Development of a Cost Functional for Evaluation of Remifentanil-Propofol Dosing Simulations of Esophageal Instrumentation in the Moderate Sedation Range

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Abstract- **An increasing number of procedures using propofol and remifentanil are performed by clinicians with no formal in anesthesiology. The rapid kinetics of these drugs can rapidly lead to adverse effects the clinician is not trained to manage. We therefore propose to investigate through simulations drug ratios and dosing regimens that allow esophageal instrumentation while minimizing the probability of adverse events. Our simulation criteria were to reach and minimize the time above the esophageal instrumentation C_{95} isobol, as well as minimize the time above the loss or responsiveness C_{99} and respiratory compromise C_{95} isobols. A cost functional would be developed to score each simulation. This score could be used to identify preferred solutions. Simulations were first sorted manually and then different cost functionals were developed to achieve similar results. A relatively simple equation selected 80% of the runs identified manually. Further work is needed in developing the cost functional to increase this percentage and to add meaning to the score.**

I. INTRODUCTION

Propofol in combination with opioids are commonly administered by clinicians with no formal training in anesthesiology for stimulating procedures of brief duration where moderate sedation is desired. Propofol interacts synergistically with opioids and can lead to worrisome adverse effects including cardiovascular depression, respiratory depression, and airway obstruction. Many clinicians who use these drugs do not have the skills to properly manage these adverse events. It would therefore be ideal to provide these clinicians with drug ratios and dosing strategies for these procedures that would minimize adverse effects in the majority of patients.

Recent advances in characterizing drug interactions and high resolution modeling to predict drug behavior have provided the theoretical means to optimize dosing to achieve desired effects quickly, maintain those effects while avoiding unwanted side effects, and minimize the time required for the effects to end once delivery is terminated.

Simulations allow a wide range of dosing strategies to be investigated for viability before conducting an actual study. The ease of simulating, however, presents a new problem. Thousands of simulations can be run rapidly, but a method is needed to quickly identify viable solutions.

We propose to develop a cost functional that will return meaningful scores for simulations of a specific procedure – esophageal instrumentation (EI). We hypothesize that this score can be used to 1) Identify the optimal dosing regimen of propofol and remifentanil (bolus versus infusion versus bolus followed by infusion, 2) Minimize the time of loss of responsiveness and respiratory compromise while allowing EI.

II. BACKGROUND

An increasing trend in patient care is to perform procedures associated with mild to moderate pain outside the operating room. Potent fast-acting anesthetics are commonly used to blunt the response to noxious stimuli associated with these procedures, but are often administered by clinicians with no formal training in anesthesiology.

This study explored the behavior of two commonly used intravenous anesthetics, propofol and remifentanil, when used in combination to blunt the response to esophageal instrumentation. Both drugs have unique and desired properties. Propofol is an anesthetic, providing loss of consciousness, preventing awareness and reducing movement response to surgical stimuli. However, at higher doses it frequently causes airway obstruction and loss of consciousness. Remifentanil at higher doses can cause respiratory depression leading to apnea.

An advantage to using these drugs in combination is their synergistic relationship. The effects of each drug are enhanced when they are administered together. Less of each drug is required to achieve a desired level of sedation than if one drug is used in isolation.

Recent developments in clinical pharmacology research have led to the development of response surface models. These models provide a three dimensional visualization of combined drug behavior. Response surfaces are particularly useful in visualizing the predicted response for all drug combinations shown. Response surfaces for EI, loss of consciousness (LOR) and respiratory compromise (RC) (combination of respiratory depression and airway obstruction) can be combined to identify ideal concentration pairs and dosing regimens that meet clinician needs yet provide patient safety.

Preliminary research must be conducted to collect the data required to build these response surfaces. Advances in technology allow further investigation to be done with modeling. Studies have developed pharmacokinetic and pharmacodynamic models for propofol[1] and remifentanil.[2] With these models, it is possible to perform simulation studies of predicted patient response to a given stimulus over a wide range of drug ratios and dosing strategies. The cost functional will aid in the identification of those combinations that closest match the defined criteria.
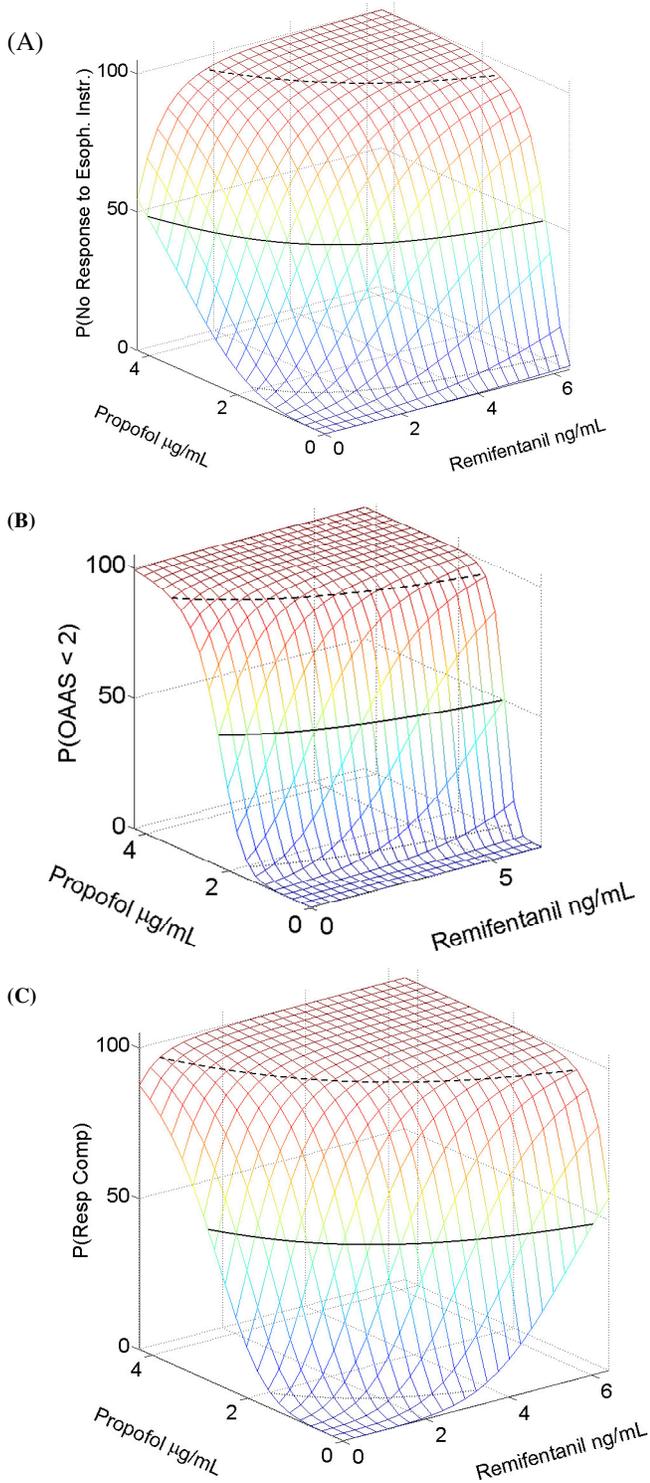
(A)

(B)

(C)

Figure 1. Response surfaces for EI (A), LOR (B) and RC (C). The remifentanil-propofol drug combinations resulting in 5% (dotted line), 50% (solid line) and 95% (dashed line) probabilities are shown.

(A) EI was considered tolerated if it was placed mid-esophageal (~40 cm) without subject discomfort, as indicated by the subject raising their hand, gag reflex, coughing, or greater than 20% increase in baseline heart rate or blood pressure.

(B) LOR was defined as OAA/S < 2, which coincides with a loss of response to shake and shout.

(C) RC is generated from the combined data of airway obstruction and respiratory depression.

$$P(E=1|C_P,C_R) = \frac{\left[\dfrac{C_R}{C_{50R}} + \dfrac{C_P}{C_{50P}} + \alpha \cdot \left(\dfrac{C_R}{C_{50R}} \cdot \dfrac{C_P}{C_{50P}}\right)\right]^n}{1 + \left[\dfrac{C_R}{C_{50R}} + \dfrac{C_P}{C_{50P}} + \alpha \cdot \left(\dfrac{C_R}{C_{50R}} \cdot \dfrac{C_P}{C_{50P}}\right)\right]^n} \quad (1)$$

III. METHODS

Data used to construct the response surfaces were collected following the procedure outlined in the methods section of last year's paper.[3] For this study, surfaces for EI, LOR and RC were constructed (Fig. 1). Response surfaces were generated using the Greco construct (Eq. 1).[4] The line on the surface formed when a plane drawn perpendicular to the effect axis intersects with the surface highlights all possible drug combinations that are expected to produce the same effect for a specific stimulus. This line is called an isobol, or iso-effect line, and is identified by the stimulus and probability associated with the effect (i.e. LOR C_{50} is the LOR 50% isobol, or drug combinations that produce a 50% probability of LOR). Isobols represent the "targets" define the different criteria.

The criteria were defined in terms of isobols. The LOR C_{99} isobol was defined as LOR. We wanted to minimize the amount of time effect site (brain) concentrations were above this line. The RC C_{95} isobol defined RC. We again wanted to minimize the amount of time above this line. EI C_{95} isobol defined the target that must be reached for placement of the instrument in the esophagus. We wanted to reach this isobol quickly while minimizing the amount of time above it.

During the study, drugs were administered using Stanpump (http://anesthesia.stanford.edu/pkpd). Simulations can be performed in Stanpump, but it is a time consuming process. Therefore, a MatLab (MathWorks, Natick, MA) implementation of Stanpump was built, thereby allowing us to run thousands of simulations and immediately process the results.

To minimize the iteration matrix and avoid impractical solutions, we defined drug ranges and step sizes to match what is clinically relevant and feasible. The simulations assumed propofol and remifentanil would be combined and administered together. It was also assumed that propofol would always be 10 mg/mL. We investigated remifentanil concentrations from 0 to 25 µg/mL, incrementing by 1.25 µg/mL each time. Because the drugs are combined, we assumed the infusion rate would be set by propofol. Rates from 10 to 150 µg/kg/min were investigated, with a step size of 10 µg/kg/min. We also investigated pretreatment with bolus injections ranging from 0 to 20 mL, incrementing by 1 mL. The patient was assumed to be 55 years old, 75 kg and 175 cm. All simulations were for a 60 minute procedure and were run for both a male and female subject.

It was decided that the best approach would be to develop three independent cost functionals, each of which would evaluate just one criteria. These three independent functionals would then be weighted and combined to yield

the final score. By convention, the closer a score is to zero, the closer it is to meeting all the criteria. The cost functional inputs are:

1. Time above RC C_{95}
2. Time above LOR C_{99}
3. Time to EI C_{95}

IV. RESULTS

Previous work has shown that it is not possible to both instrument a patient's airway and remain in the moderate sedation range.[5] It is necessary to venture into deeper sedation for patients to tolerate instrumentation. Along with this deeper sedation come adverse effects such as LOR and RC. During data collection we observed that the most stimulating part of the procedure is the actual placing of the instrument. A patient can tolerate a placed instrument at lower drug levels. Therefore, more drug must be given up front, but it can then be reduced for the duration of the procedure. Because it is impossible to perform the procedure and avoid these adverse effects, we must instead devise a dosing regimen that minimizes the time a patient is at drug levels with high probabilities of them occurring.

Of the 13,230 simulations, 2,887 (12%) never reach the EI C_{95} isobol. The average time above this isobol for the remaining runs is 29.8 minutes ± 26.6. As shown in Fig 2, the EI C_{95} isobol requires higher drug levels compared to LOR and RC. There is potential for serious complications if a patient remains at these drug levels for almost half of the procedure. It only takes a minute or two to instrument the airway. If we therefore only include those runs that are above EI C_{95} for at least 1 minute but not more than 2.5 minutes, we are left with 412 (3%). Their average time above the isobol is 1.75 minutes ± 0.4.

The average time above LOR C_{99} of those same 412 runs is 6.7 minutes ± 11. We will need to be above this isobol for at least the amount of time allowed for EI. If we further consider just those runs that are above LOR C_{99} for less than 6 minutes, we are left with 327 (2.5%). The average time above the isobol drops to 3.4 minutes ± 1.2.

Finally, the mean time above the RC C_{95} isobol for these 327 runs is 7.1 minutes ± 11.7. After limiting these to those runs that are above RC C_{95} for less than 7 minutes, 305 runs remain (2.3%). The average time above the isobol is 4.2 minutes ± 0.6. This approach has therefore eliminated 97.7% of the simulations. These are shown in Table 1.
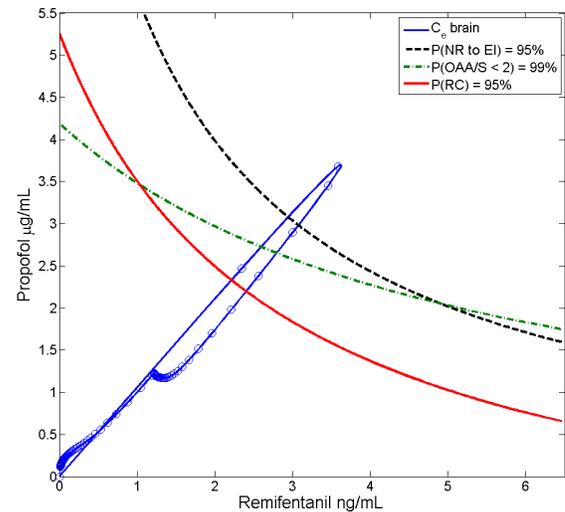

Figure 2. The target isobols are shown with the results of one simulation. A 55 year old male, 75 kg and 175 cm was pretreated with a 6 mL bolus of 10 mg/mL propofol combined with 10 µg/mL remifentanil. This was immediately followed with a 60 minute infusion at 40 µg/kg/min. Markers are displayed at whole minutes.

After having manually filtered the simulations, we next attempted to develop a cost functional that would yield a similar selection. The simplest cost functional just adds the three times to create a score. A similar number of final simulations can be obtained by eliminating all runs with scores greater than 3.5 or equal to 0. This leaves 293 simulations. However, they are all unique to those obtained previously. When manually selecting runs, all those that did not reach EI C_{95} were eliminated. When the cost functional was changed to subtract 1 from EC C_{95} time and to not assign a score to any run that did not reach EI C_{95}, 311 simulations were selected when a cutoff score of 9.5 was used. This time, only 87 runs were unique (28%). A third version eliminated all projects that were not above EI C_{95} for at least one minute, similar to the criteria used when manually selecting runs. Selecting just those runs with a score less than 9.8 resulted in 301 simulations being selected, of which 62 were unique (21%).

After looking at the isobol shapes in Fig. 2, it was noted that RC C_{95} and EI C_{95} appeared to be concentric. This

Table 1. Table showing manual filtering criteria for the simulations. The first three columns indicate the filter criteria, if any, for each time. The fourth column indicates the number of runs that met the criteria. The last column shows the percentage of runs that met all criteria.

	EI C_{95}	LOR C_{99}	RC C_{95}	# of Runs	Percent
Man #1	>0			10,343	78
Man #2	1≤tme<2.5			412	3
Man #3	1≤tme<2.5	<6		327	2.5
Man #4	1≤tme<2.5	<6	<7	305	2.3

Table 2. Table showing cost functional algorithm development for filtering the simulations. The first three columns indicate the inclusion criteria, if any, and well as any modification done for each time. The fourth column indicates the score selection criteria. The fifth column shows the number of runs that met the criteria. The last column is the percentage of the number of runs indicated that were not included in the manually selected approach.

	EI C_{95}	LOR C_{99}	RC C_{95}	Score	# of Runs	Percent Unique
CF #1	>0			<3.5	293	100
CF #2	>0, tme-1			<9.5	311	28
CF #3	>1, tme-1			<9.8	301	21
CF #4	>1, tme-1		X	<5.1	314	27
CF #5	>1, 2•(tme-1)	tme-2	X	<4.5	304	20

means the times should be highly correlated. Therefore, it is not necessary to include a time for both. After eliminating time above RC C_{95}, 314 simulations were selected by using a cutoff score of 5.1, with 86 being unique (27%). It was noted that previously we had also used a cutoff time for EI C_{95} of 2 minutes. When adding times, time above LOR C_{99} is almost always greater than EI C_{95} time because its isobol is lower on the plot. To give equal weight to both times, I doubled the weight of EI C_{95} (multiplied by 2) and subtracted 2 from the LOR C_{99} time. When using a cutoff score of 4.5, 304 runs were selected, 60 of which were unique (20%). These are all summarized in Table 2.

V. Discussion

Both manual and automated dosing evaluations were able to yield similar simulation selections. The elimination of 97.7% of simulations based upon evaluation criteria makes the task of selecting a drug ratio and dosing regimen more manageable. However, the filtering is a product of the method used. The approach taken in this study used time above three isobols. The selection might therefore identify the fastest procedure or the longest, etc. There are other parameters worthy of consideration when selecting a drug ratio and dosing regimen. For example, how long it takes for a patient to be reach the EI C_{95} isobol is important, as is how long it takes them to wake up once the infusions are turned off. Additionally, we tossed all runs that didn't reach the EI C_{95} isobol. A better approach may be to use a combination of maximum probability obtained, the time to reach it and time above it as well as time to return of consciousness.

It may also be worth including information about the drugs. Respiratory depression, the more dangerous component of respiratory compromise, is associated more with high remifentanil effect site concentrations. Onset of Airway obstruction, the more manageable component, occurs at high propofol effect site concentrations. Therefore, it is expected that a preferred dose would have a low remifentanil/high propofol drug ratio. While this information is incorporated already in the cost functional through respiratory compromise, it may be helpful to include it more directly.

Because we are running simulations, we also have the benefit of knowing the equation that describes the lines. It may be possible to take advantage of the Greco equation (Eq. 1), in whole or in part, to create a more dosing-dependent score. The isobol curves are calculated using this equation. It may also be possible to relate them somehow to develop an equation where the meaning of the score does not change if the isobol probability is changed.

Isobols can be drawn for any probability. In hindsight I would propose lowering the RC isobol to C_{50}. We do not want RC to occur so using a lower probability would increase the amount of time above it, increasing the score for being above it. Also, EI and RC isobols do not match at different probabilities. The cost functional should therefore include it. LOR, however, may be unnecessary. Unless the procedure requires the patient be alert, it may only be necessary to track RC. LOR does not provide any additional information about adverse effects. However, it does help predict wake up times after the infusion is turned off.

Future versions of the cost functional should also consider if spontaneous breathing stops and for how long. Additionally, criteria for selecting the drug levels the balance of the procedure will take place at need to be developed. Finally, the focus of this study was to create a cost functional that selected the same runs identified through a manual process. Future work, including clinical trials, is necessary to select and validate a final drug dose and dosing regimen.

VI. Conclusion

A cost functional can be developed that will reasonably match manual filtering of simulation results. Eighty percent of the runs identified were identical to both methods. The cost functional could be used to eliminate 98% of the simulations, greatly reducing the task of evaluating the simulation results.

Manually filtering the simulation results provides a baseline to compare the cost functional to. However, the techniques used are easily implemented in a program, thereby eliminating some post processing requirements. Also, we relied just on times for the manual filtering. A cost functional provides an opportunity to use more complex methods. Additional information should be included in the equation to selection of an optimal drug ratio and dosing scheme does not rely solely on times. Finally, the current score is not meaningful. Future work would modify the equation so the output would provide information about that run. So while this study looked at mimicking the results obtained by manually filtering, future work would improve upon it.

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