Journal of Anesthesia (2024) 38:275–278
https://doi.org/10.1007/s00540-024-03312-w

SHORT COMMUNICATION

General purpose propofol target-controlled infusion using the marsh model with adjusted weight input

George Zhong[1] · Xiabing Xu[2]

Received: 25 November 2023 / Accepted: 18 January 2024 / Published online: 11 February 2024

Abstract

We report a simple method for adjusting the weight input of the Marsh target-controlled infusion (TCI) model such that the resulting infusion regime closely mimics the behaviour of the Eleveld model, thereby making the Marsh model more precise for patients at the extremes of age and body mass index. To assess the performance of our method, we simulated 2768 subjects with diverse combinations of age, weight, height and sex undergoing a hypothetical four-hour propofol TCI using both the Marsh model with our weight adjustment and the Eleveld model. The weight adjusted Marsh model produced infusion regimes and corresponding effect site concentrations closely mimicking that of the Eleveld model at all time points, with median and maximum absolute performance errors less than 8.1% and 20.3%, respectively, across the entire cohort. Our weight adjustment method is a simple and robust way of improving the precision of the Marsh model in patients at extremes of age and body mass index, until general purpose TCI models for propofol, such as the Eleveld model, become more widely available in commercial infusion pumps.

Keywords Propofol · Target-controlled infusion · Marsh · Eleveld

Introduction

The Marsh model is one of the most widely available pharmacokinetic models for propofol administration via commercial target-controlled infusion (TCI) pumps [1]. Although it demonstrates acceptable accuracy in healthy adults, its performance is known to significantly degrade for patients at the extremes of age and body mass index (BMI) due to its dependence on a single covariate, weight [2]. In contrast, the Eleveld model is a general purpose model that offers improved precision across diverse patient populations [3]. Validation studies have found that the precision of the Eleveld model is within 30% of the target plasma propofol concentration, surpassing that of the Marsh model [4]. Although the Eleveld model is now included in most new commercial infusion pumps, it remains unavailable in many regions around the world.

Previous studies have attempted to improve the precision of the Marsh model by devising formulas to adjust the input weight [5, 6]. However, these adjustments have all been limited to specific patient groups, such as obesity, and do not account for advanced age. In the present study, we propose a novel method of adjusting the Marsh input weight by mimicking the behaviour of the Eleveld model, such that the resulting infusion regime is general purpose and thus more applicable to diverse patient groups.

Methods

Our method for adjusting the Marsh input weight is summarized below. Technical details of the algorithm are included as Supplementary Materials.

1. Clinician enters patient age, weight, height, sex and the desired effect site concentration (Ce) target into our algorithm.
2. Use patient covariates to generate a "gold standard" Ce versus time profile with the Eleveld model in effect site targeting mode.

✉ George Zhong
drgzhong@gmail.com

[1] Department of Anaesthesia, Concord Repatriation General Hospital, Hospital Road, Concord, NSW 2139, Australia

[2] School of Electrical and Information Engineering, University of Sydney, Sydney, NSW, Australia

3. Generate a range of infusion regimes using the Marsh model in plasma targeting mode with different input weight and induction bolus combinations.
4. Quantify how well each generated Marsh infusion regime mimics the Eleveld regime from step 2 by calculating the sum of the squared differences in the respective Ce.
5. The combination of input weight and induction bolus resulting in a Marsh infusion regime that best matches the "gold standard" Eleveld profile represents the optimal adjusted weight input and induction regime, which our algorithm recommends to the clinician.

To assess the accuracy of our weight adjustment method relative to the Eleveld model, we simulated 2768 subjects with all possible combinations of age (20–90 years, in increments of 10 years), weight (40–200 kg, increments 10 kg), BMI (13–83 kg/m^2, increments 5 kg/m^2), height (100–210 cm) and sex (male or female) undergoing a hypothetical four-hour propofol TCI using MATLAB R2023a (MathWorks Inc, MA, USA). To more closely reflect real world clinical scenarios, the propofol concentration target was varied over the four-hour period such that Ce of 4 mcg/mL was targeted on induction, the Ce target was reduced to 2 mcg/mL at 60 min, increased to 3 mcg/mL at 120 min and reduced to 2 mcg/mL at 180 min (Fig. 1). TCI was performed using both the Eleveld model (with opioid as covariate) in effect site targeting mode and the Marsh model in plasma targeting mode using our adjusted weight input and induction using a plasma overshoot as per our calculated bolus. The Ce-time profile of the augmented Marsh model was derived by inputting the Marsh infusion regime into the Eleveld model. The deviation in Ce of the augmented Marsh model from that of the Eleveld model was quantified by the median (MDPE) and median absolute (MDAPE) performance errors calculated using Varvel's method [7]. As MDPE and MDAPE were originally conceived to quantify deviations between pharmacokinetic models and plasma, we also calculated the maximum absolute performance error (maxAPE), defined as the greatest Ce deviation across all time points, to further quantify deviations between infusion regimes generated from different TCI models. All MATLAB codes and outputs are provided as Supplementary Materials.

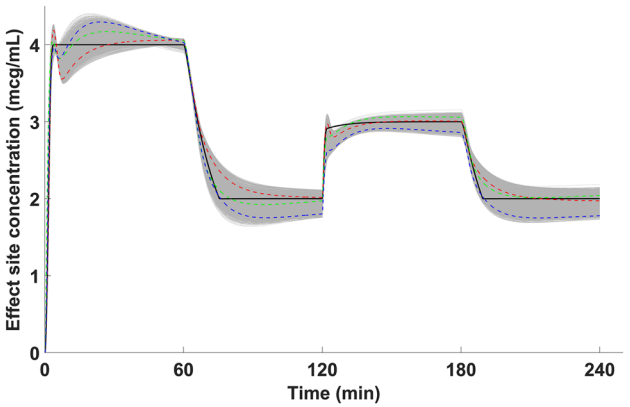

Fig. 1 Effect site concentration (Ce) profiles calculated from the Eleveld model using the infusion regime derived from the plasma targeting Marsh model with adjusted weight and induction bolus inputs for 2768 simulated subjects (gray lines) undergoing a hypothetical four-hour propofol TCI. Ce profiles of three example subjects at the extremes of age and BMI from Table 1 are highlighted using coloured dashes (subject two red line, subject four green line and subject eight blue line). The black solid line shows the Ce profile of the effect site targeting Eleveld model with Ce target set to 4 mcg/mL at 0 min, reduced to 2 mcg/mL at 60 min, increased to 3 mcg/mL at 120 min and reduced to 2 mcg/mL at 180 min for subject two

Results

Table 1 shows the Marsh adjusted body weight and typical induction boluses calculated using our optimization method as well as performance errors relative to the Eleveld model for select subjects at the extremes of age and BMI. The corresponding Ce profile from the four-hour hypothetical infusion with varying Ce target titration for select subjects is shown in Fig. 1. We found that the Ce profiles derived from the Marsh model using our adjusted weight and bolus inputs closely mimicked that of the Eleveld model at all simulated time points. The MDAPE observed in the worst performing case was 8.1%, which is below the 20% threshold that is commonly considered clinically acceptable [8]. The maximum observed maxAPE was 20.3% across our entire cohort.

Discussion

To the best of our knowledge, this is the first published method of input weight adjustment for the Marsh model that facilitates general purpose propofol TCI. Using our adjusted input weight, the Marsh model in plasma targeting mode produced an infusion regime that closely mimicked the Eleveld model in effect site targeting mode with low performance error across a wide range of simulated patients.

The main strengths of our weight adjustment method are that it is truly general purpose and not limited to any specific patient groups. It improves on traditional age-invariant parameters such as the ideal and lean body weights by adjusting for pharmacokinetic changes associated with ageing. Furthermore, our method is theoretically not limited to mimicking the Eleveld model and may also be used to approximate future three-compartment models. Our adjusted input weight and induction bolus are easy to calculate using either the included MATLAB code, spreadsheet or our free mobile App, Propofol Dreams [9].

Table 1 Marsh adjusted body weight (ABW) calculated using our algorithm for selected patient with extremes of body mass index (BMI) and age together with representative induction boluses (iBolus) for general anaesthesia (i.e. Ce target 4 mcg/mL for subjects aged 30 and Ce target 2.5 mcg/mL for subjects aged 90).

Subjects	Weight (kg)	Height (m)	BMI (kg/m^2)	Age (years)	Sex	ABW (kg)	iBolus (mg)	MDPE (%)	MDAPE (%)	MaxAPE (%)
1	200	1.58	80	30	M	129	432	1.3	2.8	18.5
2	200	1.58	80	30	F	144	452	0.4	1.4	18.2
3	40	1.63	15	30	M	43	119	2.7	2.9	17.4
4	40	1.63	15	30	F	45	123	− 0.5	1.3	10.9
5	70	1.67	25	90	M	46	78	− 1.7	4.7	13.6
6	70	1.67	25	90	F	51	81	− 3.3	6.3	14.7
7	150	1.58	60	90	M	78	139	− 3.0	4.4	12.1
8	150	1.58	60	90	F	88	147	− 4.1	5.8	12.6
9	40	1.63	15	90	M	31	50	− 0.1	3.7	12.5
10	40	1.63	15	90	F	34	51	− 2.5	6.8	15.4

Performance of the Marsh model with adjusted weight input is compared to the Eleveld model using a hypothetical four-hour TCI with varying effect site targets as shown in Fig. 1. Median performance error (*MDPE*), median (*MDAPE*) and maximum (*MaxAPE*) absolute performance errors

Our method has several limitations. Although the Marsh model using our adjusted weight input closely mimics the Eleveld model for infusions up to four hours, the Ce may drift for longer infusion durations. Titration to clinical effect using depth of anaesthesia monitoring is recommended. Furthermore, plasma targeting models have an inherent equilibration lag as compared to effect site targeting models in reaching the target Ce, especially during the induction phase. However, the clinician may easily compensate for this by manually delivering a plasma overshoot using our calculated bolus. The decrement time displayed by the Marsh model using our adjusted weight input will expectedly differ to that of the Eleveld model and clinicians should be mindful of this discrepancy during emergence. To address these limitations, we are in the process of conducting a follow up clinical validation study as well as incorporating real time displays of the Ce and decrement time into our mobile App.

Given the pilot nature of this in silico study, use of our algorithm should be considered after securing requisite authorization from the respective institution or department, if necessary. Clinical vigilance with respect to the bolus size and infusion rate must always be maintained, especially for users unfamiliar with the behaviour of the Eleveld model.

In summary, we devised a novel method for adjusting the input weight of the Marsh model such that the resulting infusion regime closely mimics the behaviour of the Eleveld model, thereby making it suitable for general purpose propofol TCI. This is a simple and robust way of improving the precision of the Marsh model, especially in patients at the extremes of age and BMI, until the general purpose Eleveld model becomes more widely available in commercial infusion pumps.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00540-024-03312-w.

Acknowledgements We acknowledge Profs Frank Engbers and Steven Shafer whose algorithms formed the basis of our MATLAB code.

Declarations

Conflict of Interest George Zhong and Xiabing Xu are co-authors of the freely available, open source Propofol Dreams app. The authors have no financial interests to disclose.

References

1. Marsh B, White M, Morton N, Kenny GN. Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth. 1991;67(1):41–8.
2. Hüppe T, Maurer F, Sessler DI, Volk T, Kreuer S. Retrospective comparison of Eleveld, Marsh, and Schnider propofol pharmacokinetic models in 50 patients. Br J Anaesth. 2020;124(2):e22–4.
3. Eleveld DJ, Colin P, Absalom AR, Struys MMRF. Pharmacokinetic-pharmacodynamic model for propofol for broad application in anaesthesia and sedation. Br J Anaesth. 2018;120(5):942–59.
4. Vellinga R, Hannivoort LN, Introna M, Touw DJ, Absalom AR, Eleveld DJ, Struys MMRF. Prospective clinical validation of the Eleveld propofol pharmacokinetic−pharmacodynamic model in general anaesthesia. Br J Anaesth. 2021;126(2):386–94.
5. La Colla L, Albertin A, La Colla G, Ceriani V, Lodi T, Porta A, Aldegheri G, Mangano A, Khairallah I, Fermo I. No adjustment vs adjustment formula as input weight for propofol target-controlled infusion in morbidly obese patients. Eur J Anaesthesiol. 2009;26(5):362–9.
6. Servin F, Farinotti R, Haberer JP, Desmonts JM. Propofol infusion for maintenance of anesthesia in morbidly obese patients receiving nitrous oxide. A clinical and pharmacokinetic study. Anesthesiol. 1993;78(4):657–65.
7. Varvel JR, Donoho DL, Shafer SL. Measuring the predictive performance of computer-controlled infusion pumps. J Pharmacokinet Biopharm. 1992;20(1):63–94.

8. Vandemoortele O, Hannivoort LN, Vanhoorebeeck F, Struys MMRF, Vereecke HEM. General purpose pharmacokinetic-pharmacodynamic models for target-controlled infusion of anaesthetic drugs: a narrative review. J Clin Med. 2022;11(9):2487.
9. Zhong G, Xu X. Propofol Dreams App. 2023. https://propofoldreams.org. Accessed 23 Nov 2023