedback-controlled propofol infusion, Pambianco *et al.*[26] found that more than 95% of patients experienced mild to moderate sedation during brief procedures (on average less than 4 min for upper gastrointestinal endoscopy and less than 14 min for colonoscopy) and a rapid recovery. There was a very low incidence of deeper than intended sedation and adverse respiratory events. Although these results are not directly comparable, simulations presented in figure 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). 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.[39,40] Thus, the simulations involving bolus drug administration are likely to be associated with more respiratory compromise than our models predict. Second, pharmacokinetic models are associated with substantial variability. For example, using target-controlled infusions, median absolute performance errors for propofol and remifentanil alone of 25%[41] and 22%[42], respectively, have been reported. The median performance error of propofol in the presence of remifentanil has been reported at 49%.[42] Third, some 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 different patient weights. Fourth, we chose dosing intervals based on a published regimen[43] but 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]

In summary, we used interaction models to make predictions of 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 had a moderate probability of conditions that allow esophageal instrumentation whereas propofol only techniques had a low probability. Once drug delivery was terminated, techniques that used a fentanyl bolus combined with propofol provided the highest likelihood of rapid return of responsiveness.

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Appendix. Target Effect-Site Concentrations and Respiratory and Esophageal Instrumentation Outcomes

Remifentanil Group								Propofol Group							
				Effect Measures								Effect Measures			
Set	n	Remi (ng/ml)	Prop (mcg/ml)	IVD	AO	RC	LREI (Revised)	Set	n	Remi (ng/ml)	Prop (mcg/ml)	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	—
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

N is the number of subjects assigned to each set based on the study design. Prop = propofol; Remi = remifentanil. Effect measures: AO = airway obstruction defined as a 30-s 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; IVD = intolerable ventilatory depression defined as a respiratory of ≤4 breaths/min, LREI = loss of response to esophageal instrumentation; RC = respiratory compromise defined as the presence of IVD and/or AO; 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.