PREDICTION VARIABILITY OF COMBINED PHARMACOKINETIC PHARMACODYNAMIC MODELS: A SIMULATION STUDY OF PROPOFOL IN COMBINATION WITH REMIFENTANIL AND FENTANYL

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Introduction: Pharmacokinetic (PK) and pharmacodynamic (PD) models are commonly used to predict intravenous drug concentrations and effect. The variability of these predictions is often not well characterized. The aim of this study was to estimate model prediction variability for both drug concentrations and drug effects at clinical points of interest during a simulated anesthetic. A secondary aim was to explore the magnitude of changes in dose necessary to distinguish a difference in predicted responses.

Methods: One thousand PK/PD parameter sets were randomly generated from published PK and PD models for propofol, remifentanil, and fentanyl and their respective reported model parameter distributions. 1000 simulated patients were generated from demographic height weight age norms. A simulated total intravenous anesthetic was applied to each of the 1000 patients using one of the 1000 model parameter sets. Predictions of four drug effects were made for the duration of the anesthetic: loss of response to laryngoscopy, loss of responsiveness, loss of response to a painful stimulus, and presence of intolerable ventilatory depression (a respiratory rate less than 4 breaths per minute). Three sensitivity evaluations were made at four clinical time points of interest; laryngoscopy (L) and tracheal intubation, surgical incision (S), emergence from anesthesia (E), and 30 minutes after surgery (P). The three evaluations included estimates of combined PK/PD model variability (i.e. for a given dose, the range of model predictions), prediction consistency, and dose distinguishability. Predictions of drug effects using published model parameters were considered the standard estimate for a given effect. Those that were within 25% of the standard estimate were considered to be consistent. Distinguishability was defined as a difference in the duration of drug effect following termination of the anesthetic as a function of dose and measured for the time to emergence, duration of analgesia effect, and duration of intolerable ventilatory depression. Time intervals were defined as the time from termination of the anesthetic until the mean of model predictions were below 50%. A difference in 5 minutes in the duration was considered to be of clinical significance.

Results: Prediction variability for each drug effect over time is presented in the Figure and Table 1. Animated presentations of drug effect variability over time are available at https://www.dropbox.com/sh/lrzosr7qt6norj9/rCQ2WQL7ys#/. Prediction consistencies were within 25% of standard estimates at induction and during the anesthetic, but dipped during emergence and then returned high 20-30 minutes after the anesthetic was terminated. The dose changes required to illicit a 5-minute difference in the duration of intolerable ventilatory depression, analgesia, and responsiveness are presented in Table 2.

Discussion: Considerable prediction variability and low consistency were observed during emergence, but at the other clinical points of interest, there was small prediction variability and high consistency. The dose change required to detect a difference in drug effects was large for remifentanil, moderate for fentanyl and propofol. These results suggest that predictions of drug effect are most variable during emergence and moderate to large dose changes are required to achieve a detectable difference in drug effect 5 minutes after terminating the anesthetic.

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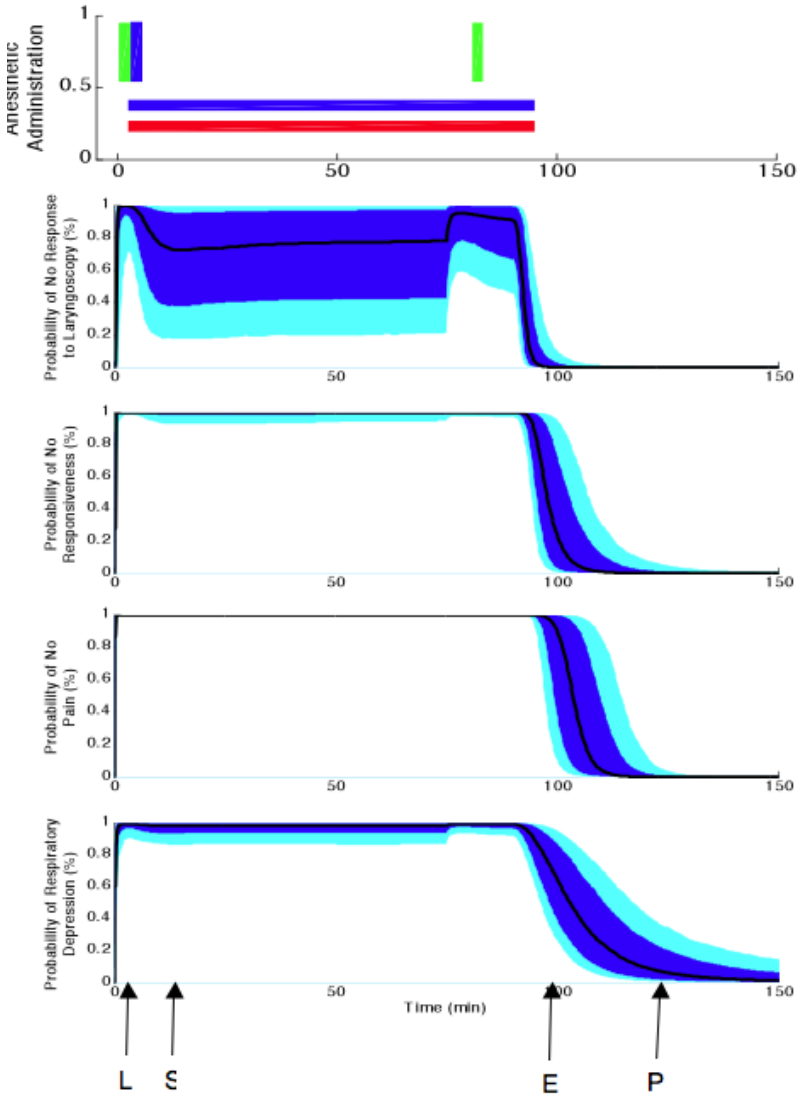

Figure 1. Pharmacodynamic effects at time points of interest: L = laryngoscopy, S = skin incision, E = emergence, and P = Post Anesthesia Care Unit. The top panel presents the dosing scheme. Induction included fentanyl 2 mcg/kg (green) followed three minutes later by propofol 2 mg/kg (blue). For maintenance, propofol and remifentanil (red) infusions were set 100 and 0.2 mcg/kg/min respectively for 90 minutes; at 75 minutes (15 minutes before the end of surgery) a 2 mcg/kg fentanyl bolus (green) of was administered. The propofol and remifentanil infusions were terminated at 90 minutes. The bottom four windows present the prediction variability over time. The black line shows the standard estimate, the dark blue shows the range of 68% of model predictions, and the light blue shows the range of 95% of model predictions.

Table 1. Median and inter-quartile ranges (in brackets) of the probability of responses at time points of interest.

Laryn = Loss of response to laryngoscopy, Resp = Loss of responsiveness, Pain = loss of response to moderate pain, and IVD = presence of intolerable ventilatory depression (respiratory rate < 4 breaths/minute). L = Laryngoscopy, S = Skin incision, E = Emergence, and P = Post-anesthesia care unit (30 minutes following termination of the anesthetic).

Clinical Interest	Time Indicator	Laryn	Resp	Pain	IVD
Laryngoscopy	L	0.99 [0.96 – 1.0]	1.0 [0.99-1.0]		
Skin Incision	S		0.99 [0.99-1.0]	1.0 [1.0-1.0]	
Emergence	E		0.86 [0.61-0.97]	0.99 [0.99-1.0]	
PACU	P			0.001 [0-0.005]	0.07 [0.03-0.16]

Table 2. Dose Distinguishability at Emergence IVD = intolerable ventilatory depression (respiratory rate < 4 breaths/minute).

Anesthetic	Dose Range	Median Dose to		
		Change Emergence by 5 minutes	Change Analgesia by 5 minutes	Change IVD by 5 minutes
Fentanyl (mcg/kg)	0 - 10	6	2	2
Remifentanil (mcg/kg/min)	0.05 - 0.50	0.40	0.30	0.20
Propofol (mcg/kg/min)	50 – 250	50	50	95