Minimizing Post-Surgery Wake Up Time While Providing Adequate Analgesia

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Abstract

Alternative drug combinations are anesthetically equipotent but have different re-emergence and nociception outcomes. The perfect drug combination - causing a short post surgery wake up time and an extended time until pain - is dependent on the patient, surgical stimulus, and previous dosing. Our goal is to create a technique to find optimized drug dosings that lessens re-emergence time and extends nociception. Method - Use records from 20 general anesthetic procedures that involved Remifentanil and Propofol we calculated equipotent concentrations with more desirable results. Results - The optimization technique improved post surgery re-emergence time on average 5.22 minutes and lengthened nociception time on average 4.22, 7.55, and 9.84 minutes for the three different cases. Discussion - This technique fulfills its primary goal to find more optimal concentrations for anesthesia. The technique is capable of clinical practice to offer optimal suggestions to the anesthesiologist during surgery.

Introduction

In anesthesia multiple drugs are used to ensure a patient’s well being during the surgical procedure. Uncertainty arises from the drug to drug interactions reacting additively, antagonistically, or synergistically; this interaction is pharmacokinetic variability. By accounting for patients’ individual physical characteristics and drug concentrations models predict the synergistic interactions and expected response to a stimulus. However, another uncertainty also exists from individual pharmacodynamic variability, which is caused by unknown reactions in the body to the drugs. Due to the elusiveness of the pharmacokinetic and pharmacodynamic variability it is difficult for the anesthesiologist to know how individual patients will react or emerge from an anesthetic experience. The anesthesiologist can only perceive the responsive cues from the patient during the surgery: pulse rate, blood pressure, and muscle activity. Alleviating part of pharmacokinetic variability during anesthesia will potentiate optimization of the anesthetic experience; especially within the range of our focus to both minimize the sedation effect and maximize the analgesic effect at the end of surgery. By tracking drug administration during surgery, we can estimate the future recovery and nociception time and recommend alternate equipotent concentrations with quicker recovery times and extended nociception times. This will be used by anesthesiologist during surgery to provide optimal drug cocktails with surgery and patient specificity.
Method

The 3 compartment pharmacokinetic drug model has been widely accepted to describe the biodistribution of drugs. The rate constants for the drug model have been found through laborious testing. The rate constants that we use are from Schnider for Propofol and Minto and Schnider for Remifentanil.\textsuperscript{1,2}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{General form of the classic 4 compartment drug model}
\end{figure}

Vuyk et al. noticed the synergistic effect of drug to drug interactions; when using two drugs they found that various drug concentrations have different wake up times.\textsuperscript{3} Consequently the quickest wake up time was found for each of the four different scenarios surgeries. Vuyk’s trial and error methods were extensive; however their findings introduced the concept of using synergistic drug interactions to decrease re-emergence time after surgery.

Kern et al. created population models of the synergistic behavior between propofol, a sedation drug, and remifentanil, an analgesic opiate.\textsuperscript{4} Assuming these models correctly depict patients anesthetic orientation we can quantify an expectation for the patient’s response due to given stimuli. Later Manyam showed similar synergistic results when remifentanil was combined with an inhaled agent, sevoflurane.\textsuperscript{5}

The data used was from a library of anesthetic cases. A technician was present for each of the 20 surgeries recording the patients physical characteristics, doses administered, and the surgical events. Each surgery included general anesthesia; there were no specifications on the surgical procedure or the equipment used by the anesthesiologist. For the surgery the anesthesiologist was only allowed to use remifentanil, fentanyl, and propofol as the anesthetic agents. The three drugs chosen for this optimization technique - remifentanil, fentanyl, and propofol - were chosen for their individual differences and highly synergistic effects. Remifentanil and fentanyl are very similar in their analgesic effects, but vary drastically in their half life times. These two analgesic drugs can be combined into an overall remifentanil effect\textsuperscript{3} although for simplicity the initial optimization will ignore the fentanyl administration, only accounting the propofol and remifentanil administrations.

A patient’s depth of anesthesia is difficult to pinpoint; however, response surface models classify levels of anesthesia and will be utilized to quantify otherwise abstract levels of consciousness.
and nociception. With response surfaces an expected response to a given stimuli corresponds to an array of drug pair concentrations. The desired reactions that need quantification are the anesthesia level, the re-emergence time, and the nociception time. We assume the level of anesthesia corresponds to the expected response to laryngoscopy response surface (lar). We also assume the average patient feels pain at the 25\% isobole on the electrical tetany response surface (tet) this will be called the nociception time or the time until pain. To quantify re-emergence time we use the observation alert assessment/sedation OAA/S < 2 response surface (oa2) to be referred to as the re-emergence time or the wake up time. Specifically for each surgery we find the point in time on the expected response to OAA/S < 2 when they woke up, this value then becomes the patients wake up point on the OAA/S < 2 surface. Thus, by using the response surfaces mentioned earlier from Kern et al. we calculate the expected response to laryngoscopy, OAA/S < 2, and electrical tetany. An example of these levels of probability to a given stimuli is shown later in fig. 4.

The response surface models are found using the equation from Kern et al.\(^3\). The values used are new values that were obtained from a more recent unpublished study by Kern et al.

\[
E = \frac{E_{max} * \left( \frac{C_A}{C_{50A}} + \frac{C_B}{C_{50B}} + \alpha * \frac{C_A}{C_{50A}} * \frac{C_A}{C_{50A}} \right)^y}{\left( \frac{C_A}{C_{50A}} + \frac{C_B}{C_{50B}} + \alpha * \frac{C_A}{C_{50A}} * \frac{C_A}{C_{50A}} \right)^y + 1}
\]

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>(C_{50R})</th>
<th>(C_{50P})</th>
<th>(\alpha)</th>
<th>(y)</th>
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<tbody>
<tr>
<td>OAA/S &lt; 2</td>
<td>2.2</td>
<td>33.1</td>
<td>3.65</td>
<td>4.99</td>
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<td>Laryngoscopy</td>
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<td>48.9</td>
<td>33.2</td>
<td>2.2</td>
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<td>Algometry</td>
<td>4.16</td>
<td>8.84</td>
<td>8.2</td>
<td>8.34</td>
</tr>
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</table>

Table 1: Response surface parameters

**My solution to the pharmacokinetic model**
The pharmacokinetic model includes 3 or 4 main compartments with rate constants describing the rate of drug transfer between compartments. The model is a simple linear system of differential equations. Infusing the drug creates a continuous piece-wise function that is not easily differentiable. Thus most solutions to this model are done with computer based iterative approximations. To solve this problem we have formulated and new 5 compartment model, adding a compartment for the effect site and the infusion. The pharmacokinetic model seen in figure 1, describes the kinetics of a drug throughout the body. Drugs are first introduced to the blood system via intravenous administration. The rate constant from the infusion compartment to the blood is governed by the infusion itself. The infusion rate constant is held constant by making the infusion compartment of near infinite size. The drug circulates in the blood till it is absorbed by the tissues. Various tissues absorb the drug quickly while other tissues saturate at a slower rate. An effect site only directly linked to the blood volume is the place of drug efficacy. This new five compartment drug model creates a linear system of differential equations of the drug bio-distribution throughout the body.

From the model the characteristic differential equations are...
\[ \frac{dA_1}{dt} = (-k_{12} - k_{13} - k_{14} - k_{10})A_1 + k_{21}A_2 + k_{31}A_3 + k_{41}A_4 + k_I A_5 \]  
\[ \frac{dA_2}{dt} = k_{12}A_1 - k_{21}A_2 \]  
\[ \frac{dA_3}{dt} = k_{13}A_1 - k_{31}A_3 \]  
\[ \frac{dA_4}{dt} = k_{14}A_1 - k_{41}A_4 \]  
\[ \frac{dA_5}{dt} = -k_{51}A_5 \]  

Which can also be written in the form  
\[ \frac{dA}{dt} = [M]A \]  

Let \( v \) = the matrix of eigen vectors of \( M \)  
Let \( p = [v]^{-1}A \)  
Then for \( i = 1, \ldots, 5 \)  
\[ A_i = p_1 e^{\lambda_{i1} t} v_{i,1} + p_2 e^{\lambda_{i2} t} v_{i,2} + p_3 e^{\lambda_{i3} t} v_{i,3} + p_4 e^{\lambda_{i4} t} v_{i,4} + p_5 e^{\lambda_{i5} t} v_{i,5} \]  

\( A \) is the amount of drug in the specific compartment. \( K \) is the corresponding rate constant between compartments, which are notably different for each drug.  

With the analytical solution we first need to understand visually the difference between the pharmacokinetics of the drugs. Each drug has different kinetics, as shown in fig. 12, and must be tracked individually.
Figure 3: Examples of bio-dispersion of Remifentanil and Propofol after infusions. Shown to compare the differences in half life between Remifentanil and Propofol. Infusion duration was the same for both simulations starting with initial concentrations of 0 in all the compartments.

<table>
<thead>
<tr>
<th>Surgery Number</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>93.4 (kg)</td>
</tr>
<tr>
<td>Height</td>
<td>180 (cm)</td>
</tr>
<tr>
<td>Age</td>
<td>20 (years)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
</tbody>
</table>

Table 2: Patient # 15 characteristics

As an example of the optimization technique for patient # 15 from the study will be shown, this patient was chosen randomly. The patient’s individual characteristics are represented in tab. 2. The drug administration from the anesthesiologist is shown in fig. 2.

According to this patient’s characteristics and the drug administration that they received we find the concentrations for each drug in each compartment. The effect site concentrations are shown in fig. 3. The population expectation to surgical events is calculated for the patient according to their drug administration as seen in fig. 4.

Next we want to optimize the surgery. The optimization can not allow the patient to fall below the current anesthetic level and sedation level, this is assuming that the anesthesiologist knew the required level of anesthesia for the patient. We need to choose the best concentrations that produce at least the same expected response. Thus the canonization is set by the re-emergence and anesthetic level curves and is represented by the fig. 4. The concentrations can not fall below either curve, thus the possible optimal points are the red curve to the left and the blue curve to the right of the current dose. Each possible optimal point has a different wake up and nociception profile. To find this profile we use a TCI technique to reach the intended concentration then the infusions are shut off and the drugs eliminate from the body. Using the response surface models and the previous assumptions on re-emergence and nociception we achieve the profile times for that concentration. This is repeated for each possible concentration keeping the TCI duration constant for each one; TCI reached the target after a minute or two, but the duration constant was...
set for 5 minutes to allow adequate time for quasi-equilibration. The profile times are shown for the example case in fig. . The concentration pairs are referred to as a concentration index for easier bookkeeping where each change in concentration index corresponds to a .1 change in propofol concentration. The re-emergence time is measured by the difference in time between the end of surgery (all infusions turned off) and the expected re-emergence point. The nociception time is the difference in time between the re-emergence time until the time the patient is expected to feel pain.

What concentration index corresponds to the best outcome? This depends on the preference of the anesthesiologist. If the goal is to minimize post surgery wake up time then the best concentration will be at the minimum of the re-emergence curve. However, if a minute can be spared on the expected post surgery wake up time then the expected time until pain increases by about 4 minutes, in this example. There is no distinct answer to this balance situation, other than; How much does the anesthesiologist value analgesia at the expense of post-surgery re-emergence?

A linear combination of the two profile times with multipliers allows for easy change of priority. The weighting function designed to minimize re-emergence time and maximize nociception time is

\[ f = A \text{(re-emergence time)} - B \text{(nociception time)} \]

The multipliers indicate the anesthesiologist priority a high A indicates a strong inclination to wake the patient shortly after surgery to a low A indicates the anesthesiologist doesn’t care how long it takes them to wake up as long as they don’t feel any pain. The multipliers role is seen in the fig. 7. They multipliers can be any real number but are normalized to one.

The example was shown for one point in time. If this technique is repeated every five minutes, then a more optimized set of dosing can be compared to the original administered dosing. For the example run the optimized doses are shown compared to the original dosing from the anesthesiologist in fig. 8. These alternative doses produce an anesthetic effect at least as potent as the effect from the original dosing.
Figure 5: Original doses as administered by the anesthesiologist during surgery. Blue line indicates the drug concentration in the effect site, the green line is the drug concentration in the plasma, the red line is the drug concentration in the fast equilibrating tissues, and the black line is the drug concentration in the slow equilibrating tissues.

Results

Our goal to minimize wake up time while providing adequate analgesia was successful. The results depend on the weights used, but each optimization produced a decrease in the wake up time by about 5 minutes on average and the nociception time was increased by 4 to 10 minutes, as is shown in fig. . This allows for a general improvement and flexibility depending upon the specific surgical case. The optimized cases are all closer to the more optimal part of the figure shown. Also notice that the optimization technique limited the expected deviation presented by the decrease in length the bars of the same figure.

To illustrate the differences between the optimized dosing and the original dosing the end concentrations are plotted in fig. ?? These differences are the last optimization right before the end of surgery. The results from the weights \( a=.25 \) \( b=.75 \) and \( a=0 \) \( b=1 \) are nearly equivalent to the results from the weights \( a=.5 \) \( b=.5 \) and thus are not shown in the figure.

Conclusion

This optimization technique showed improvement for “typical” cases and has the capability to vastly optimize longer or complex surgeries. This technique analyzed Remifentanil and Propofol use which are fast acting drugs more drastic results are expected if slower acting drugs were used. This optimization technique will be able to help the anesthesiologist achieve a better understanding of the anesthetic orientation of the patient, which will help avoid overdosing and under dosing.
Re-emergence time and nociception time are dependent. There is no absolute best concentration of drugs to use for the best re-emergence and nociception times, however they are always changing due to the patients, demographics of the surgery, and previous drug administrations and will keep changing as the surgery itself continues.

How useful is this recommended dose for the anesthesiologist? Due to the fact of the pharmacodynamic variability this technique is not exact for the individual patient, but is based on a population of patients. The surface models predict the expected response to stimuli which correlate with re-emergence time and time until nociception returns. These values are approximations and not exact; however they do find concentrations with more optimal elimination profiles from the body. Future research is looking for ways to adapt the response surfaces with individual patient specificity to eliminate more of the pharmacodynamic variability.

The best application of this will be with longer surgeries that last many hours when the slower equilibrating drugs have had time to fully saturate all the compartments in the body. The longer the slow equilibrating compartment has to fill then the longer it will take that compartment to empty. It is emptied through the blood or the main compartment and prolongs the anesthetic effect, of sedation, long after the infusion is attenuated.

References

2. Anesthesiology 1999: 90(6) 1502-16
Figure 7: Ending possibilities, isoboles for given stimuli with same expected response, the possible drug combinations can not fall below either of the curves. The current dose indication is the one point on the curve.

Figure 8: Expected re-emergence and nociception times for the possible concentrations. The current dose indication is the one point on the curve. Note here that the current dose is almost the minimum of the re-emergence profile curve, choosing a point to the left of the current dose will increase nociception time while keeping re-emergence time close to the current value.
Figure 9: Weight function, the minimal point is indicated with the black dot. This shows the difference of weighting possibilities depending on how important the anesthesiologist deems re-emergence or nociception time.

Figure 10: original doses vs optimized doses
Figure 11: Nociception time plotted against the re-emergence time. Circles indicate the average time and the bars indicate the standard deviation.
Figure 12: The three different weights. Top left figure $A = 1, B = 0$; Top right figure $A = .75, B = .25$; Bottom figure $A = .5, B = .5$