A Novel Dosing Algorithm for High-Dose Propofol Administration for the Treatment of Depression

Presenting Author: Carter Lybbert, B.Sc., University of Utah
Co-Authors: Brian J. Mickey, MD, Ph.D, Kai Kuck, Ph.D., Scott C. Tadler, MD, Jason Huang, M.S., University of Utah

Introduction: Recent evidence suggests that high doses of anesthetics produce significant and durable antidepressant effects in those with drug-resistant depression, comparable to the positive effects of electroconvulsive therapy (ECT) [1][2]. Maintaining a 70-90% EEG burst suppression ratio (BSR) for ~15 minutes seems to yield the strongest antidepressant effects [2]. To date, no dosing guidelines or algorithms have been published by any group to aid anesthesiologists in achieving 15 minutes of 70-90% burst suppression with the administration of these drugs in human subjects.

We have developed a novel dosing recommendation algorithm that gives anesthesiologists an estimate of the levels of Propofol that they will need to administer to a patient to achieve 70-90% BSR for 12-15 minutes. This algorithm is based upon the Eleveld pharmacokinetic/pharmacodynamic (PK/PD) model of Propofol [3], with some adjustments. The objective of this study was to assess how well these dosing algorithms perform in giving recommendations that achieve the desired BSR in participants.

Methods: Following IRB approval and informed consent, each of 13 participants (69% female, 29-51 years old, 52-119 kg) underwent 3-6 treatments of high doses of Propofol. This analysis represents a retrospective look at these treatments. Two separate algorithms were used for dosing the first treatment and all subsequent treatments. For the first treatment of every participant, mean values for Ke0, Hill and EC50 from all treatments, except for those of the particular subject for whom the dosing recommendation was being made, were used to estimate the PK/PD behavior of the drug. For subsequent treatments, Ke0, Hill and EC50 parameters were estimated based on a log-log linear regression of the second-by-second observed BSR of the most recent past treatment to the effect site concentration predicted by the Eleveld model for that treatment. Based on these model parameters, an iterative approach was then used to find an estimated bolus and infusion rate for Propofol that would achieve a 70-90% BSR target range for 12-15 minutes for that participant.

To assess the effectiveness of these a priori dosing recommendations, they were compared to retrospectively determined ideal dosing levels. These ideal dosing levels considered were the actual administered bolus size and mean infusion rate that the anesthesiologist administered during the treatment.

Results: We found that there was a MdAPE of 21.6% with an interquartile range of 38.8% between the recommended prospective and the retrospective ideal infusion rate and a MdAPE of 18.2% with a 35.1% interquartile range between the recommended and ideal bolus.

Discussion: The error of prospective dosing recommendations before treatments when compared to ideal dosing levels made based on retrospective data collected after the treatment is considerable. However, the error lies well within the 20% to 30% range that is considered acceptable for MdAPE of PK models alone [4]. Limitations of our findings include that the findings result from a relatively small sample size of participants and represent a secondary analysis of data from a study that was not primarily designed as a PK/PD modeling study.

Conclusion: This dosing model represents an imperfect but useful first prototype for dosing Propofol during high-dose anesthetic treatments for depression.

References:

[1] *J ECT*, vol. 24, no. 2, p. 5, 2008.
[2] *Current Opinion in Anaesthesiology*, vol. 31, no. 4, pp. 439–445, Aug. 2018.
[3] *British Journal of Anaesthesia*, vol. 120, no. 5, pp. 942–959, May 2018.
[4] *British Journal of Anaesthesia*, vol. 119, no. 5, pp. 918–927, Nov. 2017.