AN ANESTHESIA DISPLAY FOR A SPACE STATION: CLINICAL VALIDATION OF NEUROMUSCULAR BLOCKADE MODELS

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Abstract

An anesthesia drug display that shows the predicted effects of medication may be extremely useful on a space station and in situations where an inexperienced person could be performing experiments on animals or emergency treatments to fellow astronauts. Such a drug display shows drugs given and predicts their effects on the person or animal. In order for such a display to be useful, the predictions must be validated to ensure accuracy of and instill confidence in those who use the display. This study consists of validation of rocuronium which is a drug used for neuromuscular blockade (muscle relaxation). The effects of this drug have currently been studied on 12 patients. Qualitatively, the effects of this drug appear to be in line with the kinetic model predictions. Data will be gathered from more patients and will be statistically analyzed and compared with the model predictions for validation.

Introduction

On the space station, animals may be put to sleep for biology experiments such as dissections or small implant surgeries. Humans may also be anesthetized in the case of a painful accident. Astronauts come from all disciplines and rarely, if ever, are trained in anesthesiology. An anesthesia display such as the one developed in our lab (Fig. 1) could be extremely useful in such a situation. Either the drugs given can be automatically tracked or the astronauts could enter the information by hand, stating what drug was given at what time. The anesthesia drug display could then calculate in real time what the predicted effects of the drug are on the animal or astronaut.

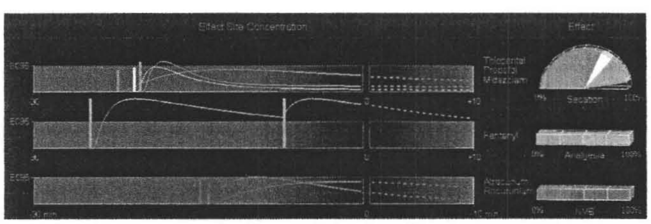

Figure 1. Anesthesia Drug Display Prototype. The bottom line shows an example of the muscle relaxants.

The drug display currently shows the administration and effects of three different drugs: measuring sedation, pain, and muscle relaxation. The y-axes of the graphs show the amount of drug, and the x-axes are time. The vertical lines show a bolus of the drug, and then the solid line is the predicted drug effect site concentration (from the model). The dotted lines show what the drug levels will be in the near future, allowing time for the anesthesiologist to better think ahead and adjust medications if necessary. On the far right of the display, the predicted clinical effect is shown.

During surgery or any kind of serious treatment anesthesia may be used for sedation (rendering the patient unconscious and unaware of their surroundings), analgesia (pain medication), or for neuromuscular blockade (muscle relaxation). The drug display shows this information in real time and may eventually adapt to specific patients due to age, weight, height, gender, and drug sensitivity levels. The plot on the left shows the drug concentrations predicted in the subject's body, while the plot on the right shows the predicted effect of the patient to the drug given. In the case of muscle relaxants, a commonly used measure of effect called Train-of-four (TOF) is displayed.

The purpose of relaxing a patient is to avoid unwanted muscular responses. One example of this is intubation[1]. As the anesthesiologist places a tube down the patient's throat and connects it to a ventilator, the patient may have a gag reflex. Another possible reaction would be contractions in the abdomen due to a surgical stimulus[1]. The doctor does not want a person's (or animal's) abdomen to contract while he has sensitive surgical instruments (i.e. a knife) in the area. Muscle relaxants (neuromuscular blocking agents) suppress reactions like this to allow easier care and management by healthcare professionals[2].

Monitoring of neuromuscular blockade and its effects is most often accomplished with train of four stimulation and measurement. TOF measurement consists of four short stimulations, which cause the adductor pollicis (thumb and index finger) to twitch four times[3]. As the muscle relaxant takes effect, the patient response reduces to three twitches, then two, one, and finally zero. At zero twitches the neuromuscular blockade is in full effect and the patient is very relaxed and muscles should not respond to a given stimuli. At four twitches the TOF ratio is used. This is a measure of the strength of the fourth twitch divided by the strength of the first twitch. Using this measure allows more fidelity in determining how close to normal a person is with respect to neuromuscular function. A ratio of 100 percent means that their neuromuscular function is normal and they have four full twitches. The lower the ratio, the more relaxed a person is and the weaker they feel and respond to a given stimulus.

The models used to predict patient reactions to the drug can be split into two categories: pharmacokinetic and pharmacodynamic[4]. Pharmacokinetic models are those that predict the concentration of the drug in the patient, and the pharmacodynamic models take this drug concentration and predict an effect on the patient at any given concentration.

The pharmacokinetic model used in this study is the Plaud two compartment model. The two compartments are the bloodstream and the effect site in the body. The model includes parameters which account for equilibration between these compartments. The drug display is the same implementation as Stanpump, a well known anesthesia modeling simulation

The pharmacodynamic model used this study is still being developed. The first step to this development is using the Hill equation to calculate the strength of the first twitch (from the effect site drug concentration, at the hand)[3]. From this information the train of four count and then ratio may be calculated.

Methods

To date there have been 12 subjects, out of a total of 24 for the study. The patient population is a healthy set of laparoscopic patients (most are gall bladder removals and hernias). Data collected includes all drugs given to the patient, as well as vital signs such as blood pressure, heart rate, and any patient responses throughout the surgery. The neuromuscular data consists of train-of-four monitoring with the Datex-Ohmeda Electrosensor and NMT module.

During preparation for surgery in the operating room, the sensor is placed on the patient's thumb and index finger and taped in place. A temperature sensor is placed on the palm, and the arm is then wiped with an alcohol pad to remove oil from the skin and allow better electrode performance. As soon as the patient loses consciousness, the electrodes are placed on the arm at the ulnar nerve (a mini stimulator is used to ensure that the nerve is found and the electrodes are placed optimally). Figure 2 shows the electrode and sensor placement. The monitor calibrates the sensor by finding the supramaximal current with 100 μsec pulses. Train-of-four measurements are taken at 20-second intervals throughout the case. Before the patient regains consciousness, the sensor and electrodes are taken off of the patient.

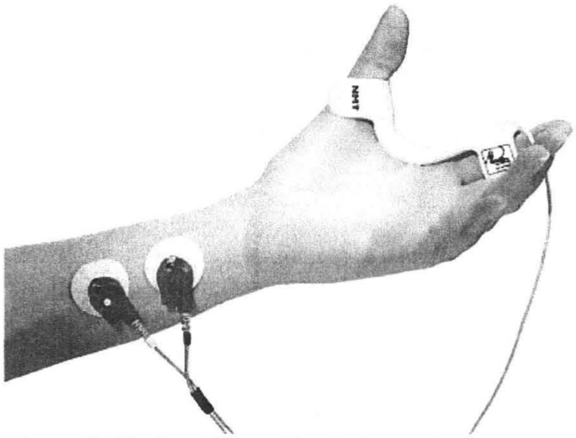
Figure 2. Train of four stimulator and sensor. (Image source www.datex-ohmeda.com.)

Throughout the surgery data is collected with a laptop through Rugloop, which is a program that collects all data from the Datex monitor.

Preliminary Results and Conclusions

The following graphs are of one patient's neuromuscular data throughout a surgery. This specific set of graphs is comparable to the others in the dataset. Currently the analysis has taken into consideration the t1 ratio, TOF count, and TOF ratio.

The first important graph (Figure 3) shows the times that the drugs were administered. In this case there was a bolus of rocuronium at the beginning of the case (the spike at about 700 seconds). The spike at the end of the case is due to administration of a reversal agent, neostygmine.

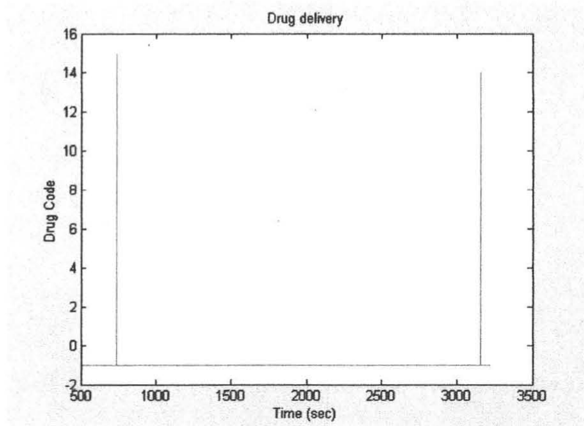

Figure 3. Drug administration. The first spike is due to the muscle relaxant, rocuronium. The second spike is the reversal agent, neostygmine.

The t1 ratio shows the strength of the first twitch to the baseline/calibrated value. This measure shows the quick onset of muscle relaxation effects, as soon as rocuronium was delivered. It is clear that before rocuronium administration, the twitch was at or near 100% of its original value. There is a slight delay after administration but then this twitch quickly disappears (Figure 4). The slow return of a full strength twitch as the effects of the drug wear off is also apparent.

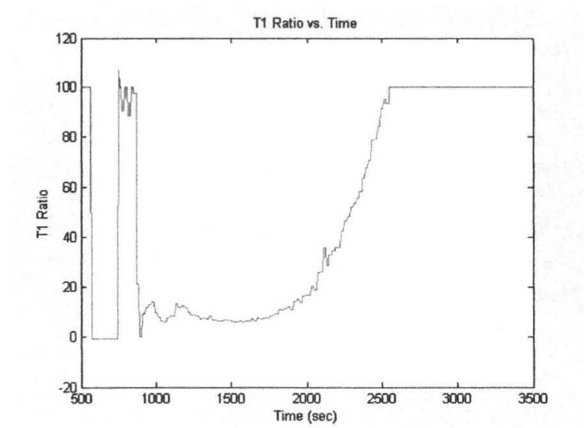

Figure 4. The t1 ratio is shown above. This is the quantitative value showing the strength of the first twitch. Note that it declines rapidly and then recovers more slowly.

The pharmacokinetic model used to predict drug concentrations is the Plaud model, and the drug display has been tested against the Stanpump implementation for accuracy. Figure 5 shows the pharmacokinetics predicted throughout the case. These drug concentration levels are what is shown on the drug display.

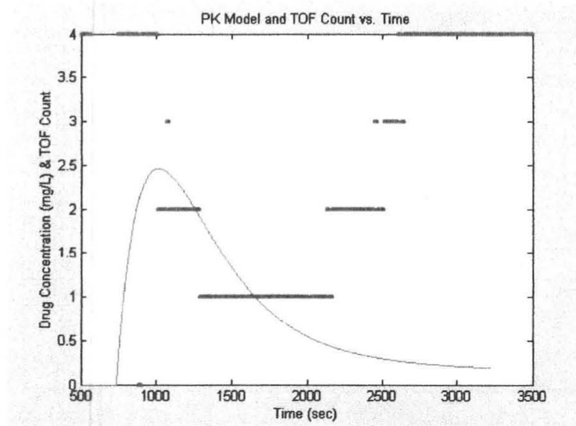

Figure 5. Effect site drug concentration calculated with the Plaud pharmacokinetic model. Train of four count is also shown. Note that as the drug levels are high, the number of twitches decrease, and that there is a slight delay in this process.

At the beginning of the surgery, the patient had 4 twitches showing that their neuromuscular function is normal. As predicted drug levels increase, there is a slight delay but the twitch count decreases as the patient's reflexes decrease. The twitch count rises as drug concentration levels decline and the neuromuscular function returns to normal.

At the point where there are four twitches, the train of four ratio is used. This is a measure of the strength of the fourth twitch divided by the strength of the first twitch. As the muscle relaxant begins to effect the patient, this ratio decreases. The ratio increases to 100% when neuromuscular function returns to normal. Figure 6 shows the results of this measurement.

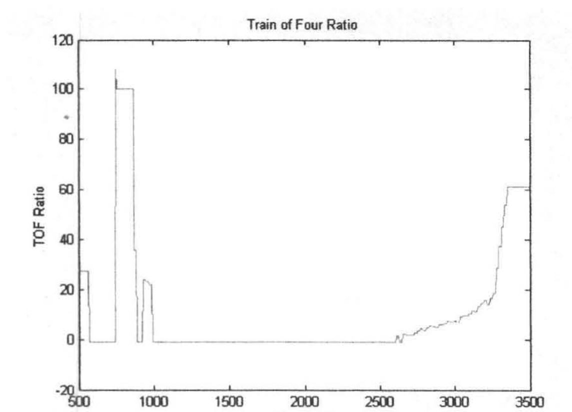

Figure 6. TOF ratio. Zeros are when the TOF count was less than four. Note that this ratio drops off sharply and rises back up slowly.

There is a slight delay after rocuronium administration, but the ratio does decline rapidly as the muscles become relaxed. The ratio slowly increases toward normal function until the reversal agent is given. This information is consistent with the characteristics of rocuronium[1]. Once this occurs the slope sharply increases as neuromuscular function quickly returns to normal. In this case the data ends at 60% recovery due to shutting off the equipment. (This maximizes patient comfort as they wake up from the anesthesia).

A qualitative look at these results are promising for drug model validation. Some work will be done to look at the pharmacodynamic model of predicted TOF count vs. actual TOF count. Statistical methods of analyzing the data are being explored and will be performed soon.

Future Work

Once the drug models are validated, the display will be tested in the operating room to show that this is an extremely valuable tool. Models may also be adapted according to patient parameters such as height, weight, and age. This will make the display patient specific and therefore more accurate and useful.

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