Predicting Propofol-Induced Burst Suppression Using an Individualized Model-Based Approach Over Repeated Treatments

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***Abstract* – Our group is investigating the antidepressant effects of high-dose propofol, but dosing propofol to induce standardized changes in EEG activity ("burst suppression") is challenging due to limited knowledge of each subject's pharmacokinetics (PK) and pharmacodynamics (PD). In this paper, we approximated PK-PD models for propofol-induced burst suppression (PIBS), based on multiple subjects over repeated treatments. We then applied these models to predict BSR in each subject's repeated treatment, then evaluate their predictive performances. We hypothesized that predicting BSR from a greater number of previous treatments would improve performance, but our current results are not conclusive enough to validate the hypothesis. We discuss our contributions, limitations, and adjustments for future studies.**

I. CLINICAL BACKGROUND

An estimated 17.3 million US adults suffered a depressive episode in 2017 [1]. One third of patients do not respond to first-line antidepressants [2] and are left with limited treatment options. While electroconvulsive therapy (ECT) has been proven an effective option for severely depressed patients [3], the induced-seizure and patients' perceptions of ECT's side effects may deter many from considering it as a treatment option [4]. Novel pharmacological alternatives are being investigated, which include common intravenous anesthetics, for example nitrous oxide, ketamine, isoflurane, and propofol.

Our group is investigating the antidepressant effects of propofol [5], an intravenous hypnotic typically used to induce and maintain anesthesia. By suppressing cortical activity via GABA-ergic mechanisms [6] in the brain, propofol can directly suppress EEG activity [7]. At higher doses, propofol can also significantly reduce cerebral blood flow and metabolic rate of oxygen, which has been used to provide neuroprotection during neurosurgery [8], and relieve intracranial hypertension [9] and refractory status epilepticus [10].

Propofol can induce EEG patterns ("burst suppression") that are similar to those seen with ECT, but without the induced seizure. Our group has reported preliminary indications of propofol's antidepressant effects [11]. The burst suppression EEG pattern of alternating periods of activity and quiescence alone may be sufficient for antidepressant efficacy [12]. However, accurately controlling propofol-induced burst suppression (PIBS) and administering a standardized effect remains a challenge.

II. TECHNICAL BACKGROUND

Proper dosing of propofol to induce a standardized level of burst suppression, across different subjects and over repeated treatments, must consider the variabilities in pharmacokinetics (PK, how drug distributes throughout body) and pharmacodynamics (PD, how drug affects body). Neither can be intraoperatively validated nor practically estimated. Published PK-PD models could alternatively be used to help predict BSR, but they are not fully individualized to each subject and still result in inaccuracies when predicting the concentrations of propofol in the body [13].

Quantifying Burst Suppression

Burst suppression is commonly quantified by the burst suppression ratio (BSR): the relative time that the subject's EEG is suppressed over a given epoch (e.g. 60 sec). Burst suppression probability (BSP) has also been

proposed to quantify burst suppression with a statistical basis [14].

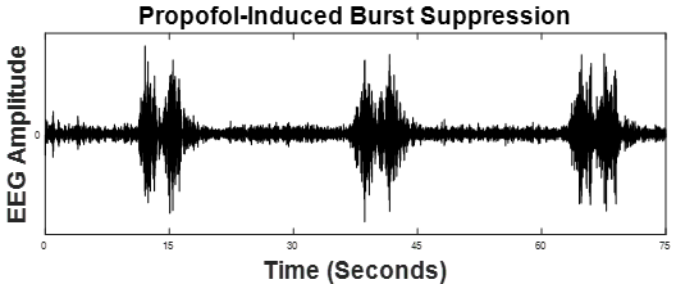

Figure 1. EEG recording of propofol-induced burst suppression, which includes alternating periods of "bursts" and quiescence. Propofol suppresses the EEG, while BSR quantifies the relative time (percentage) of suppressed EEG activity.

Pharmacokinetics

The amount of propofol administered and three compartment PK models (e.g. Schnider, Marsh, and Minto [15]) are typically used to estimate patients' accumulation and decay of propofol concentration over time. They include a central compartment along with a fast- and a slow compartment. They account for factors such as sex, height, age, and weight which affect the rate constants between the compartments.

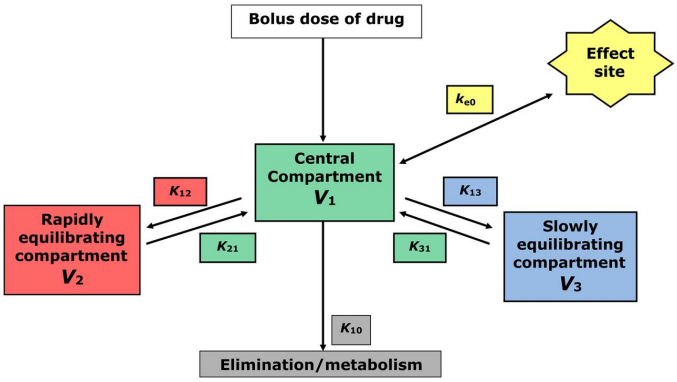

Figure 2. Layout of a classic three compartment PK model, which includes multiple rate constants. Drug is administered to the central compartment; then transferred between the rapid peripheral, slow peripheral, and effect site compartments; and eventually eliminated from the system. Source: Al-Rifai et al. BJA Education 16(3), 2016

Given that there is generally a delay between changes in the central compartment's concentration of propofol and changes in observed response (e.g. BSR), a fourth compartment is often included to represent the "effect site" or "biophase" with its own rate constant (k_{e0}) [16]. Each model's k_{e0} depends on the underlying PK model and method (e.g., arterial vs. venous blood sampling), as well as the measured effect [17]. To our knowledge, a k_{e0} or PK-PD model specific to PIBS and BSR has not been reported before. Understanding biophase is essential to modeling the relationships between dose and effect-site concentration, and the relationship between the effect-site concentration and the observed response (PD).

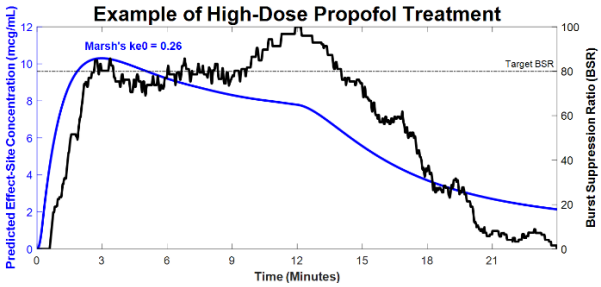

Figure 3. BSR (black) and predicted effect-site concentration (pCe, blue) during a high-dose propofol treatment. BSR generally correlates with administration of propofol and accumulation of pCe, but the relationship is inexact and nonlinear. The PK parameters used (Marsh model) have not been clinically validated for BSR.

Pharmacodynamics

Pharmacodynamic models for propofol are generally modeled through a sigmoidal Hill curve [18], which reflect a lower threshold to observe the effect and saturation of the effect at higher concentrations, similar to how biochemical receptors behave [19]. Our study's fitted-PD models specifically relate the predicted effect-site concentration (pCe(t), mcg/mL) to the observed burst suppression ratio (BSR) for each high-dose propofol treatment.

Hill Equation: $$pBSR = \frac{[pCe]^{Hill}}{EC_{50}{}^{Hill} + [pCe]^{Hill}}$$

pBSR represents the model's predicted BSR. The Hill coefficient characterizes the general steepness of the PD response curve. The EC50 parameter defines the pCe associated with 50% BSR.

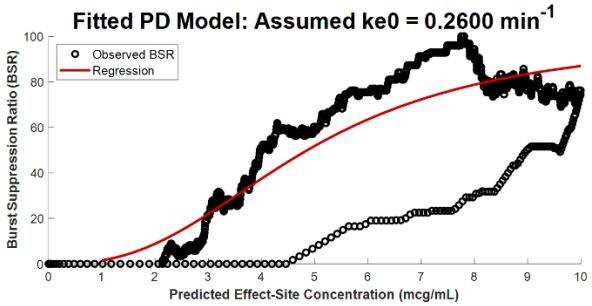

Figure 4. pCe (same from Figure 3) plotted directly against the observed BSR (black). Hysteresis has not yet been resolved.

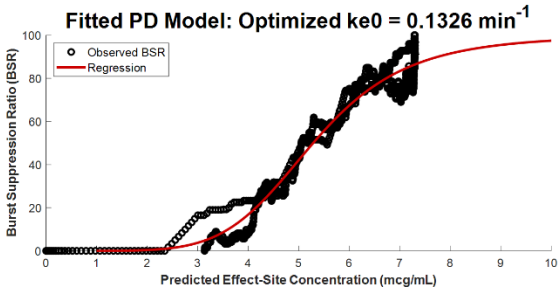

Figure 5. Relationship between pCe vs BSR (black) improved by optimizing the ke0 to minimize the regression's root mean square error (RMSE) and maximize fit to the Hill curve (red).

Model-Based Predictions

Beyond analyzing each high-dose propofol treatment and individualizing the fit of each PK-PD model, our group is interested in the model's application and utility in predicting the observed BSR over repeated treatments, for example to guide or control propofol dosing. However, we first need to quantify the predictive performance of these model-based predictions before implementation.

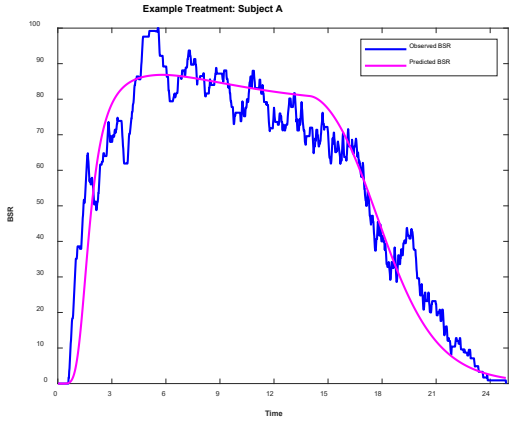

Figure 6. Observed BSR (blue) compared with the Predicted BSR (magenta), which is based on an individualized PK(predicted)-PD model from the previous treatment.

III. OBJECTIVES

Despite the challenges in predicting and controlling BSR, we believe that dosing can be individualized by inferring PK-PD parameters from previous treatments. In this paper, our objectives are to 1) approximate and optimize a PK-PD model for each high-dose propofol treatment and then 2) apply models to predict BSR in future treatments and evaluate their performances.

We hypothesize that predicting BSR from a greater number of previous treatments and models will improve the accuracy of predicting BSR.

IV. METHODS

We conducted a post hoc study of an ongoing randomized-controlled trial (NCT: NCT03684447 on *ClinicalTrials.gov*) at the University of Utah. We analyzed the high-dose propofol treatments, in which clinicians target a BSR of 80% ± 10% for 15 min. Propofol was the only hypnotic that was administered. We fitted and individualized PK-PD models for propofol-induced burst suppression, then analyzed how the models performed predicting BSR in future PIBS treatments.

Data Collection

Following IRB approval and informed consent, each of five patients (3:2 female:male, 33-51 yo, BMI 18.3-33.9 kg/m^2) underwent 4 to 8 PIBS treatments within a 3-week period each. For each treatment, we recorded the administered boluses and infusion rates for propofol, along with the BSR(t) from a BIS™ Vista Monitor (Medtronic, Dublin, Ireland).

Demographic Parameters					
Subject	Sex	Height (cm)	Age (yr)	Weight (kg)	n (1)
A	M	183	34	92	5
B	M	175	37	104	8
C	F	187	51	69	6
D	F	173	40	81	6
E	F	170	51	67	8

Table 1. Summary of the subjects' demographic parameters, along with the number of treatments (n) analyzed in this paper.

PK-PD Modeling

For each treatment, we derived pCe(t) (concentration domain) from the recorded administrations of propofol (dose domain). We used each subject's demographic parameters (sex, height, age, and weight) to approximate their pharmacokinetics via Eleveld's PK model [17], then calculated pCe(t) (concentration) using Shafer's simple pocket calculator approach [20].

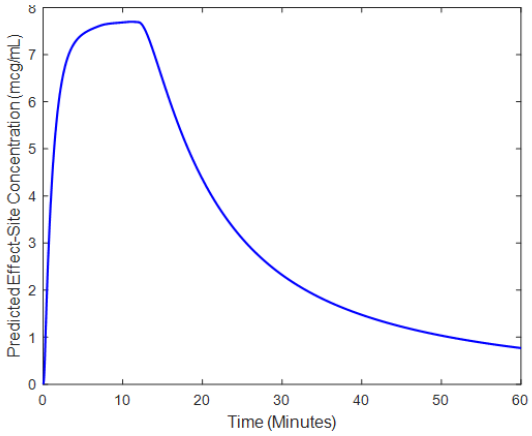

Figure 7. A typical example of how pCe(t) changes during a high-dose propofol treatment, which includes an initial bolus and base infusion.

We then related pCe(t) to BSR(t) for each treatment by first optimizing ke0 to maximizing the relationship's fit to the Hill Equation. Specifically, we used an iterative method to test ke0 between 0.80 and 2.00 min^{-1} and minimized the regression's root mean squared error (RMSE). After optimizing ke0, the regression for the Hill curve provided the corresponding Hill and EC50 parameters for each treatment.

Predicting BSR from Previous Treatment(s)

For each subject, after their first treatment, we compared each of following treatment's BSR(t) with the pBSR(t), which was based upon the individualized PK-PD model(s) from previous treatment(s). For each treatment after the second treatment, pBSR(t) was determined using two methods: the "Prior Treatment" approach (PTA) and the "Rolling Average" approach (RAA).

Prior Treatment Approach: For each repeated treatment, pCe(t) was derived from the original recordings of administered propofol, by applying the Eleveld PK model and the optimized ke0 from the previous treatment. pBSR(t) was then derived from pCe(t) using the Hill equation and parameters (Hill coefficient and EC50) from the immediately preceding treatment.

Rolling Average Approach: For each repeated treatment, pCe(t) was derived from the original recordings of administered propofol, by applying the Eleveld PK model and taking the median of the optimized ke0s from all of the previous treatments of that particular patient. pBSR(t) was then derived from pCe(t) using the Hill equation and median of the parameters (Hill coefficient and EC50) from all of the previous treatments.

Analysis

For each repeated treatment, we quantified each approach's performance by measuring the median percentage error (MdPE), median absolute percentage error (MdAPE), median magnitude error (MdME), median absolute magnitude error (MdAME), and *Controlled*—percentage of treatment time within ± 5% BSR error [21]. Percentage error (PE) was defined as $(BSR_{predicted} - BSR_{observed})/BSR_{observed}$. ME was defined as $(BSR_{predicted} - BSR_{observed})$.

We compiled and compared the performances between the two BSR-prediction approaches across all five subjects and their repeated treatments. For each subject, the second treatments were omitted in the comparison, because both approaches' pBSR(t) are derived solely from the first treatment's individualized model and thus equivalent.

V. RESULTS

For each subject and each of their repeated treatments, we optimized and recorded ke0, along with Hill and EC50. We characterized each subject's inter-treatment distribution for the three parameters in Table 2, which offers preliminary insight into intra-subject PK/PD variability.

PK(predicted)-PD Modeling						
Param.	**ke0 (min^{-1})**		**Hill**		**EC50 (mcg/mL)**	
Subject	**Mean**	**CV**	**Mean**	**CV**	**Mean**	**CV**
A	0.11	17%	6.4	46%	5.4	8%
B	0.14	53%	12.4	48%	4.3	37%
C	0.11	57%	7.2	49%	5.9	42%
D	0.11	37%	6.1	77%	6.5	23%
E	0.11	20%	8.8	45%	4.4	13%

Table 2. Summary of each subject's optimized model parameters and insight into their inter-treatment variabilities. Distribution characterized by the mean and log-normal coefficients of variations (CV).

For each subject and across their repeated treatments, the performances for both predicted-BSR approaches are summarized in Tables 3 and 4. Between

different subjects, the predictive performance of each approach also differed.

Prior Treatment Approach (PTA)					
Subject	MdPE	MdAPE	MdME	MdAME	Controlled
A	-2.3%	9.0%	-0.8%	4.1%	58.5%
B	-9.5%	24.4%	-2.1%	9.0%	35.8%
C	-13%	46.6%	-3.1%	18.6%	19.3%
D	0.0%	24.4%	-0.1%	14.5%	26.4%
E	1.0%	11.8%	0.4%	6.6%	39.7%

Table 3. Predictive performance for Prior Treatment Approach.

Rolling Average Approach (RAA)					
Subject	MdPE	MdAPE	MdME	MdAME	Controlled
A	-2.1%	9.9%	-0.7	4.7%	51.9%
B	30.7%	50.8%	4.8%	9.0%	35.6%
C	14.0%	44.4%	4.2%	13.3%	25.5%
D	1.7%	14.3%	0.5%	6.8%	35.9%
E	2.6%	10.3%	1.7%	4.3%	55.8%

Table 4. Predictive performance for Rolling Average Approach.

Table 5 shows the median performance across all 23 repeated treatments for each metric. Across treatments and compared to the Prior Treatment Approach (PTA), the Rolling Average Approach (RAA) improved the Controlled metric by 11.7 percentage points. While RAA increased the median error (MdPe, MdME), RAA decreased the absolute error compared to PTA.

Compiled BSR-Prediction Performance					
Method	MdPE	MdAPE	MdME	MdAME	Controlled
PTA	-2.2%	18.1%	-0.8%	8.0%	35.8%
RAA	2.6%	14.3%	1.3%	5.5%	47.5%
Δ	+4.8%	-3.8%	+2.1%	-2.5%	+11.7%

Table 5. Compiled performances for the Prior Treatment Approach (PTA) and Rolling Average Approach (RAA), then differences (Δ) in performances summarized in the bottom row. Results that support hypothesis are colored in green.

VI. DISCUSSION

In this study individualized PK-PD model parameters were determined for PIBS, based on multiple subjects and across repeated treatments. Our results offer preliminary insight into inter- and intra-subject PK/PD variabilities, which may impact the performance in predicting BSR. Inter- and intra-subject variabilities in model parameters, along with predictive performance, may be confounded by demographic and clinical factors.

Compared to PTA, RAA seems to demonstrate slightly better performance in predicting BSR, based on the Controlled and absolute performance metrics – but slightly worse performance based on the non-absolute metrics. The differences do not reach statistical significance (likely because of a too small sample size) and do not allow conclusions about the hypothesis. Additionally, the experiment was not designed primarily as a pharmacokinetic or -dynamic study. RAA's compiled MdAPE (14.3%) to predict BSR was considerably larger than a PD model that predicted BIS with an MdAPE of 4.85% [22].

Future studies may be warranted and should target the PK-PD aspects in their experimental design and pursue a larger sample size. Furthermore, different approaches to predict BSR beyond PTA and RAA could also be considered to test the hypothesis. This includes how model parameters are derived from previous treatment(s), and ways to further optimize ke0 and other PK parameters to improve the model's fit.

VII. CONCLUSION

Despite the challenges in dosing propofol, understanding each subject's unique PK/PD, and targeting a specific BSR for a specific duration, individualized models from previous treatments may be helpful in predicting and controlling BSR. Standardizing how PIBS is administered would reduce confounding in our group's clinical investigation, and may also be useful in clinical practice. Our study explored model performance across multiple treatments, but was not able to demonstrate whether predictive performance can be improved across repeated treatments of PIBS. Future studies and adjustments are necessary to fully explore our hypothesis.

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