General Purpose Propofol Target Controlled Infusions Using the Marsh Model with Adjusted Body Weight

George Zhong (✉ drgzhong@gmail.com)  
Concord Repatriation General Hospital

Xiabing Xu  
University of Sydney

Short Report

Keywords: Propofol, Target Controlled Infusion, Marsh, Eleveld

Posted Date: August 28th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3296215/v1

License: © ☕ This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

Purpose

We report a novel method for adjusting the input weight of the Marsh target controlled infusion (TCI) model so that it mimics the behavior of the Eleveld model. In this study, we compare the performance of our weight adjusted Marsh model with the Eleveld model across diverse patient groups.

Methods

We simulated 2,768 subjects with diverse combinations of age, weight, height and sex undergoing a hypothetical four-hour propofol TCI with either the Eleveld model or the Marsh model using our adjusted input weight. The performance of our augmented Marsh model was compared with the Eleveld model using established methods.

Results

The Marsh model using our adjusted weight input produced infusion regimes and effect site concentrations closely mimicking that of the Eleveld model for all simulated patients. The median and maximum absolute performance errors of our augmented Marsh model were less than 8.1% and 20.3%, respectively, compared to the Eleveld model.

Conclusion

By adjusting the input weight using our novel algorithm, the infusion regime of the Marsh model produced effect site concentrations closely mimicking that of the Eleveld model. We believe this is a robust way of improving the precision of the Marsh model, especially in patients at extremes of age and body mass index, until the Eleveld model becomes more widely available in commercial infusion pumps.

Introduction

The Marsh model is one of the most widely available pharmacokinetic models for propofol administration via commercial target-controlled infusion (TCI) pumps [1]. While it demonstrates acceptable accuracy in healthy adults, its performance significantly degrades for patients at 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]. However, the Eleveld model is currently not widely available on commercial infusion pumps worldwide.

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. In the present study, we propose a novel method of adjusting the Marsh input weight by mimicking the behavior of the Eleveld model, such that the resulting infusion regime is general purpose and thus applicable to diverse patient groups.

**Method**

Our method for adjusting the Marsh input weight is summarised below:

1. Use patient covariates (age, weight, height, and sex) and the desired effect site concentration (Ce) target as inputs for the Eleveld model to generate the Ce versus time profile.
2. Use $W_{\text{guess}}$ as the weight input, $B_{\text{guess}}$ as the induction bolus and the Ce obtained in step one as the plasma target input for the Marsh model to generate the infusion rate versus time profile.
3. Use the same patient covariates from step one and the Marsh infusion regime obtained in step two as inputs for a separate Eleveld model to generate a second Ce versus time profile.
4. Calculate the squared difference in Ce between the infusion profiles obtained in steps one and three at each time step.
5. Iterate steps two to four to determine the combination of $W_{\text{guess}}$ and $B_{\text{guess}}$ that minimizes the squared difference in step four.
6. The resulting $W_{\text{guess}}$ represents the optimized adjusted Marsh input weight and $B_{\text{guess}}$ represents the optimized induction bolus to mimic effect site targeting.

To assess the accuracy of our method, we simulated 2,768 subjects with all possible combinations of age (20 to 90 years, in increments of 10 years), weight (40 to 200 kg, increments 10 kg), BMI (13 to 83 kg.m$^{-2}$, increments 5 kg.m$^{-2}$), height (100 to 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 scenarios, the Ce target of the propofol TCI was varied over the four-hour period such that Ce of 4 mcg.mL$^{-1}$ was targeted on induction, the Ce target reduced to 2 mcg.mL$^{-1}$ at 60 min, increased to 3 mcg.mL$^{-1}$ at 120 min and reduced to 2 mcg.mL$^{-1}$ at 180 min. TCI was performed using either the Eleveld model (with opioid as covariate) in effect site targeting mode or the Marsh model in plasma targeting mode using our adjusted weight input and induction using a plasma overshoot as per our calculated bolus. The performance of our Marsh infusion regime was quantified by the median (MDPE), median absolute (MDAPE), and maximum absolute (maxAPE) performance errors calculated using established methods [7]. All MATLAB codes and outputs are provided as Supplementary Materials.

**Results**

Table 1 shows the Marsh adjusted body weight and induction bolus calculated from our algorithm 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 time points. The MDAPE and maxAPE were less than 8.1% and 20.3%, respectively, across all simulated subjects.
Table 1
Performance of the Marsh model using calculated adjusted body weight input (ABW) and induction bolus (iBolus) as compared to the Eleveld model for selected patient with extremes of body mass index (BMI) and age undergoing 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.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Weight (kg)</th>
<th>Height (m)</th>
<th>BMI (kg.m(^{-2}))</th>
<th>Age (years)</th>
<th>Sex</th>
<th>ABW (kg)</th>
<th>iBolus (mg)</th>
<th>MDPE</th>
<th>MDAPE</th>
<th>MaxAPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>200</td>
<td>1.58</td>
<td>80</td>
<td>30</td>
<td>M</td>
<td>129</td>
<td>432</td>
<td>1.3%</td>
<td>2.8%</td>
<td>18.5%</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>1.58</td>
<td>80</td>
<td>30</td>
<td>F</td>
<td>144</td>
<td>452</td>
<td>0.4%</td>
<td>1.4%</td>
<td>18.2%</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>1.63</td>
<td>15</td>
<td>30</td>
<td>M</td>
<td>43</td>
<td>119</td>
<td>2.7%</td>
<td>2.9%</td>
<td>17.4%</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>1.63</td>
<td>15</td>
<td>30</td>
<td>F</td>
<td>45</td>
<td>123</td>
<td>-0.5%</td>
<td>1.3%</td>
<td>10.9%</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>1.67</td>
<td>25</td>
<td>90</td>
<td>M</td>
<td>46</td>
<td>125</td>
<td>-1.7%</td>
<td>4.7%</td>
<td>13.6%</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>1.67</td>
<td>25</td>
<td>90</td>
<td>F</td>
<td>51</td>
<td>132</td>
<td>-3.3%</td>
<td>6.3%</td>
<td>14.7%</td>
</tr>
<tr>
<td>7</td>
<td>150</td>
<td>1.58</td>
<td>60</td>
<td>90</td>
<td>M</td>
<td>78</td>
<td>226</td>
<td>-3.0%</td>
<td>4.4%</td>
<td>12.1%</td>
</tr>
<tr>
<td>8</td>
<td>150</td>
<td>1.58</td>
<td>60</td>
<td>90</td>
<td>F</td>
<td>88</td>
<td>243</td>
<td>-4.1%</td>
<td>5.8%</td>
<td>12.6%</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>1.63</td>
<td>15</td>
<td>90</td>
<td>M</td>
<td>31</td>
<td>83</td>
<td>-0.1%</td>
<td>3.7%</td>
<td>12.5%</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>1.63</td>
<td>15</td>
<td>90</td>
<td>F</td>
<td>34</td>
<td>85</td>
<td>-2.5%</td>
<td>6.8%</td>
<td>15.4%</td>
</tr>
</tbody>
</table>

Discussion
We devised a novel method for adjusting the input weight of the Marsh model, improving its precision for general purpose propofol TCI. The resulting infusion regime from our augmented Marsh model in plasma targeting mode closely mimicked the Eleveld model in effect site targeting mode with low performance error across a wide range of patients.

The main strengths of our method for adjusting the Marsh input weight are that it is general purpose and not limited to any specific patient groups. Furthermore, our adjustment method is not limited to 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 [8].

Our method has several limitations. While 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 anesthesia monitoring is recommended. Furthermore, plasma targeting models have an inherent equilibration lag compared to effect site targeting models in reaching the target Ce. However, the clinician may easily compensate for this manually by giving a plasma overshoot using the calculated bolus.

Conclusion
We devised a novel method for adjusting the input weight of the Marsh model such that it closely mimics the behavior of the Eleveld model, thereby making it suitable for general purpose propofol TCI. We believe 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.

Declarations

Competing Interests

GZ and XX are co-authors of the freely available, open source Propofol Dreams app. The authors have no relevant financial interests to disclose.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Author Contributions

All authors contributed to literature search, data analysis and writing of the manuscript. G.Z. conceived the study design and adjustment algorithm.

Acknowledgments

We acknowledge Profs Frank Engbers and Steven Schafer whose algorithms (Eleveld and STANPUMP, respectively) formed the basis of our MATLAB code.

References


**Figures**

**Figure 1**

Effect site concentration (Ce) calculated from the Eleved model using the infusion regimes derived from the Marsh model in plasma target mode with adjusted weight and induction bolus inputs for subjects two (red), four (green) and eight (blue) from Table 1. The black solid line shows the Ce corresponding to the infusion regime from the Eleved model in effect site target mode with Ce target set to 4 mcg.mL$^{-1}$ at 0 min, reduced to 2
mcg.mL$^{-1}$ at 60 min, increased to 3 mcg.mL$^{-1}$ at 120 min and reduced to 2 mcg.mL$^{-1}$ at 180 min for subject two.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx
- MATLABPtSim.csv
- PropofolDreamsEleMarsh.xlsx
- SupplementaryMaterialsIndex.docx
- SupplementaryMaterialsIndex.docx
- MATLABPtSim.csv
- pdmarsh.m
- peaking.m
- PropofolDreamsEleMarsh.xlsx
- pkmodel.m
- regimetest.m
- tci.m