Approximating the Inter- and Intra-Patient PK/PD of Propofol-Induced Burst Suppression

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Introduction: Our group is investigating the antidepressant effects of high-dose propofol[1] over repeated treatments. Propofol is titrated to induce a standardized depth and duration of burst suppression. Accurately controlling propofol-induced burst suppression (PIBS) is challenging due to limited knowledge of each patient's pharmacokinetics (PK) and pharmacodynamics (PD). Approximating a PK-PD model for PIBS, and optimizing the model over repeated treatments, could support individualized propofol dosing. In this exploratory study, we fitted model parameters to characterize the relationship between propofol administered, predicted effect-site concentration (pCe), and BSR. In particular, we sought to study the intra-patient (inter-treatment) and inter-patient distribution of model parameters.

Methods: Following IRB approval and informed consent, each of six patients (5:1 female:male, 33-51 yo, BMI 18.3-36.7 kg/m^2) underwent 4 to 8 treatments within 3 weeks, targeting a burst suppression ratio (BSR) of 80% ± 10% for 15 min. We recorded the administered boluses and infusion rates, along with the BSR(t) from a BIS™ Vista Monitor (Medtronic, Dublin, Ireland). The patients' demographics (sex, height, age, weight) were used to approximate PK parameters via the Eleveld Model[2], then used Euler's numeric approximation to calculate pCe(t). The ke0 parameter was iteratively determined for each treatment by maximizing the least squares fit (R^2) to the Hill Equation[3] between pCe(t) and the observed BSR(t). The regression also identified the corresponding Hill and EC50 parameters for each treatment. For each patient, we determined the inter-treatment mean and geometric coefficient of variation[4] (CV) for all three parameters. We also determined the overall mean and CV for all three parameters across all treatments in all patients.

Results:

	ke0 (min^{-1})		Hill		EC50 (mcg/mL)		Treatments	Demographics		
Patient	Mean	CV	Mean	CV	Mean	CV		Sex	Age (yr)	BMI (kg/m^2)
A	0.124	24%	5.50	15%	5.49	5%	**6**	M	33	27.6
B	0.189	23%	8.54	80%	7.63	10%	**4**	F	48	36.7
C	0.124	39%	9.13	94%	6.27	28%	**6**	F	49	18.3
D	0.128	35%	4.64	79%	6.81	24%	**6**	F	39	27
E	0.101	67%	7.85	39%	5.75	46%	**6**	F	51	20
F	0.121	22%	7.76	48%	4.40	13%	**8**	F	51	23.2
Overall	0.126	60%	7.39	90%	5.88	48%				

Discussion: Our study approximated the PK/PD characteristics of PIBS and offers preliminary insight into intra-patient PK/PD variability. Results provide an initial indication that PK/PD parameters might have less intra-patient variability than inter-patient variability. Our study is limited by its small sample size and by the experimental design, which did not primarily pursue a pharmacological characterization. The inter-patient variability of model parameters could also be confounded by demographic differences. If confirmed in a larger study, these results indicate PK/PD-inspired models could be optimized over repeated treatments, then further used to individualize high-dose propofol dosing and improve control of PIBS.

References:

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