Minimizing Emergence Time While Providing Adequate Post-Operative Analgesia

Carl Tams BS, Noah Syroid MS, Ken Johnson MD,

Talmage Egan MD, Dwayne Westenskow PhD

Abstract

Intro - Differences in anesthetic technique when using propofol, remifentanil and fentanyl can result in different emergence and nociception outcomes. After surgery, a brief emergence period combined with an extended duration of analgesia is desired. We propose to use pharmacokinetic $(PK)_{1-4}$ and pharmacodynamic $(PD)_{5,6}$ models to find optimized ratios of propofol and remifentanil to shorten emergence time and extend the time until inadequate analgesia is experienced during patient recovery. Modeling has been used to find the optimum effect site concentrations (C_es) for rapid wake up[7]; however, an optimization technique which also accounts for analgesic effect is desirable. **Method** - Anesthesiologists gave general anesthesia to 21 patients for laproscopic procedures using propofol, remifentanil, and fentanyl using a standard of care anesthetic technique. Baseline model predictions for C_es were calculated for remifentanil, fentanyl, and propofol. PD response surface models were used to calculate the probabilities of unconsciousness and response to noxious stimulus (30 PSI tibial pressure algometry, a surrogate of postoperative pain) during and after the anesthetic. Post-hoc optimized PK and PD model predictions were made for both sedation and analgesia by varying the ratio of propofol and remifentanil C_es, constrained to the same or higher PD model predicted probabilities, and leaving fentanyl C_es unchanged from baseline. For each patient, optimized changes to the recorded propofol and remifentanil infusions were made every 5 minutes during the general anesthetic. The theoretical improvement provided by the optimization was measured by comparing the time differences between the baseline model predictions and the optimized prediction of the emergence time and time to inadequate analgesia. **Results** - The baseline model predictions found an average emergence time of 8.2 ± 5.6 minutes after end of surgery and a duration of analgesia of 9.9 ± 13.6 minutes after patient emergence. The optimized remifentanil and propofol C_es theoretically reduced the emergence time to 3.9 ± 1.6 ($p < 0.01$, t-test) minutes and increased the duration of adequate analgesia to 15.4 ± 12.5 ($p < 0.05$, t-test) minutes. **Discussion** - Optimized ratios of propofol and remifentanil resulted in a theoretically shorter emergence time and a longer period of adequate postoperative analgesia. These results require clinical verification in a new study, but the optimization algorithm shows potential for real-time clinical guidance in drug management.

Introduction

Population models predict the pharmacodynamic and pharmacokinetic effects and interactions between propofol and remifentanil. [1−6] Pharmacokinetic approximations of drug bio-distribution are used to translate anesthetic drug administrations to pharmacodynamic estimations of expected responses to noxious stimuli. Assuming these approximations and estimations correctly depict the patient's state of anesthesia, we hypothesize to decrease the expected emergence time (return of consciouness, ROC) and extend the period of adequate analgesia (return of nociception, RON).

Vuyk et al. found concentration ratios for Propofol with either Remifentanil, Fentanyl, Alfentanyl, or Sufentanil to decrease ROC. [7] Virtual simulations were performed on virtual patients using pharmacodynamic and pharmacokinetic models. Four different infusion durations were run at two different pharmacodynamic levels. The optimal concentrations were dependent on the infusion length and pharmacodynamic level.[7]

The algorithm is to be tested with post-hoc simulations but will be validated and used clinically in future studies and therefore needs to be robust for varying surgery lengths and levels.

Methods

Anesthetically relevant data was recorded from 21 surgeries. Pharmacokinetic and pharmacodynamic models were applied to each of the anesthestic administrations. An optimization algorithm was theoretically run post-hoc with the same pharmacodynamic levels but with different remifentanil effect site concentrations (R_es) and propofol effect site concentrations (P_es). The ROC and RON times will be the comparison metric for the simulated times from in vivo administrations and the simulated times from the administrations of the optimization algorithm.

Surgical Procedure

Anesthesiologists gave general anesthesia to 21 patients for laproscopic procedures administering propofol, remifentanil, and fentanyl via TIVA and a standard of care anesthetic technique. Midazolam and rocuronium were also administered to each of the patients. A study investigator was present for each of the cases to record; the surgical events, the anesthetic events, the administered drug doses, the return of consciousness time, OAA/S (observers assessment of alertness and sedation) scores , and patients' physical characteristics (age, sex, height, and weight). The average surgical time was 165 ± 96 minutes. This database of patient drug administrations and vitals was collected by Johnson et al. in a previous study that evaluated pharmacodynamic response surface models. [6] More patient information is included in the appendix.

Pharmacokinetic and Pharmacodynamic Simulation

The three compartment pharmacokinetic model[8], was used to calculate effect site concentrations (C_e) using volumes and clearances from Schnider, Minto, and Schafer. [1−4,9] Fentanyl $C_e's$ were converted to a remifentanil equivalent using the equivalence ratio of 1:1.2. [6] All data analysis and simulations were calculated in Matlab. The Greco parmacodynamic model predicted the expected responses to various stimuli, as shown in equation 1, the parameters are listed in table 2.

$$E = \frac{E_{max} * (\frac{C_p}{C_{50p}} + \frac{C_r}{C_{50r}} + \alpha * \frac{C_p}{C_{50p}} * \frac{C_r}{C_{50r}})^\gamma}{(\frac{C_p}{C_{50p}} + \frac{C_r}{C_{50r}} + \alpha * \frac{C_p}{C_{50p}} * \frac{C_r}{C_{50r}})^\gamma + 1} \tag{1}$$

Stimulus	C_{50P}	C_{50R}	α	y
OAA/S < 2	2.2	33.1	3.65	4.99
Laryngoscopy	5.6	48.9	33.2	2.2
Algometry	4.16	8.84	8.2	8.34

Table 1: Response surface parameters

Where E is the probability to effect, E_{max} is the maximal possible effect. C_p and C_r are the effect site propofol and remifentanil concentrations. C_{50p} and C_{50r} are the individual effect site concentrations that produce 50% of the maximal effect. α and γ are the curve fitting fitting parameters.

Optimization Algorithm

The algorithm uses the pharmacodynamic effect for the administered remifentanil, propofol, and fentanyl infusions. Every five minutes after induction the algorithm finds a new optimal concentrations for remifenatnil and propofol, the fentanyl concentrations are kept the same.

The optimal C_p and C_r pair is dependent upon the past infusions$_{10}$ and the remaining duration of surgery$_7$. To find alternative C_p and C_r pairs, the equipotent pharmacodynamic levels are found for both laryngoscopy and OAA/S > 2 from the administered C_es. There are two options: either increase the C_r and decrease the C_p while following the OAA/S < 2 isobole or increase the C_p and decrease the C_r along the laryngoscopy isobole. Infusions are changed according to the pharmacokinetic models to maintain each C_es with the correst pharmacokinetic compartment amounts for an estimated approximation of the remainder of surgery.

The ROC and RON times are calculated for each C_p and C_r pair by tracking the drug elimination over the pharmacodynamic response surface model.

ROC (min) = (time at 50 % OAA/S < 2)-(time at end of surgery)

The end of surgery is the point when one of the infusions are terminated. ROC is the elapsed time until the C_e's cross the 50 % isobole on the pharmacodynamic OAA/S < 2 surface.

RON is the time when decreasing C_es are between the 50% OAA/S < 2 isobole and the 25 % algometry isobole.

RON (min) = (time at 25 % algometry isobole)- (time at 50 % OAA/S < 2)

The ROC and RON times each have a parabolic shape. For easier computation the parabolas are interpolated using numerical linear least squares. Cubic splines were tested but required more calculated points for accuracy than the least squares method.

Our goal is to find the minimum ROC time and the maximum RON time. The optimal C_e is also dependent upon the anesthesiologist's priority on ROC versus RON. Let W_{ROC} be the percentage of weight on ROC and W_{RON} for RON. Minimizing the function (eq. 2) of the linear combination of the weights, ROC times, and RON times allows for an easy investigation for the optimal concentration. The function f will be a continuous piecewise function with a parabolic shape.

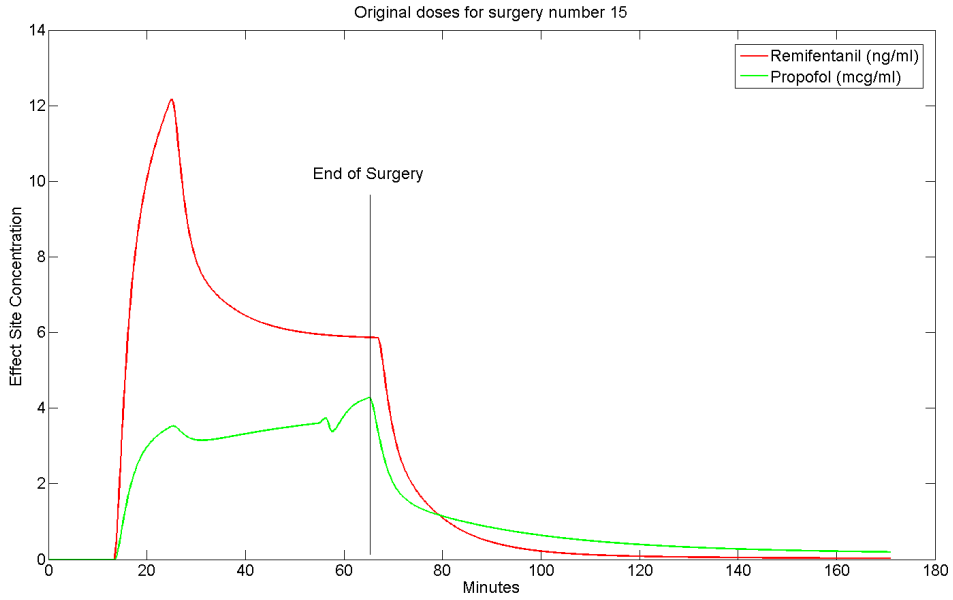

Figure 1: Original effect site concentrations as administered by the anesthesiologist during surgery. For this example the data collection started about 17 minutes before the intial dose was administered. The drug wash out was plotted for 100 minutes after the end of surgery.

$$f = W_{ROC} * (\text{ROC}) - W_{RON} * (\text{RON}) \tag{2}$$

Post-hoc simulation provides the exact remaining surgery time. To avoid the technique from knowing exatly when the surgery would end an estimated surgery end was used until the last ten minutes of surgery. The estimated end of surgery is the end of surgery rounded down to the nearest half hour. We assumed the anesthesiologist would have an idea of when the surgery will end to the nearest thirty minutes. For the last optimization with less than ten minutes left in the surgery a R_e limit of 10 $\frac{ng}{ml}$ was enforced to avoid respiratory compromise.

Assessment of optimization performance

Vuyk's assesment was stricly ROC time for the simulated results. We want to compare the ROC and RON times between the simulated in vivo administrations with the simulated optimized administrations.

We will run the optimization on all 21 surgeries five different times, each with a different weight ratio. The average ROC and RON times for the 21 surgeries will be recorded for each weight. Also the average difference between each simulated ROC and RON times and the control ROC and RON times will be reported, as the average possible improvement. A student t-test (the function ttest in matlab) will be calculated five times, for each weight, between the control times and the simulated times. We're assuming a p-value for the student t-test of $p < .05$ implies statistical independence.

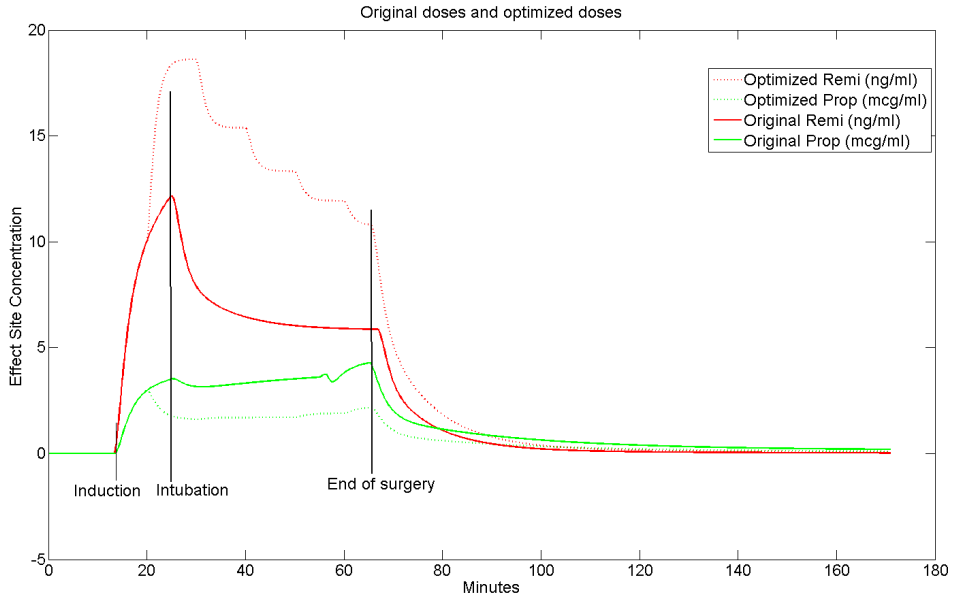

Figure 2: Original dosing vs optimized dosing, using weights roc = .9 and ron = .1.

Results

Post-hoc simulations were performed on 21 laproscopic surgeries, to find optimal pharmacodynamic equipotent administrations. The optimized C_p and C_r for surgery # 15 with $W_{ROC} = .9$ and $W_{RON} = .1$, when 90 % priority was given to ROC and 10 % to RON, are shown in fig. 2. These alternative C_e decrease the expected ROC time from 7.6 to 5.2 minutes while increasing the RON time from 6.3 to 9.3 minutes as seen in fig. 3.

The optimization was performed for each of the 21 surgeries with 5 different weights. The average ROC and RON times with standard deviations for each of the 5 weights versus the control are shown in table 2 and fig. 4. Delta is listed to show the average theoretical improvement for each surgical case from 2 - 5 minutes shorter ROC time and 3 - 19 minutes extended RON time. W_{ROC} values less than .6 are not shown because the results found are very similar, in almost all of the simulations every optimized dosing for $W_{ROC} < .6$ was exactly the same as the optimized dosing for $W_{ROC} = .6$.

Discussion

The results show that Pk and Pd models can be used to find equipotent effect site concentrations (C_e) of Propofol and Remifentanil that either shorten ROC time or lengthen RON time. However when 85 % of the priority was given to ROC and 15 % to RON ($W_{ROC} = .85$, $W_{RON} = .15$) then both the ROC time was decreased and the RON time was increased by an average of 2.51

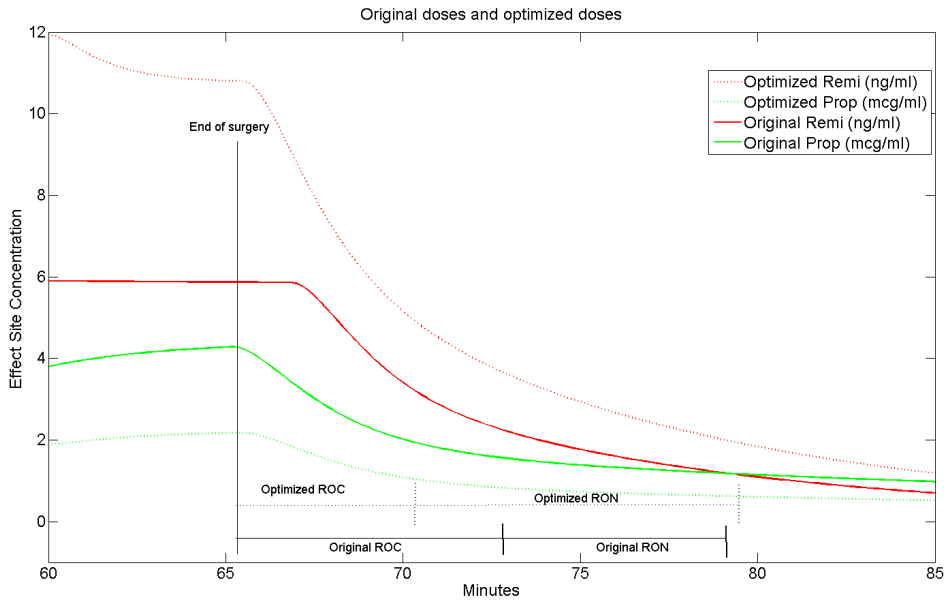

Figure 3: Close up of the end of surgery # 15 with the ROC and RON times for both the control(origina) and optimized simulations.

W_{roc}	W_{ron}	mean $\pm$ std (min)	P-value	Δ (min)	95% CI
ROC Times					
Control		8.20 ± 5.63			
1	0	3.70 ± 1.63	$< .001$	5.15	$5.08 \rightarrow 5.22$
.95	.05	4.14 ± 1.99	$< .001$	4.72	$3.82 \rightarrow 5.62$
.9	.1	5.20 ± 3.17	.002	3.65	$2.23 \rightarrow 5.07$
.85	.15	6.34 ± 3.03	.04	2.51	$1.15 \rightarrow 3.87$
.6	.4	6.95 ± 2.95	.12	1.899	$.58 \rightarrow 3.22$
RON Times					
Control		9.91 ± 13.57			
1	0	11.95 ± 13.21	.23	3.02	$-1.32 \rightarrow 8.92$
.95	.05	11.33 ± 10.57	.247	2.40	$0 \rightarrow 7.12$
.9	.1	12.30 ± 11.08	.13	3.37	$0 \rightarrow 8.33$
.85	.15	15.89 ± 12.29	$< .01$	6.95	$1.45 \rightarrow 12.45$
.6	.4	18.98 ± 13.34	$< .001$	18.98	$13.02 \rightarrow 24.94$

Table 2: Comparing the wake up and nociception times with the original administration. The values are found using the 21 surgeries for each coefficent. The p-value, is acquired using the t-test of the optimized wake up times and nociception times against the control times. Δ is the average difference for each simulated surgery with the control surgery. The 95% CI is the 95 percent confidence interval around Δ using the standard error.

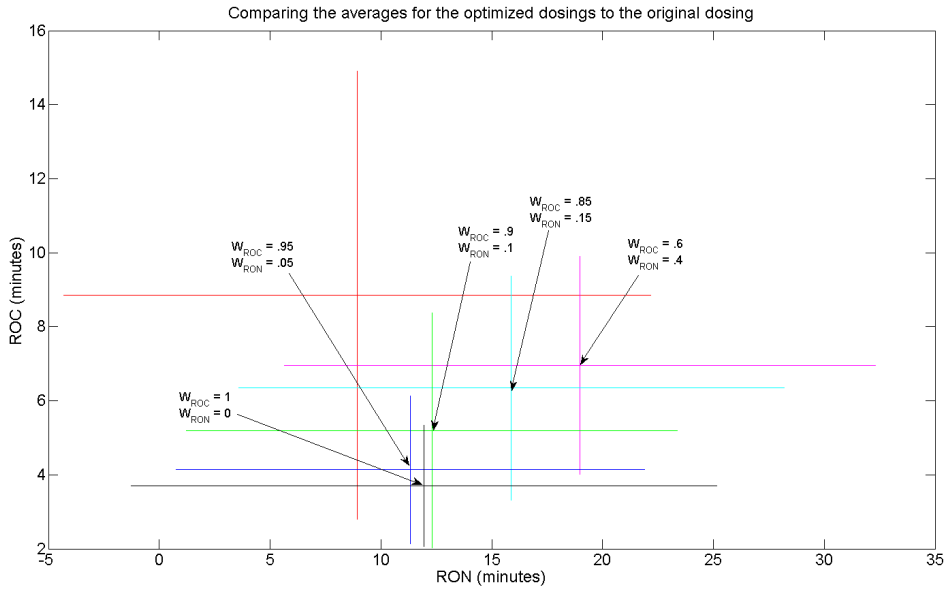

Figure 4: The normal administration (red) in comparison to the optimized administrations for five different weights. The bars indicate the standard deviation, the averages are where the two bars meet. Note the curve made by the averages of the optimizations shows the tradeoff dilema between wake up time and time until pain.

minutes and 6.95 minutes respectively. These results are an average of 21 different surgeries and are theoretical thus require clinical validation.

Optimal concentrations that minimize ROC time and maximizes RON time depend upon the priorities indicated by the anesthesiologist. The anesthesiologist' priority for minimizing ROC versus RON is like a dial. The assigned weights are the percentage of priority to the outcome of either ROC or RON. The weights will be chosen before each surgery dependent upon the patient and the surgery for a more personalized medicine.

To optimize C_p and C_r, anesthetic levels of hypnosis and sedation can not be compromised. The hypnotic and sedation levels are assumed to be represented by the pharmacodynamic response surface model of Laryngoscopy and OAA/S < 2, respectively. The OAA/S < 2 model is the Observers Assesment of Alertness and Sedation response to shake and shout. The surrogate for adequate analgesia or post-operative pain (nociception) is the pharmacodynamic response surface model of 30 psi tibial pressure algometry.

The technique is constrained to use the Propofol and Remifentanil administrations during the induction period and all of the Fentanyl administrations. To avoid respiratory depression Remifentanil C_es must be below $10\frac{ng}{ml}$ by the end of surgery.[12,13]

How useful is this recommended dose for the anesthesiologist since it is using population pharmacodynamic models? The technique finds the concentration ratios with the optimal elimination profiles from the body. It may not be the exact time for that patient, but it should be the best exit track from the surgery for that patient. There is variability that causes general assumptions: high drug tolerance changes the actual C_{50} values and the ROC/RON slopes and variability in cardiac output and blood flow alter the rate constant k_{e0}.

How reliable is this recommendation since Vuyk's fastest emergence time is 5.1 minutes while ours is 3.7 minutes? The shorter emergence time may be cause by multiple factors; different pharmacodynamic and pharmacokinetic model parameters, Vuyk's infusions were steady (causing drug accumulation in, the slow compartment, V3), the different classification in return of consciousness, and the different remifentanil to fentanyl potentcy ratio.

Vuyk's optimization pioneered the concept to target alternative C_es for minimal ROC time. This is not used clinically because anesthesiologist know adequate analgesia is also requisite. Another reason is because only four surgery lengths were tested with two pharmacodynamic levels. All three of these issues were overcome with the proposed technique. We expect this concept to be generalized to more drugs and be used in the operating room

This technique showed expected improvement for "typical" cases and we expect has the capability to vastly optimize longer or complex surgeries, when the slow equilibrating tissue compartment saturates. This technique analyzed remifentanil and propofol which are fast acting drugs; the possibility for more drastic results are expected if slower acting drugs were used. This is what Vuyk et al. found as well that with just using remifentanil over fentanyl, alfentanil, or sufentanil decerased the average wake up times by a factor of 1.5-3. This optimization technique will be able to help the anesthesiologist achieve a better understanding of the anesthetic orientation of the patient, which will possibly help avoid overdosing and under dosing and their associated complications.

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Appendix

Put the patient information here. Anything that seems viable like all the ages, heights, ...