PK/PD-Inspired Dosing Approach for Propofol-Induced Burst Suppression

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Background: High-dose propofol can induce similar EEG states as electroconvulsive therapy, and may also achieve similar antidepressant effects.[1] We are developing an individualized propofol-dosing approach to achieve specific EEG levels of propofol-induced burst suppression (PIBS). However, dosing propofol to accurately and reliably controlling the burst suppression ratio (BSR) is challenging, because of pharmacokinetic (PK) and pharmacodynamic (PD) uncertainties in each patient. We hypothesize that individualized dosing can be inferred from a subject's initial BSR response to a standard bolus and infusion rate. In this study, we evaluated the feasibility of adjusting the dosing based on the initial BSR response.

Methods: We simulated n = 1000 subjects (1:1 male:female, 150-200 cm, 20-50 years of age, 60-120 kg); published PK coefficients of variations[2]; and our own unpublished observed estimations of ke0 (mean ± SD of 0.136 ± 0.027 1/min), Hill coefficient (6.57 ± 1.70), and EC50 (7.40 ± 1.61 mcg/mL) which is the effect-site concentration when BSR = 50%. Each subject (the "actual subject") would receive a standard 200 mg bolus and 200 mcg/kg/min infusion of propofol. The initial BSR response during the first 180-seconds of PIBS, or up until reaching 50% BSR, was compared to responses of 1000 additionally simulated "reference subjects" of the same patient demographics, but their PK/PD parameters were further randomized. The median absolute percentage error was used to identify the reference subject, which initial BSR response was most similar. The reference subject's PK/PD parameters were used to determine the optimal adjustment in dosing (additional bolus and changes in infusion rate) to be applied 30-seconds after 50% BSR was achieved, or 210-seconds into treatment, whichever came first. This optimal adjustment was designed to achieve a BSR range of 70%-90% within a 10-minute simulated treatment. We evaluated the BSR response after applying the optimal adjustment to the actual subject. Specifically, we determined the BSR at 6-minutes after the initial bolus (BSR_6), the BSR averaged from 6 to 10 minutes ($BSR_{6\text{-}10}$), the time ($\tau_{70\%\ BSR}$) from the initial bolus to when a BSR of 70% was reached, and the duration ($\Delta t_{0\text{-}10}$) within the initial 10min, for which the BSR was within the target range, i.e. between 70%-90%.

Results:

		Target	Mean (SD)	Below Target (%)	Within Target (%)	Above Target (%)
BSR_6	**(%)**	70–90%	77.4 (10.3)	19.8	**71.3**	8.90
$BSR_{6\text{-}10}$	**(%)**	70–90%	75.9 (10.7)	24.9	**68.1**	7.00
$\tau_{70\%\ BSR}$	**minutes**	1.5–6 min	N/A	4.40	**80.6**	15.0*
$\Delta t_{0\text{-}10}$	**minutes**	>4 min	4.37 (2.55)	33.4	**66.6**	N/A

*14.2% of subjects did not surpass a BSR of 70% within the 10-minutes of treatment.

*These subjects' **$\tau_{70\%\ BSR}$** were not measured, but they were considered "Above Target."

Conclusions: Using only the initial BSR response, our simulation-derived dosing adjustments successfully induced target BSR levels in more than 2/3 of the 1,000 subjects. The dosing adjustments are simple to implement and do not require advanced or TCI pumps: adjustments consist of an additional bolus or infusion pause, and an infusion rate adjustment at a later time. Our dosing approach is imperfect, but is a first step towards individualized PIBS dosing. Additional control strategies must be developed in order to correct inadequate and excess levels of burst suppression, which still persist.

References:

[1] Mickey BJ, White AT, Arp AM, et al. Propofol for Treatment-Resistant Depression: A Pilot Study. *Int J Neuropsychopharmacol*. 2018;21(12):1079–1089.

[2] Schnider TW, Minto CF, Gambus PL, et al. The Influence of Method of Administration and Covariates on the Pharmacokinetics of Propofol in Adult Volunteers. *Anesthesiology* 1998;88(5):1170-1182.