Following Anesthetic Course in Pharmacological Space

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Procedural sedation, also known as conscious sedation is used for minimally invasive procedures performed outside the operating room where pain or surgical stimulation is not great enough to require general anesthesia. These cases include procedures such as catheter placement, endoscopy, certain plastic procedures, dental procedures, dermatological procedures and certain pulmonary procedures.

These are procedures where sedation and a light analgesic effect are needed but anesthetic depth requiring intubation and mechanical ventilation is avoided. Unfortunately, these sedations are not typically attended to by a fully trained anesthesiologist so the caregiver administering the drug does not have a very intuitive feel for the anesthetic depth of their patient. Accordingly, it is quite common for the caregiver to under dose leading to elevated heart rate and blood pressure or even regain of consciousness (which I myself experienced once when undergoing a dental implant procedure) or over dosing causing apnea. In the latter case the caregiver has to call an anesthetist to bag ventilate or intubate and mechanically ventilate the patient until spontaneous breathing is regained. Both situations are very undesirable.

To help prevent such dosing errors, Dwayne Westenskow has developed a simulation system to predict the synergistic effect for Propofol (Prop), a sedative, and Remifentanil (Remi), an opioid, when administered together. Remi and Prop are commonly administered together in varied amounts to get a desired sedation and pain relief in both general anesthesia as well as procedural sedation. This simulator uses pharmacokinetic models to determine effect site concentration from the drug
administrations, and then uses pharmacodynamic models to map these concentrations to a probabilistic drug effect surface. The effect of Prop and Remi together are so highly non-linear and synergistic that it’s easy to understand why caregivers less experienced with anesthetic drugs can easily over or under dose during procedural sedation. However, with the simulator described above, a close estimate of drug effect site concentration and remi/prop synergy can by calculated from the dosing regimen and displayed graphically. This can provide the caregiver an idea of anesthetic depth, which is difficult to assess from simple observation. Of greater value is the model’s ability to predict the future drug effect on-line so the caregiver can see what the anesthetic level will be over the next few minuets and take action before a critical event occurs.

As a validation of this model, we obtained a data set for eight subjects undergoing procedural sedation wherein the investigator started the subject on a specified dosing regimen of remi and prop and requested the subject to squeeze a ball about every 16 seconds. The time required for the subject to respond by squeezing the ball was recorded. We used the dosing regimen to model the effect site concentration of remi and prop at each data point and color-coded the data according to the response time. We plotted the data on a two dimensional plot with remi and prop effect site concentrations as the x and y-axis. The z-axis or third dimension of the plot is the population probability of response or no response to the selected stimulus surface. We selected the algometry surface. A population probability surface for algometry shows the probability of responding to the stimulus at a given effect site concentration of remi and prop for any member of the population. Thus, the x-axis and y-axis show remi and prop
concentrations and the z-axis is a scale from 0 to 1 or 0% to 100% indicating the probability of not responding to algometry.

Figure 1 is an example graph for one of the eight data sets. The two horizontal dark lines represent slices through the surface at 50% probability of non-response (EC\textsubscript{50} isobol) and 95% probability of non-response (EC\textsubscript{95} isobol). If a subject has an effect site concentrations of remi and prop that correspond to any point along the EC\textsubscript{50} isobol, we expect the subject to have a 50% probability of responding to algometry.

To make the figure printable in black and white, we replaced the color-coding of each data point with a simple solid black/open white scheme indicating response or non-response. Subjects that responded in less than 14 seconds by squeezing the ball were
marked as responders. In figure one we can follow the course of anesthetic starting at 0,0. We can see that this subject received a bolus of Remi followed by an infusion of Prop after the Remi nears its peak effect. Then the subject is maintained near the EC95 with infusions and small boluses. We can make two interesting observations from this data set. First, a high probability of non-response is reached and maintained for more than a minute before loss of response is observed. This can most likely be attributed to surgical stimulus. A subject’s ability to respond to verbal or other types of stimulus is highly dependent on the stimulus caused by the procedure at that moment. So a subject experiencing algometry in isolation would very likely not respond near the EC95. But with the added stimulus of the procedure, some stimulus threshold is more easily crossed and the surface is less reliable. The second interesting observation is that the subject does not start to respond again until the effect site concentration has almost reached zero probability of non-response or zero on the z-axis. It would be a stretch to attribute such lack of responsiveness entirely to lack of surgical stimulus, indicating that hysteresis of the drug effect causes a greatly shifted surface for return of response as compared to loss of response. These two observations are seen in all eight data sets.

This is a three-dimensional surface but typically it is given in a two dimensional graph with two curves corresponding to the EC50 and EC95. This does not illustrate the complete shape of the surface but indicates roughly the probability of non-response. Figures 2 through 9 show the eight data sets in a two dimensional form. Compare figure one with figure nine to see the difference in visualization between the two methods.
Note the great variability in drug sensitivity among the eight subjects. Some subjects are less sensitive, continuing to respond above the EC95 as in figure 3 or losing response below the EC50 as in figure 6.
Despite variability, the model does predict effect site concentrations between the EC50 and EC95 when loss of response was observed for most of the eight subjects, thus the data presented would be valuable to the care giver if viewed during the procedure in real time as a means of estimation anesthetic depth. To date, the simulator has the ability to indicate drug effect site concentration and the subject’s probability to responding to some stimulus. We have become interested in adding another level of assessment by using end tidal CO$_2$ and minute volume to predict and display an isobol line on the surface indicating the effect site concentrations of remi and prop which would result in the patient becoming apneic. In other words, the model currently shows if the patient is sedated enough. We hope to add the other boundary showing if the patient is too sedated for conscious sedation and likely to stop breathing.

Creating a surface describing ventilation or minute volume as a function of the two drug concentrations is more complex and prone to error than the simple response to stimuli surfaces because ventilatory drive is so heavily dependent on arterial CO$_2$, drug sensitivity and surgical stimulus. As anesthesia is induced, ventilatory drive decreases leading to decreased minute ventilation. This causes an elevation in arterial CO$_2$. The increased CO$_2$ increases ventilatory drive so the patient continues breathing. This cycle
holds unless the induction of anesthesia is too rapid, and the CO$_2$ cannot elevate fast enough or if anesthetic depth is sufficiently great such that elevated CO$_2$ no longer affects ventilatory drive. This interplay is further complicated because elevated CO$_2$ causes elevated heart rate, carrying the drug to the effect site (the brain in our case) more quickly causing accelerated drug effects. A population surface for ventilation would have to be determined for each level of arterial CO$_2$.

We are currently considering a more patient specific approach by measuring end tidal CO$_2$ and minute volume both before drug is administered and during the procedure then fitting the rough ventilation surface reported in literature to the patient’s actual values to give a more accurate estimate of when apnea may occur. This would be accomplished by applying a simple function reported in literature, which relates minute volume as a function of CO$_2$ for subjects without sedatives. This model would be shifted such that its predicted resting minute volume and CO$_2$ match that of the subject. The surface would be fit to pass through this point at the zero remi and prop conc. point on the 3-D surface. The second point that the surface would be forced to pass through would be the patient’s actual minute volume at the modeled concentration of remi and prop. Thus the surface would be shifted and tilted to fit the subject’s actual minute volume in real time giving a more accurate prediction of the danger of apnea. If this method proves successful, caregivers administering remi and prop in procedural sedation will be warned of a possible critical event before it happens and better determine the dosing necessary to maintain their patient at a safe level of sedation.