AN ANESTHESIA DISPLAY FOR A SPACE STATION: CLINICAL VALIDATION OF SEDATION AND ANALGESIA MODELS

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Abstract

Real-time visualizations of drug pharmacokinetics and pharmacodynamics may help anesthesiologists more accurately titrate intravenous anesthetics for sedation and analgesia in a critical care setting. To assess synergism between propofol and opioids, our laboratory has developed response surface pharmacodynamic interaction models for remifentanil and propofol. These models use surrogate measures of analgesia and sedation from a volunteer study but must be validated before they are applied to patients in a real-time display; the surrogate measures used in the volunteer study must be related to clinical patient responses. The aim of this study is to explore the pharmacodynamic relationship between the surrogate and clinical responses. We hypothesize that the surrogate stimuli from the volunteer study can be mapped to surgical stimuli; we expect the levels of anesthesia required to moderate responses to the surrogate measures relate to levels of sedation and analgesia needed to prevent responses to surgical stimuli in the operating room.

Introduction

During the development of an anesthetic, considerable resources are used to create pharmacokinetic profiles. Simply put, pharmacokinetics describe what the body does to the drug; pharmacokinetic models give the concentration of the drug in the body as a function of time. Once the drug is administered, it is transported in the blood to different body tissues, in particular the biophase or effect site. The biophase consists of the specific tissues, membranes, receptors, and enzymes where the drug exerts its pharmacologic effect; the central nervous system is the biophase for anesthetics. The concentration of anesthetics at the effect site can be predicted using pharmacokinetic models.[1]

Our lab developed a computer simulation that visualizes the pharmacokinetics of remifentanil and propofol, two, commonly used, intravenous anesthetics. (See Figure 1.) Anesthesiologist study subjects were asked to maintain a target therapeutic drug concentration and stable hemodynamics in a simulated patient by directing drug administrations. Subjects who were shown the display more closely maintained the target concentration and had shorter periods of inadequate anesthesia than subjects who only used traditional anesthesia monitors. The results suggest that the visualization of pharmacokinetic models may assist in clinical decision-making.[2] However, anesthesiologists typically are worried less about the drug concentrations than they are about the drug effects on their patients.

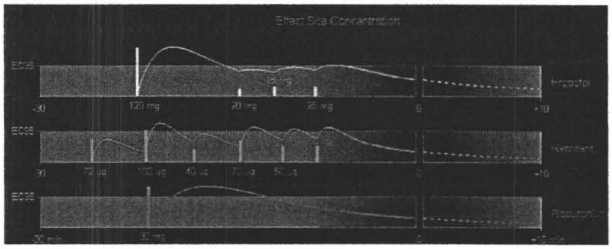

Figure 1. Screen shot of computer visualization of anesthesia pharmacokinetics, 20 minutes in the past to 10 minutes in the future. The colored vertical bars represent drug boluses.

Pharmacodynamic models can be defined as what the drug does to the body; pharmacodynamics describe the drug effects as functions of the drug concentrations at the effect site. Pharmacodynamic models are typically sigmoidal in shape for anesthetics. (See Figure 2.) The midpoint of the curve is called the EC50 value, and is the effect-site concentration at which there is a 50% probability that the patient is adequately anesthetized.[1] Anesthesiologists generally target the EC95 value such that there is a 95% probability that their patients will not respond to stimuli. Together, pharmacokinetic and pharmacodynamic models describe the rate of onset of a drug and the expected duration of drug effect. However, anesthesia is generally provided using several drugs in combination.

When more than one anesthetic is used, there are several possible drug interactions. (See Figure 3.) The axes concentrations of Drug A and Drug B and the lines indicate an equal level of

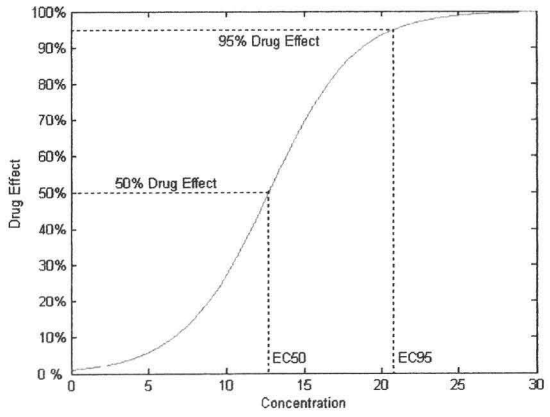

Figure 2. Sigmoidal shape of a typical pharmacodynamic function for a single drug.

anesthetic effect, called an isobole. When the isobole bows towards the origin, the drugs are synergistic, such that the drugs given in combination reduces the total amount of drug needed to provide a target effect level. A straight line suggests that the drugs are additive, meaning that there is no interaction between them. If the isobole bows away from the origin, then the relation is infraadditive or antagonistic, such that the higher the concentration of one drug, the greater the concentration of the other drug to maintain the effect level. When a full range of drug effect, instead of a single isobole, is represented, a response surface is created.

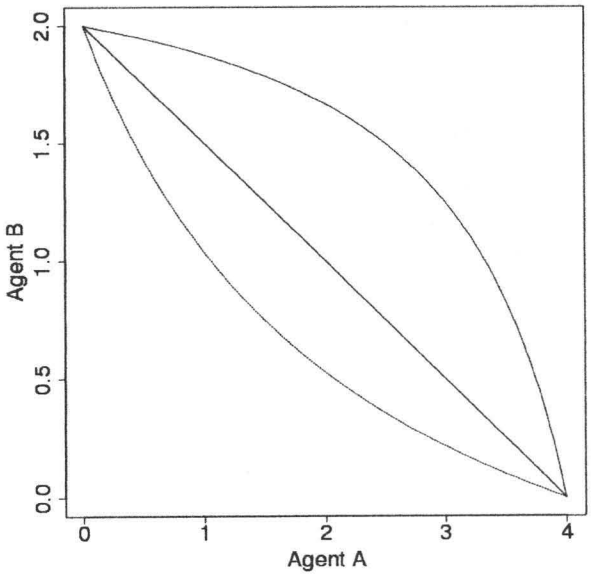

Figure 3. Isoboles represent pharmacodynamic interactions that exert the same drug effect for two drugs in combination.

Our lab has created response surfaces for propofol and remifentanil that describe the drug effect for clinical propofol and remifentanil effect-site concentrations in a non-surgical volunteer study. At several propofol-remifentanil concentration pairs, noxious stimuli, surrogates for surgical stimuli, were applied to the volunteers. The surrogate measures were assessment of the subject's alertness (using the OAA/S scale), laryngoscopy, electrical tetany, and pressure algometry. The response surfaces for these four surrogates showed significant synergism between remifentanil and propofol.[3,4] The surfaces for sedation and for laryngoscopy are shown in Figure 4. Other studies have shown fentanyl cogeners to have related pharmacodynamic effects that might be related to one another using a scaling factor.[5] Because remifentanil is a fentanyl derivative, it is believed that the response surface for propofol and remifentanil may actually model propofol-opioid pharmacodynamic interactions by using different scaling factors for each opioid.

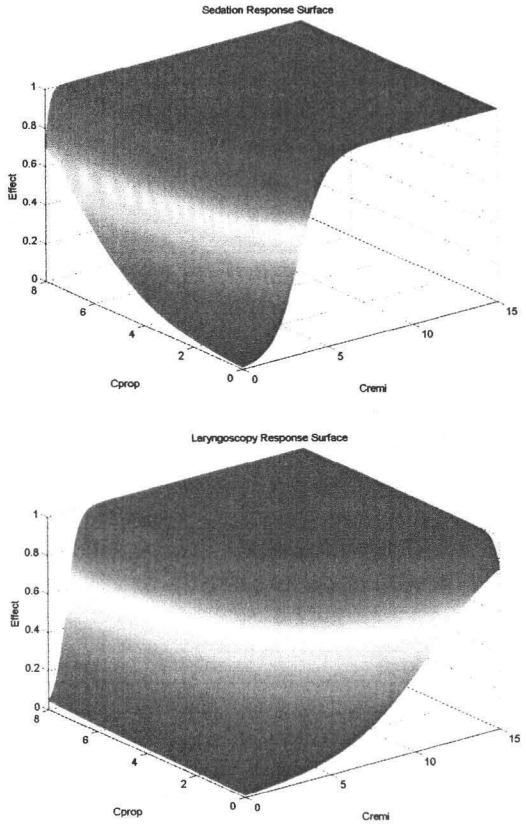

Figure 4. Response surfaces for suppressing a response to surrogate stimuli (the sedation or OAA/S surface is above, the surface for laryngoscopy below). Note that much higher levels of drug are needed to provide sufficient analgesia for laryngoscopy compared to simply sedating a patient. Also note the synergism between propofol and remifentanil.

Methods

Data Collection

With institutional review board approval from the University Hospital and informed consent, we studied 16 patients (6 males and 10 females) ages 25 to 64 scheduled for abdominal laparoscopic surgery under total intravenous anesthesia. 13 patients received midazolam (1.5 mg) as a sedative before entering the operating room (OR). The infusion rates of propofol and of remifentanil were digitally acquired. Drug boluses were recorded by hand. Patient hemodynamics (non-invasive blood pressure and heart rate) and bispectral index (BIS) were also acquired digitally.

The times at loss of consciousness (LOC) and recovery of consciousness (ROC) were recorded. The adequacy or inadequacy of the anesthetic (indicated by movement or a 20% increase in baseline heart rate) was observed at selected milestones of the surgery (i.e. laryngoscopy and intubation, skin incision, trocar placement, intra-abdominal manipulation, wound closure, and skin closure). To ensure that a rise in heart rate was indicative of a new painful stimulus, the "baseline heart rate" was the average heart rate over the past 10-15 minutes.

At the end of surgery, the patient was followed into the post-anesthetic care unit (PACU). The patient's alertness was scored using the observer's assessment of awareness and sedation (OAA/S) once every 5 minutes for a total time of 30 minutes. (A subject in a deep sleep receives a score of 1 and a score of 5 indicates that the subject is alert.) During this time the patient rated the perceived pain (resulting from the surgery) on a scale of 0-10 (0 being absolutely no pain, 10 being the greatest pain ever experienced). The drug doses were also recorded.

Pharmacokinetic Validation

Before validating the pharmacodynamic models, we validated that the effect-site drug concentrations predicted by our program are accurate. Predictions from our computer program were compared to those of STANPUMP, another research pharmacokinetic simulator. (STANPUMP is freely available from the author, Steven L. Shafer, MD, Anesthesiology Service (112A), PAVAMC, 3801 Miranda Ave., Palo Alto, CA 94304.) We used the Marsh model, based on the Gepts model, for propofol, the Minto, Schnider model for remifentanil, and the Shafer, Varvel, Aziz, and Scott model for fentanyl.[6,7,8] Because the pharmacodynamic response surfaces are functions of propofol and remifentanil (an opioid), only the simulation scenarios shown in Table 1 were compared.

Table 1: Pharmacokinetic Simulation Scenarios for Prediction Comparison

Anesthetic	Administration	Dose
Propofol	Bolus	100 mg
Propofol	Infusion	100 μg /kg/min
Remifentanil	Bolus	250 μg
Remifentanil	Infusion	.20 μg /kg/min
Fentanyl	Bolus	200 μg

Pharmacodynamic Validation

To validate the pharmacodynamic models, responses (and non-responses) of patients to surgical stimuli were compared to the model predictions. To visualize relationships between responses to surgical stimuli versus surrogate measures, the predicted anesthetic concentrations at the surgical stimuli were plotted on the pharmacodynamic response surfaces from the volunteer study.

Results

Comparison between the pharmacokinetic simulations showed that our implementations of the kinetic models match published models. The results of the pharmacokinetic simulations for boluses are shown in Figure 5. The infusion simulations showed even fewer differences. The model parameters were loaded externally into STANPUMP, as the internal models were modifications of published models. It is also significant to note the challenge of modeling rapidly changing drug concentrations, such as occur when a bolus is administered.

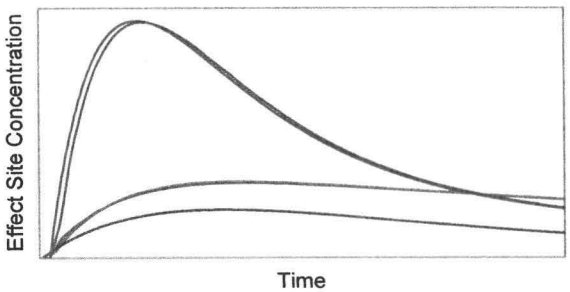

Figure 4. Comparisons between pharmacokinetic model implementations (our simulations and those of STANPUMP) for propofol (the two highest curves), fentanyl (the middle curves that are visually indistinguishable), and remifentanil (the lowest curves, also indistinguishable).

Figure 5 contains top-down or topographical views of the propofol-remifentanil pharmacodynamic response surfaces with EC50 and EC95 isoboles. Data points are the predicted concentration pairs of propofol and remifentanil at selected clinical events. X's represent responses while O's represent no response on the laryngoscopy and electrical tetany surfaces. Diamonds on the sedation surface represent patient recovery of consciousness. For laryngoscopy, 2 of 5 responses and 5 of 7 non-responses were accurately predicted by the model EC95 isobole. For skin incision, we observed no responses and 19 of 31 non-responses were accurately predicted by the model EC95 isobole. For recovery of consciousness, 6 of 11 wake-ups followed the model EC95 prediction EC95.

Discussion

The preliminary data set indicates that the electrical tetany and OAA/S response surfaces correlate to skin incision and recovery of consciousness, respectively. The lack of intraoperative responses presents a challenge for validating the response surfaces. It is hoped that data from the PACU will include patient responses to pain as the anesthetic effect-site concentrations decrease. Complete validation and the necessary adaptation of the PD models will require a larger sample size. To extend the models' clinical relevance, PD interactions between more anesthetics (IV and volatile) are needed.

References

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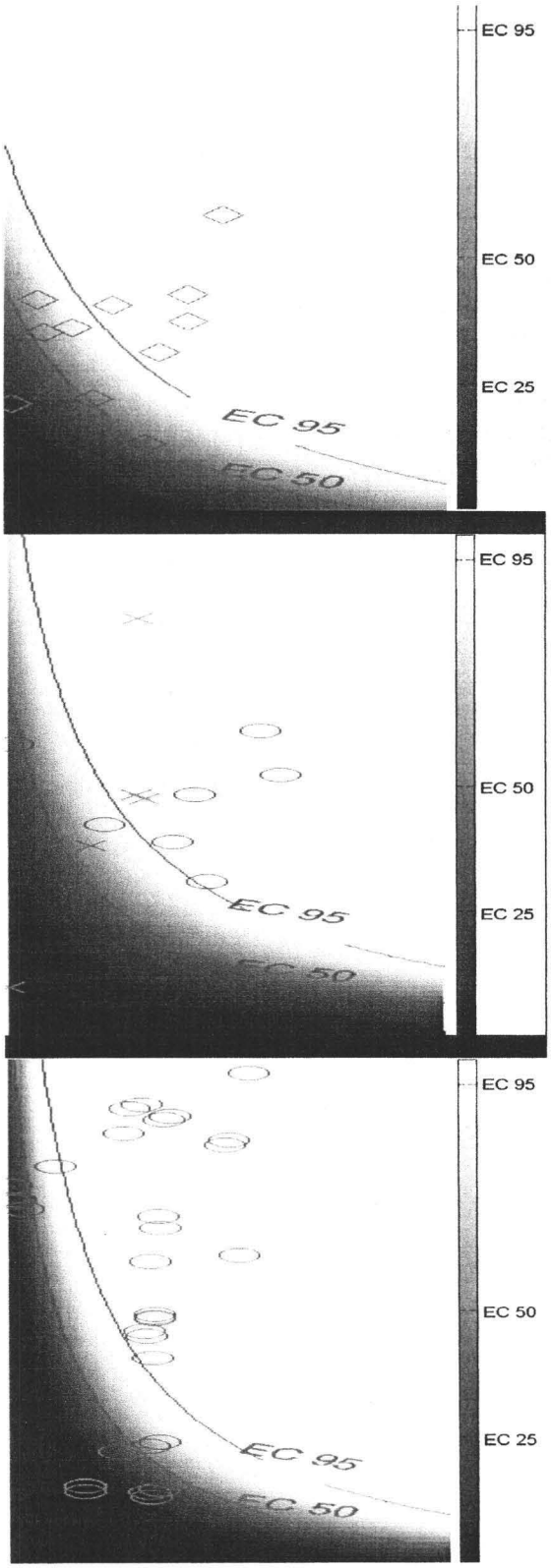

Figure 5. Response data plotted on response surfaces for sedation (top), laryngoscopy (middle), and electrical tetany (bottom).

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