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Prediction Variability of Combined Pharmacokinetic Pharmacodynamic Models: A Simulation Study of Propofol in Combination with Remifentanil and Fentanyl

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Abstract

Introduction: The aims of this study were to estimate model prediction variability for drug concentrations and effects during a simulated propofol-remifentanil-fentanyl anesthetic and identify the change in propofol infusion rates or fentanyl bolus doses necessary to detect changes in the duration of selected drug effects. We hypothesized that drug effect variability is large when drug concentrations are within the dynamic range of concentration effect curves (i.e. during emergence from anesthesia), but when drug concentrations are above or below the dynamic range variability is small.

Methods: 1000 parameter sets were randomly generated from published pharmacokinetic model parameters and their metrics of variability and published pharmacodynamic remifentanil-propofol interaction model parameters and their metrics of variability for loss of response to laryngoscopy, loss of responsiveness, analgesia, and intolerable ventilatory depression. 1000 simulated patients were administered 90-minute combined remifentanil (0.20 mcg/kg/min) and propofol (100 mcg/kg/min) infusions, and two fentanyl boluses at 0 and 75 minutes of 2 mcg/kg.

Results: The drug effect site concentration variability was larger for remifentanil than for propofol. The drug effect variability was minimal during the anesthetic but large during emergence. Moderate changes in infusion rates and bolus sizes caused minimal changes in the duration of drug effect following termination of the anesthetic.

Conclusion: Simulations in part confirmed our hypotheses; during the anesthetic, despite considerable concentration variability, drug effect variability is small at points of clinical interest. The combined low dose propofol and high dose remifentanil infusions provide a high probability of unresponsiveness and analgesia throughout the anesthetic. During emergence, however, drug effect variability is large and substantial dose changes are required to detect a difference in duration of selected effects.

Keywords: Pharmacokinetic; Pharmacodynamic; Model variability

Introduction

Pharmacokinetic (PK) models are commonly used to predict drug concentrations that drive target controlled infusions. To a lesser extent, PK and pharmacodynamic (PD) interaction models are used to provide predictions of drug concentrations and effect real time on clinical drug displays. Recent work has explored numerous anesthetic drug effects such as loss of response to laryngoscopy, loss of responsiveness, loss of response to painful stimuli, and presence of intolerable ventilatory depression for a variety of anesthetic drug combinations [1-12]. These population PK and PD models were built from observations in numerous patients or volunteers and most of them included estimates of variability about their model parameters, but the clinical implication of this variability is difficult to interpret. In general, when combining population based models to predict the time course of drug effect of individual patients, it is likely that there will be large prediction variability and to some degree be wrong [13].

The overall aim of this study was to characterize the combined pharmacokinetic and pharmacodynamic variability for a total intravenous anesthetic technique using propofol, remifentanil, and fentanyl. To our knowledge this has never been explored. Specifically, the primary study aims was, through simulation, to use published models and their associated metrics of variability to estimate prediction variability of drug concentrations and selected drug effects at time points of interest to an anesthesiologist. These time points include induction, surgical incision, emergence, and 30 minutes after surgery. We hypothesized (1) with typical dosing regimens, concentration variability would be large and (2) that when concentrations were within the dynamic range (slope) of concentration effect curves (i.e. during emergence from anesthesia) variability in predictions of drug effect would be large, but when drug concentrations are above or below the dynamic range (i.e. during induction of anesthesia, laryngoscopy and tracheal intubation, and the post-operative period), variability in predictions of drug effect would be small.

A second aim was to characterize the magnitude of dose changes (bolus, infusion rates, or both) necessary to detect differences in the duration of selected anesthetic effects following emergence from anesthesia. We hypothesized that within a range of clinically relevant doses, dosing intervals exist for propofol, remifentanil, and fentanyl that are distinguishable from one another.

Methods

Previously published PK and PD models and their associated

metrics of variability were used to estimate drug effect site concentrations for propofol, remifentanil, and fentanyl and various effects to include loss of responsiveness, loss of response to laryngoscopy, analgesia, and intolerable ventilatory depression.

PK and PD models

PK models of remifentanil [1-4], propofol [5,6], and fentanyl [7] used to simulate effect site concentrations are presented in Table 1. The propofol and remifentanil models included metrics of parameter variability, the coefficient of variation, which were previously estimated in NONMEM [1-6]. These metrics assumed a normal distribution about each model parameter. No metrics of parameter variability are available for fentanyl; for simulation purposes, parameter variability for this model was assumed to be similar to the variability remifentanil model parameters.

Remifentanil propofol interaction models used to simulate drug effects are presented in Table 2. Effects included models of loss of response to a moderately painful stimulus (30 PSI of anterior tibial pressure) [9,10], intolerable ventilatory depression (defined as a respiratory rate less than 4 breaths per minute) [11], loss of responsiveness [12], and loss of response to laryngoscopy with tracheal intubation [12]. The prediction of response to these effects per remifentanil and propofol effect site concentrations is represented with response surface models. No metrics of parameter variability are available for the model of loss of response to a moderately pain stimulus; for simulation purposes, parameter variability for this model was assumed to be similar to the variability of the loss of response to laryngoscopy model.

Simulating model and patient variability

One thousand model parameter sets were randomly sampled from the distribution of original 7 pharmacokinetic parameters (Table 1) and 4 interaction model parameters (Table 2). For each new model parameter set, a set of unique demographic data (height, weight, and age) were randomly sampled from values that typify an average adult are presented in Table 3 [14].

Simulated dosing scheme

A simulated general anesthetic was applied to the 1000 model parameter sets described above. It consisted of induction with a fentanyl bolus 2 mcg/kg followed three minutes later by a propofol bolus 2 mg/kg. After induction, propofol and remifentanil infusions were initiated at 100 mcg/kg/min and 0.2 mcg/kg/min respectively for 90 minutes. At 75 minutes (15 minutes before the end of surgery) a second 2 mcg/kg fentanyl bolus was administered. The propofol and remifentanil infusions were terminated at 90 minutes.

Prediction Variability Analysis

Two evaluations of variability were made at four clinical time points of interest; laryngoscopy and tracheal intubation, surgical incision, emergence from anesthesia, and 30 minutes after surgery. They included estimates of effect site concentration variability and drug effect variability.

Effect site concentration variability

Effect site concentrations were estimated and plotted over time for each drug (fentanyl, remifentanil, and propofol). At each clinical time point of interest, the concentration kinetic variability was reported as a mean and standard deviation. Concentration variability was also reported as a distribution of propofol remifentanil concentration pairs. To include fentanyl, it was converted into remifentanil equivalents. The range of concentration variability for all drugs combined was presented

PK Parameters	Propofol [5,6]		Remifentanil [1-4]		Fentanyl [7]			
	Estimate	CV (%)	Estimate	CV (%)	Estimate	CV (%)	Estimate	
V1 (L)	4.27	4.04	5.1-0.0201*(A-40)+.072*(lbm-55)	26	0.105*M			
V2 (L)	18.9 -.391*(A-53)	0.9	9.82-.0811*(A-40)+.108*(lbm-55)	29	0.446*M			
V3 (L)	238	14.35	5.42	66	3.37*M			
CL1 (L/min)	1.89 ʻ +.0456*(M-77) -.0681*(lbm-59) +.0264*(H-177)	10.05	2.6-.0162*(A-40)+.0191*(lbm-55)	14	0.00838*M			
CL2 (L/min)	1.29-.024*(A-53)	0.9	2.05-.0301*(A-40)	36	0.0474*M			
CL3 (L/min)	.836	11.79	.076-.00113*(A-40)	41	0.0199*M			
Ke0 (min⁻¹)	.456	42	.595-.007*(A-40)	68	0.15			

V is the compartment volume in liters; CL is the clearance from that volume in liters per minute. M is the mass of the patient in kg, H is the height of the patient in cm, A is the age of the patient in years, and lbm is the lean body mass. CV is the coefficient of variation for the parameter estimate. Ke0 is the elimination rate constant from the effect site to outside the body. * indicates multiplication.

Table 1: Pharmacokinetic parameters and estimates of parameter variability for propofol, remifentanil, and fentanyl.

Stimulus	C_{50P}	CV (%)	C_{50R}	CV (%)	α	CV (%)	γ	CV (%)
Probability of unconsciousness or sedation [12] (no response to OAA/S<2)	2.16	19	19.0	9	2.13	16	7.94	33
Probability of adequate surgical analgesia [12] (no response to tracheal intubation, laryngoscopy)	5.63	22	19.0	9	2.13	16	7.94	33
Probability of adequate post-operative analgesia [9,10] (no response to pressure algometry)	4.16	-	8.84	-	8.2	-	8.34	-
Probability of intolerable ventilatory depression [11] (respiratory rate <=4 breaths/minute)	7.0	26	4.1	24	3.0	38	3.2	25

C50P and C50R are effect site concentrations to produce a 50% probability of effect for propofol and remifentanil respectively. Alpha is the synergistic value for characterizing the interaction between remifentanil and propofol. Gamma is the slope of the response surface characterizing the dynamic range. CV indicates the coefficient of variation. OAA/S < 2 is the observers assessment of alertness score when a patient will respond to shaking and shouting, indicative of a patient's responsiveness. Pressure algometry is defined as 50 PSI of tibial pressure, CV for pressure algometry was not available. They were assumed to be similar to the CV for tracheal intubation.

Table 2: Pharmacodynamic interaction model parameters for propofol and remifentanil with estimates of parameter variability for selected drug effects

	Male	Female
Height	176 9 cm	162 6 cm
Weight	80 10 kg	70 10 kg
Age	40 10 years	40 10 years

Data are presented as mean and standard deviation. Gender distribution was assumed to be 50%/50% for male/female. The distribution of the simulated patient's demographics for height, weight, and age followed a normal distribution [14].

Table 3: Simulated patient population demographics.

as a distribution of propofol-remifentanil concentration pairs at each clinical time point of interest. The distribution of pairs are presented as a set of concentric elliptical lines that describe 68%, 95%, 99%, and 100% of the concentration pairs.

The rationale for presenting propofol-remifentanil concentration pairs in this format (concentric ellipses) was to superimpose them over interaction model iso-effect lines, known as isoboles for each drug effect. The isoboles represent the concentration pairs that produce the same probability of effect.

Drug effect variability

Drug effect variability was estimated and plotted over time for loss of responsiveness, loss of response to laryngoscopy, pain (loss of response to tibial pressure), and intolerable ventilatory depression. Drug effect variability at selected clinical points of interest were presented as a 3-dimensional ellipsoid superimposed over a 3-dimensional rendering of each drug effect, known as a response surface model; where the x and y axes represented remifentanil and propofol effect site concentrations and the z axis represented the probability of drug effect.

Predictions of a response to laryngoscopy and tracheal intubation and predictions of responsiveness (awake versus asleep) were obtained 2 minutes after the propofol bolus. Predictions of a response to a painful stimulus as a surrogate of skin incision and predictions of responsiveness were made 15 minutes after the start of the anesthetic. Predictions of responsiveness and a response to a painful stimulus were made 5 minutes after the anesthetic was terminated to assess drug effects during emergence from anesthesia. As a surrogate of respiratory depression and analgesia following surgery, predictions of intolerable ventilatory depression, response to a painful stimulus, and responsiveness were made 30 minutes after the anesthetic was terminated.

Dose distinguishability at emergence

To explore the change in effect during emergence for various doses, simulations were performed over a range of infusion rates and bolus doses for propofol, remifentanil, and fentanyl respectively. Propofol infusions included 80, 100, and 120 mcg/kg/min; and fentanyl boluses included 1, 2, and 3 mcg/kg. The remifentanil infusion was set to 0.10 or 0.20 mcg/kg/min. An additional set of simulations were performed where the propofol infusion rate was decreased from 100 to 50 mcg/kg/min 15 minutes prior to the end of the 90 minute anesthetic. At each dose increment, 1000 simulations were conducted. Patient demographics (height, weight, age, gender) were randomly selected from Table 3 [14].

Dose distinguishability was defined as a detectable difference in the duration of effect following termination of the 90-minute anesthetic. The duration of effect was defined as the time from termination of the anesthetic to a 50% probability of effect for loss of responsiveness, analgesia, and intolerable ventilatory depression.

To determine the difference between dosing schemes for the loss of responsiveness and intolerable ventilatory depression we looked for schemes which had at least a 3 minute difference. While to determine a difference in the analgesic effect we looked for dosing schemes that had at least a 5 minute difference.

Results

Effect site concentration variability

Kinetic prediction variability over time is presented in Table 4 and Figure 1. Drug concentration variability is largest at maximal concentrations. The 95% confidence interval for remifentanil effect concentration at 90 minutes was 3 times greater than that of propofol. The variability of remifentanil (and remifentanil equivalents for fentanyl) versus propofol effect site concentrations at induction and emergence are shown in Figure 2 overlaid on pharmacodynamic return of responsiveness isoboles. During induction, although there is substantial kinetic variability, most of the concentration pairs are above the 95% isobole suggesting that despite the kinetic variability, the drug effect will be similar. During emergence, the kinetic variability spans all isoboles suggesting that there will be considerable variability in the time required to emerge from this anesthetic.
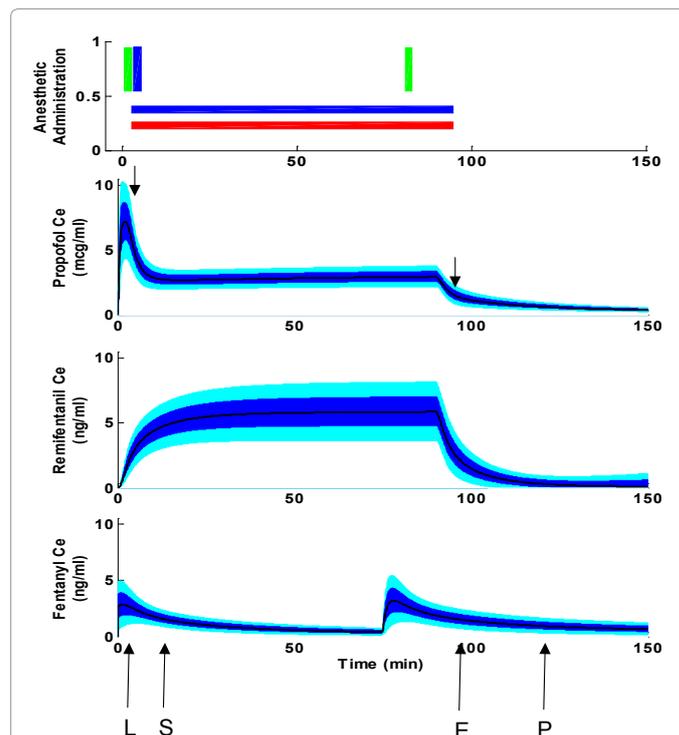
Figure 1: Effect site concentration versus time illustrating the PK variability following a bolus and/or infusion administrations of propofol, remifentanil, and fentanyl. The top figure shows a visualization of the anesthetic administrations; the vertical green bars indicate fentanyl bolus administrations, the horizontal red bar indicates the length of the remifentanil infusion administration, the vertical blue bar indicates the time of the propofol bolus administration, and the horizontal blue bar indicates the length of the propofol infusion administration. The bottom three figures illustrate the distribution of the effect site concentration predictions the black line shows the PK prediction, the dark blue shows the middle 68% predictions, and the light blue shows the variance of 95% of the predictions. The left arrow indicates the peak induction pharmacodynamic effect and the right arrow indicates the 50% probability of emergence. The four clinical time points of interest are indicated by the black arrows on the bottom figure at the time point of laryngoscopy (L), skin incision (S), emergence (E), and time to enter PACU (P).

Figure 2: Topographical view of propofol-remifentanil kinetic model variability superimposed on model predictions of loss of responsiveness at induction (left) and emergence (right). The blue lines present the distribution of prediction variability; the percentage of concentrations from the largest to the smallest are 100%, 99%, 95%, and 68%. The black lines represent the 5, 50, and 95% isoboles for the pharmacodynamic response surface model for loss of responsiveness.
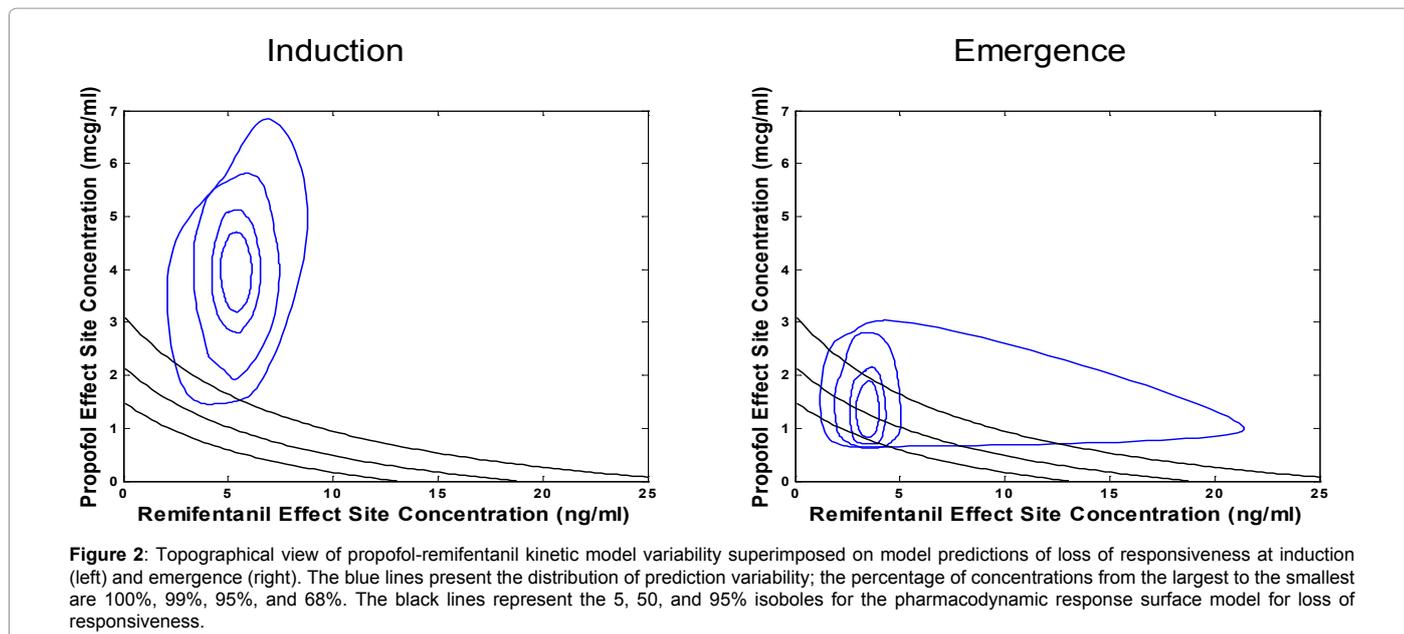
Clinical Interest	Time Indicator	Propofol (mcg/ml)	Remifentnail (ng/ml)	Fentanyl (ng/ml)
Laryngoscopy	L	7.2 (1.5)	1.1 (0.4)	2.8 (0.9)
Skin Incision	S	2.7 (0.4)	5.3 (1.0)	1.2 (0.3)
Emergence	E	1.6 (0.4)	2.8 (0.9)	1.9 (0.7)
PACU	P	0.6 (0.1)	0.3 (0.3)	1.0 (0.4)

The drug effect site concentration mean (standard deviation) at clinical points of interest for simulated dosing scheme as described in the methods. The clinical points of interest are the times for induction, skin incision, re-emergence, and post-anesthesia care unit (PACU) arrival. The time indicators for each of the clinical interest points are shown in figure 1.

Table 4: Mean and (standard deviation) of the drug effect site concentration at clinical time points of interest for selected response surface models as presented in Figure 1.

Clinical Interest	Time Indicator	Laryn	Resp	Pain	IVD
Laryngoscopy	L	0.99 [0.70-1.0]	1.0 [0.98-1.0]	1.0 [1.0-1.0]	
Skin Incision	S		0.99 [0.93-1.0]	1.0 [1.0-1.0]	
Emergence	E		0.87 [0.25-1]	0.99 [0.91-1.0]	
PACU	P		0 [0-0.08]	0.001 [0-0.14]	0.10 [0.01-0.43]

The pharmacodynamic response probability intervals of the variability at clinical points of interest are the median and inter-quartile ranges for the response to laryngoscopy (Laryn), return of responsiveness (Resp), response to moderate pain (Pain), and intolerable ventilatory depression (IVD). The clinical points of interest are the times for induction, skin incision, re-emergence, and post-anesthesia care unit (PACU) arrival. The clinical time points in terms of minutes from the beginning of the 90 minute anesthetic simulation are 2, 15, 95, and 120 respectively. The time indicators for each of the clinical points of interest are shown in figure 3. Only the stimuli for relevant points of interest are shown in the table.

Table 5: Median and inter-quartile ranges (in brackets) of the probability of drug effects at clinical time points of interest for selected response surface models as presented in Figure 3.

Drug effect variability

Combined PK/PD variability over time for loss of response to laryngoscopy and tracheal intubation, loss of responsiveness, loss of response to moderate pain, and intolerable ventilatory depression are

presented in Figure 3. Median and inter-quartile ranges of prediction variability at clinical points of interest are presented in Table 5. Combined PK/PD variability at induction and emergence as a function of propofol concentrations, remifentanil equivalent concentrations, and loss of responsiveness are presented as ellipsoids at induction and emergence in Figure 4.

Following induction, 84% of the simulations had a greater than 95% probability of no response to laryngoscopy and tracheal intubation and 99% of the simulations had a greater than 95% probability of unresponsiveness.

At skin incision, 82% of the simulations had a greater than 95% probability of unresponsiveness and 99% had a greater than 95% probability of no response to a painful stimulus.

5 minutes after termination of the propofol and remifentanil infusions, 33% of the simulations had a greater than 95% probability of unresponsiveness, 92% had a greater than 95% probability of loss of response to a painful stimulus, and 34% had a greater than 95% probability of intolerable ventilatory depression.

Thirty minutes after anesthetics <1% of simulations had greater than 95% probability unresponsiveness, analgesia, and intolerable ventilatory depression.

Animated presentations of drug effect variability over time for each effect measure on a response surface plot are available online at https://www.dropbox.com/sh/lrzosr7qt6norj9/rCQ2WQL7ys#/

Dose distinguishability at emergence

The average time to a 50% probability of return of responsiveness for each of the nine dosing schemes is presented in Table 6. Similar tables present times to loss of analgesia and intolerable ventilatory depression (Tables 7 and 8).

Differences in the duration of return of responsiveness of at least 3 minutes were only predicted when both the fentanyl bolus and the propofol infusion were increased by 1 mcg/kg and 20 mcg/kg/min respectively or the propofol infusion was increased by 40 mcg/kg/min (Table 6).
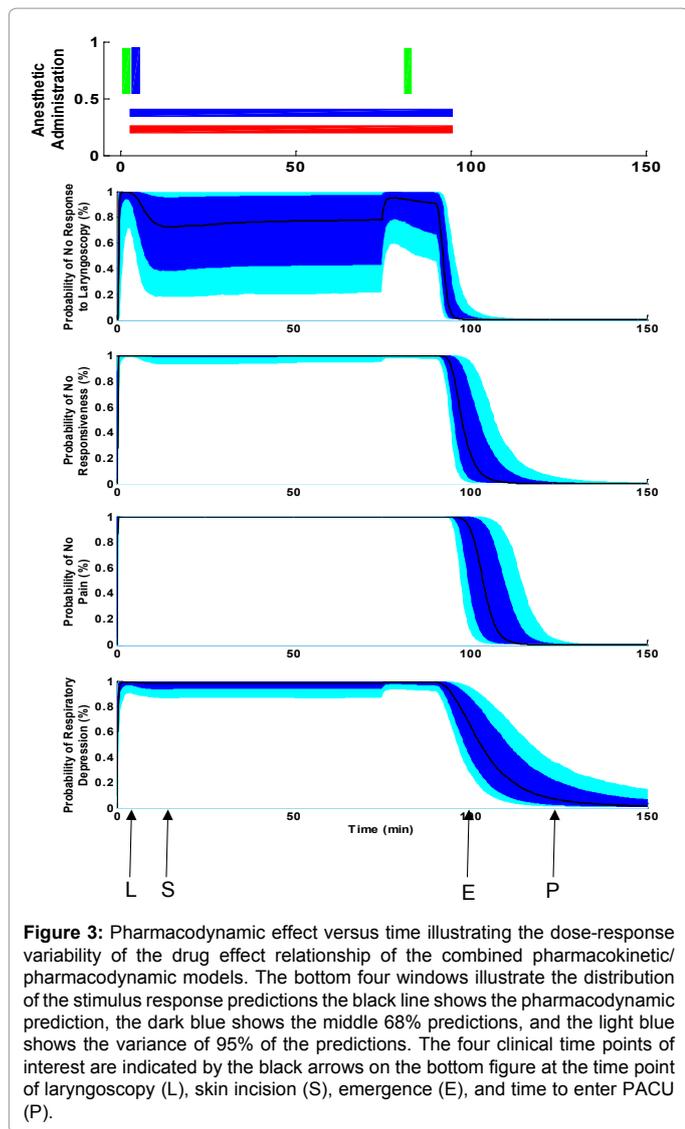
Figure 3: Pharmacodynamic effect versus time illustrating the dose-response variability of the drug effect relationship of the combined pharmacokinetic/ pharmacodynamic models. The bottom four windows illustrate the distribution of the stimulus response predictions the black line shows the pharmacodynamic prediction, the dark blue shows the middle 68% predictions, and the light blue shows the variance of 95% of the predictions. The four clinical time points of interest are indicated by the black arrows on the bottom figure at the time point of laryngoscopy (L), skin incision (S), emergence (E), and time to enter PACU (P).

		Propofol (mcg/kg/min)		
		80	100	120
Fentanyl (mcg/kg)	1	6 (3)	7 (4)	9 (5)
	2	6 (4)	8 (5)	10 (5)
	3	7 (4)	9 (5)	11 (6)

Data are presented as the mean (standard deviation) time (in minutes) from termination of the propofol and remifentanil infusions to 50% return of responsiveness for each dosing scheme. The remifentanil infusion was held constant at 0.2 mcg/kg/min. A difference of 3 minutes was considered to be of clinical significance.

Table 6: Duration of return of responsiveness following termination of the anesthetic.

		Propofol (mcg/kg/min)		
		80	100	120
Fentanyl (mcg/kg)	1	14 (5)	16 (6)	18 (6)
	2	17 (6)	19 (7)	22 (7)
	3	20 (7)	22 (8)	25 (9)

Data are presented as the mean (standard deviation) time (in minutes) from termination of the propofol and remifentanil infusions to 50% loss of analgesia for each dosing scheme. The remifentanil infusion was held constant at 0.2 mcg/kg/min. A difference of 5 minutes was considered to be of clinical significance.

Table 7: Duration of analgesia following termination of the anesthetic.

		Propofol (mcg/kg/min)		
		80	100	120
Fentanyl (mcg/kg)	1	10 (4)	11 (4)	12 (4)
	2	12 (5)	13 (5)	15 (5)
	3	15 (6)	16 (6)	17 (7)

Data are presented as the mean (standard deviation) time (in minutes) from termination of the propofol and remifentanil infusions to 50% intolerable ventilator depression (IVD) for each dosing scheme. The remifentanil infusion was held constant at 0.2 mcg/kg/min. A difference of 3 minutes was considered to be of clinical significance.

Table 8: Duration of intolerable ventilator depression (IVD) following termination of the anesthetic.

Differences in the duration of analgesia of at least 5 minutes were predicted when either the fentanyl bolus was changed by 1 mcg/kg or the propofol infusion was changed by 20 mcg/kg/min (Table 7).

Differences in the duration of intolerable ventilatory depression of at least 3 minutes were predicted when the fentanyl bolus and the propofol infusion were changed by 1 mcg/kg and 20 mcg/kg/min respectively or the fentanyl bolus was increased by 1 mcg/kg when the propofol infusion is greater than 100 mcg/kg/min.

The average changes in the return of responsiveness, duration of analgesia, and duration of intolerable ventilatory depression were 1-2 minutes when comparing the remifentanil infusion rate of 0.20 to the rate of 0.10 mcg/kg/min (data not shown).

When the propofol infusion was decreased by 50 mcg/kg/min 15 minutes before the end of infusions the return of responsiveness was 2 minutes shorter than if the propofol infusion was held constant (data not shown).

Discussion

We explored the estimated variability of kinetic and dynamic model predictions of selected anesthetic drug concentrations and drug effects. We hypothesized that concentration variability would be large, but that this variability would not be translated to a wide variability in drug effect except under conditions when the concentration variability was within the dynamic range (slope) of response surface models. We also hypothesized that within a range of clinically relevant doses, dosing intervals exist for propofol, remifentanil, and fentanyl that are distinguishable from one another. Our hypotheses were in part confirmed.

Despite considerable concentration variability at the clinical points of interest (induction, skin incision, emergence, 30 minutes after emergence), the drug effect variability was actually quite small except during emergence (Figure 4). An example of this is shown in variability at skin incision in Figures 1 and 3. Figure 1 shows the large concentration variability at skin incision that correspondence with small effect variability as seen in Figure 3. Although variable, most drug concentrations were associated with high (>95%) probabilities of drug effect.

Prior work in our laboratory has reported observed emergence times in 21 patients receiving a total intravenous anesthetic using propofol, remifentanil and fentanyl [9]. Using a similar dosing and somewhat longer anesthetic the emergence times were consistent with our predictions presented in Table 6 using a similar dosing regimens.

We explored the impact of large dose changes in individual drugs and found that by themselves did not change the duration of analgesia,

Figure 4: Pharmacokinetic and pharmacodynamic variability for loss of responsiveness at induction (left) and during emergence (right). For orientation the 5, 50, and 95 % isoboles of the response surface model are shown in black. The response variability of 1000 simulations on the response surface model is represented as a red cloud with cloud shading indicative of the distribution of variability. The shells of distribution calculated were 100%, 99%, 95%, and 68% of the total variability. A front view and a side profile view of the response surface model are shown for each.

unresponsiveness, or intolerable ventilatory depression. Only when the dosing changes were combined, did the duration of predicted drug effects reach a 3 minutes difference for loss of responsiveness and a 5 minutes difference for loss of response to a painful stimulus. This illustrates the synergistic pharmacodynamic interaction between propofol and opioids. By contrast singular changes in remifentanil infusion rates had no impact on the duration of drug effects once the anesthetic was terminated consistent with its rapid elimination.

Limitations

There are several limitations and assumptions used to complete this analysis. Major limitations include: (1) Models were based on observations in healthy volunteers and used to predict drug effects in patients. These models are likely mis-specified due to the influence of patient comorbidities, body habitus, age, chronic opioid consumption, among others on kinetic and dynamic behavior. (2) Multiple models from different laboratories were used to make predictions for a single individual. The ideal approach is to use kinetic and dynamic models built from a single data source and not mix models built from different sources and ensure that the predictions of drug concentrations and effects were within the range of the measured data used to build the models. (3) Pharmacodynamic models that predict sedation and unresponsiveness are built from data collected in otherwise un-stimulated volunteers or patients. During surgery, stimuli are present that likely shift the dose-effect relationship to the right for models of unresponsiveness. Thus prediction probabilities may have a high bias, although the magnitude of the bias as not been fully explored.

Authors have expressed a concern with dose distinguishing analyses in that there are countless possible dosing schemes [15]. In our analysis, we confined our analysis to three drugsandr four anesthetic effects. Our sample dosing schemes may not have adequately explored a range of doses, concentrations, and effects to properly characterize drug effect variability.

Clinical Significance

The study represents a preliminary characterization of the time course and magnitude of variability in drug effect predictions for a total intravenous anesthetic. This prediction variability may be of interest to clinicians who use point of care drug displays real time as an advisory when administering an anesthetic. Our study suggests that prediction variability is highest during emergence from anesthesia and this may in part explain the previously reported observed variability in the time to emergence [9]. Additional work is warranted to explore prediction variability as a function of time (short versus long anesthetics) and in other anesthetic techniques such as combined potent inhaled agent-opioids techniques.

A common practice is to decrease the propofol infusion before the end of a procedure to expedite emergence. In our simulations, a substantial decrease in the propofol infusion rate (from 100 to 50 mcg/kg/min) 15 minutes prior to terminating the infusions had some impact on the duration of effect. It decreased the average duration of unresponsiveness by 2 minutes at the cost of slightly reducing the probability of no response from 99% to 97%. Given that both drugs dissipate so quickly, our simulations suggest that there is not a substantial benefit when titrating down propofol infusion rates prior to emergence for procedures of relatively short duration (60 to 90 minutes).

Using this low propofol-high remifentanil dosing regimen, our simulations suggest that the high probability of unresponsiveness and analgesia during the anesthetic is adequate for most patients. A potential concern is the possibility of inadequate sedation and hypnosis. Despite the lower propofol infusion rate, the probability of unresponsiveness in the presence of remifentanil remained very high suggesting this concern is not warranted.

Conclusions

In this simulation analysis of a total intravenous anesthetic, despite considerable concentration variability, drug effect variability is small at points of clinical interest. The combined low dose propofol and high dose remifentanil infusions provide a high probability of unresponsiveness and analgesia throughout the anesthetic. During emergence, however, drug effect variability is large and substantial dose changes are required to detect a difference in duration of selected effects.

Acknowledgement

References

1. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, et al. (1997) Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 86: 10-23.

2. Minto CF, Schnider TW, Shafer SL (1997) Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. Anesthesiology 86: 24-33.

3. Egan TD (1995) Remifentanil pharmacokinetics and pharmacodynamics. A preliminary appraisal. Clin Pharmacokinet 29: 80-94.

4. Egan TD, Lemmens HJ, Fiset P, Hermann DJ, Muir KT, et al. (1993) The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. Anesthesiology 79: 881-892.

5. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, et al. (1998) The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology 88: 1170-1182.

6. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, et al. (1999) The influence of age on propofol pharmacodynamics. Anesthesiology 90: 1502-1516.

7. Shafer SL, Varvel JR, Aziz N, Scott JC (1990) Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. Anesthesiology 73: 1091-1102.

8. Greco WR, Bravo G, Parsons JC (1995) The search for synergy: a critical review from a response surface perspective. Pharmacol Rev 47: 331-385.

9. Johnson KB, Syroid ND, Gupta DK, Manyam SC, Egan TD, et al. (2008) An evaluation of remifentanil propofol response surfaces for loss of responsiveness, loss of response to surrogates of painful stimuli and laryngoscopy in patients undergoing elective surgery. Anesth Analg 106: 471-479, table of contents.

10. Kern SE, Xie G, White JL, Egan TD (2004) A response surface analysis of propofol-remifentanil pharmacodynamic interaction in volunteers. Anesthesiology 100: 1373-1381.

11. LaPierre CD, Johnson KB, Randall BR, White JL, Egan TD (2011) An exploration of remifentanil-propofol combinations that lead to a loss of response to esophageal instrumentation, a loss of responsiveness, and/or onset of intolerable ventilatory depression. Anesth Analg 113: 490-499.

12. Bouillon TW1, Bruhn J, Radulescu L, Andresen C, Shafer TJ, et al. (2004) Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. Anesthesiology 100: 1353-1372.

13. Shafer SL (2012) All models are wrong. Anesthesiology 116: 240-241.

14. http://www.cdc.gov/nchs/data/nhsr/nhsr010.pdf

15. Zanderigo E, Sartori V, Sveticic G, Bouillon T, Schumacher P, et al. (2006) The well-being model: a new drug interaction model for positive and negative effects. Anesthesiology 104: 742-753.