A PRELIMINARY ASSESSMENT OF RESPONSE SURFACE MODEL PREDICTIONS FOR OPIOID TOLERANCE

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Introduction: Clinical observations, along with several supporting studies, suggest that patients who repeatedly consume opioids often require higher than normal levels of analgesia during and after surgery. Response surface models have been effective in predicting effects of sedation, analgesia and neuromuscular blockade during and after administration of anesthesia, but it is unclear if prior opioid usage would alter these predictions. We hypothesized that a response surface model to predict adequacy of analgesia would be associated with higher probabilities of loss of response to painful stimuli for opioid-consuming patients than opioid-naive patients.

Methods: We studied ten patients who had a substantial history of opioid use and nine who were classified as opioid-naive. Patients were selected from a retrospective review of laparoscopic appendectomies at the University of Utah over a period of two years. For each anesthetic, time-stamped records of administered inhalants, opioids, and neuromuscular blockers were gathered from the peri-operative anesthesia monitoring database (Centricity, GE Healthcare, Milwaukee WI). The drug doses, pharmacokinetic simulation and a response surface model were used to calculate the probabilities of no response (NR) to pressure algometry, a surrogate for adequacy of post-operative analgesia, over a period of ten minutes centered around tracheal extubation. Model predictions of patients with opioid history were visually compared to a baseline set of model predictions derived from each patient in the opioid-naive group. Additionally, a 2-tailed student’s T-test was used to compare the probabilities between opioid history and opioid naive groups at the time of extubation.

Results: At extubation, the model predictions for probability of no response to pressure algometry was 55.3%± 29.5 for the opioid-naive group and 72.9%± 23.6 for the group with opioid history (p>0.05), an insignificant increase for the group with opioid history. However, a visual inspection of the data (Figure 1) shows a cluster of opioid-consuming patients initially at the top of the graph. Eight of ten patients in the opioid-consuming group were titrated beyond a 70% probability in the minutes leading up to and during tracheal extubation, as opposed to three of nine patients in the opioid-naive group. Progressing past extubation, though, that disparity disappeared as roughly half of the patients in each group were held above the 70% level of analgesia. It is interesting to note that the only patient with a reported history of opioid abuse remained at high probabilities through the time period (95.958%±0.3).
Conclusions: With this preliminary data analysis, we are unable to conclude whether or not the pharmacokinetic-pharmacodynamic simulations are able to discriminate between patients that have a history of opioid use and those that do not. Because the visual inspection of the data shows some potential differences, additional data analysis, include mixed-effects modeling, is planned. If the analyzed results appear promising, we propose to include additional patients in our retrospective study, with the sample size determined from a power-analysis of this data set. We also plan to study additional response surface models with different and perhaps more appropriate pharmacodynamic endpoints, including respiratory compromise.

References:

Figure 1: The response surface model predictions for analgesia (probability of no response to post-operative pain) 5 min before and after tracheal extubation. Dashed black lines represent model predictions for opioid-naïve patients while solid blue lines depict patients in the opioid-consuming group.