An Adaptation of the Eleveld Pharmacokinetic-Pharmacodynamic Model for a Burst Suppression Endpoint

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Introduction

Repeated administration of high doses of certain anesthetics, such as propofol, to patients with treatment-resistant depression (TRD) has been shown to produce antidepressant effects in several small clinical trials [1]. These effects can be elicited when the patient's EEG burst-suppression ratio (BSR) is maintained at 70-90% for approximately 15 minutes in repeated treatments [1]. This deep-anesthesia domain lies beyond the range of current propofol pharmacokinetic/pharmacodynamic (PK/PD) models. In this study, we adapt the Eleveld PK/PD model for use at deep anesthesia levels with a BSR endpoint, with the goal of aiding anesthesiologists in estimating the dosage of propofol needed to achieve 70-90 % BSR for 12-15 minutes. We test the ability of the adapted model to predict BSR for these treatments in human subjects.

Methods

Twenty participants underwent 6-9 treatments of high doses of propofol (5-7 of which were included in this analysis) for a total of 115 treatments. To adapt the Eleveld model for this endpoint, we optimized the model PK parameter Ke0 and PD parameters γ and C_e50 for this endpoint. These parameters were then used in the adapted model to estimate second-by-second BSR for each treatment. For periods where BSR was >30 %, estimated BSR was compared with observed BSR for each treatment of each participant. Estimated vs observed treatment duration was also compared. Median absolute performance error (MdAPE) was calculated for each between estimated and observed BSR and treatment duration.

Results

MdAPE between the estimated and observed BSR (25^{th}-75^{th} percentile) was 6.63 (3.79-12.96) % points and 8.51 (4.32-16.74) % between the estimated and observed treatment duration. MdAPE for treatments 2-5 was lower than the MdAPE for treatment 1, for both BSR and treatment duration predictions. Only treatment 3 MdAPE of the treatment duration measurement was statistically significantly lower than treatment 1 ($p = 0.006$).

Discussion

Our results of MdAPE of 6.63 % points for predicting BSR cannot be directly compared to the Eleveld model performance reported by Vellinga *et al.* [2] for predicting BIS, because BSR and BIS are not identical measures of anesthetic depth. Once transformed to an equivalent BIS performance error via BIS = 50-(BSR/2), our MdAPE (25^{th}-75^{th} percentile) is 3.32 (1.90-6.48) BIS [3]. This is considerably lower than the MdAPE (25^{th}-75^{th} percentile) BIS error of the standard Eleveld model reported by Vellinga *et al.* of 7.88 (1.95-17.9) [2]. This better performance may be due to the adaptation of the model parameters for treatments 2-5 of each participant to reflect their individualized pharmacokinetics and pharmacodynamics. Even though the differences between treatments 2-5 and treatment 1 were not statistically significant, their difference nevertheless played a strong role in the excellent BSR estimation performance of our model.

Conclusion

We have shown that the Eleveld PK/PD model can be effectively adapted for use in a high-dose propofol treatment scenario to predict BSR as a PD endpoint. The model performs with excellent accuracy. This tool may be used to provide and improve dosing guidance for high-dose propofol treatments. Future work should further validate these results with larger and more diverse participant populations and with studies specifically designed for PK/PD analysis. Doing so will facilitate the successful implementation of high-dose anesthetic treatments for those suffering from TRD.

References

[1] Tadler SC, Mickey BJ (2018) Emerging evidence for antidepressant actions of anesthetic agents. Curr Opin Anaesthesiol 31(4):439-445.

[2] Vellinga R, Hannivoort LN, Introna M, Touw DJ, Absalom AR, Eleveld DJ, Struys MMRF (2021) Prospective clinical validation of the Eleveld propofol pharmacokinetic-pharmacodynamic model in general anaesthesia. Br J Anaesth 126(2):386-394.

[3] Bruhn J, Bouillon TW, Shafer SL (2000) Bispectral Index (BIS) and burst suppression: revealing a part of the BIS algorithm. J Clin Monit Comput 16(8):593–596.