

Optimising propofol induction in elderly patients by constraining peak plasma concentration or infusion rate during Eleveld target-controlled infusions: an in silico simulation study

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Research Article

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Abstract

Effect-site targeting with the Eleveld propofol pharmacokinetic–pharmacodynamic model often delivers a large initial propofol bolus because the model uses a relatively slow plasma-to-effect-site equilibration rate constant. This produces a marked plasma concentration overshoot, which may be undesirable in elderly or frail patients with limited haemodynamic reserve. Strategies to mitigate this include gradual up-titration of the effect-site target, use of plasma targeting mode, or limiting the maximum infusion rate, but these invariably delay achievement of the effect-site target. To examine the trade-off between induction speed and plasma overshoot, we performed an *in silico* simulation of an 80-year-old, 70 kg, 170 cm male receiving propofol target-controlled infusion with the Eleveld model (including opioid as a covariate). We compared standard effect-site targeting with two augmentation strategies: limiting the peak plasma concentration or limiting the maximum infusion rate. We analysed time to effect-site target, peak plasma concentration, and cumulative propofol dose over the first 15 min. Limiting either the maximum plasma concentration or the infusion rate significantly reduced plasma overshoot with minimal delay in achieving the effect-site target. Standard effect-site targeting achieved an effect-site target of $3.0 \mu\text{g}\cdot\text{mL}^{-1}$ in 250 s, with a peak plasma concentration of $14.1 \mu\text{g}\cdot\text{mL}^{-1}$. Delaying the time to effect-site target by 68 s reduced the peak plasma concentration by 52% (to $6.7 \mu\text{g}\cdot\text{mL}^{-1}$) with the peak plasma-limiting strategy and by 32% (to $9.6 \mu\text{g}\cdot\text{mL}^{-1}$) with infusion-rate limitation. All strategies required similar propofol doses at 15 min. Clinical studies are required to determine whether this pharmacokinetic trade-off translates into improved haemodynamic or electroencephalographic outcomes in elderly patients.

Introduction

Target-controlled infusion (TCI) systems use pharmacokinetic models to calculate drug infusion rates in order to achieve the specified plasma or effect-site target concentrations.¹ The primary goal of effect-site targeting is to achieve the target concentration at the site of drug effect as rapidly as possible, which necessitates a transient overshoot in plasma concentration (C_p).

The Eleveld propofol model is a general-purpose pharmacokinetic-pharmacodynamic model developed from a broad population.² Validation studies have demonstrated that the Eleveld model has good precision over a wide range of patient demographics, including the extremes of age and body mass index.³ However, one feature of the Eleveld model is its use of a relatively slow blood-to-effect-site equilibration rate constant (ke_0), particularly when compared with alternative models such as the Schnider model.⁴ During effect-site targeting, this slower ke_0 translates into a longer time for the effect-site concentration (C_e) to reach its target and thus a larger initial propofol bolus with a greater C_p overshoot.

Propofol can produce clinically significant reductions in blood pressure during induction of anaesthesia through both systemic vasodilation and myocardial depression.⁵ The magnitude of this haemodynamic perturbation is related to the dose and rate of propofol administration in a complex manner.^{6,7} The

greater haemodynamic perturbations that result from induction with the Eleveld model in effect-site targeting mode may be undesirable in older patients or those with reduced cardiovascular reserves. This provides a clinical rationale for considering induction strategies that deliberately trade induction speed for reduced C_p overshoot, such as slow up-titration of the C_e target, limiting the peak C_p ,⁸ or limiting the maximum infusion rate.⁹

In the present *in silico* simulation study, we aim to examine the pharmacokinetic effects of limiting the peak C_p or the maximal infusion rate during effect-site targeting with the Eleveld model in a representative elderly patient. We assessed the trade-off between the time required to achieve a C_e target of $3.0 \mu\text{g}\cdot\text{mL}^{-1}$, peak C_p and cumulative propofol dose over the first 15 min.

Methods

We performed an *in silico* simulation in a representative 80-year-old male weighing 70 kg and 170 cm tall undergoing propofol induction with effect-site targeting using the Eleveld TCI model with opioid included as a covariate. The C_e target was set at $3.0 \mu\text{g}\cdot\text{mL}^{-1}$. A propofol concentration of $10 \text{ mg}\cdot\text{mL}^{-1}$ was assumed and the maximum infusion rate was set at $1200 \text{ mL}\cdot\text{h}^{-1}$. The Eleveld pharmacokinetic equations were computed numerically at 0.1 second time steps to derive concentration and infusion rate-time profiles. All calculations were performed in MATLAB R2025b (MathWorks Inc, MA, USA) and all source code is included in the Supplementary Materials.

Three induction strategies were evaluated:

- (1) Standard effect-site targeting without additional constraints. This served as the reference regime.
- (2) Effect-site targeting with peak C_p limitation. Infusion commenced in plasma targeting mode at the maximum rate until reaching the imposed ceiling C_p target, after which the infusion rate was reduced to maintain the C_p at this level. The infusion was then stopped at the exact time point which allowed C_e to reach $3.0 \mu\text{g}\cdot\text{mL}^{-1}$ without overshoot.
- (3) Effect-site targeting with maximum infusion rate limitation. Infusion commenced at a constant ceiling rate (below the maximum infusion rate) for a calculated duration, followed by cessation of infusion until C_e reached $3.0 \mu\text{g}\cdot\text{mL}^{-1}$ without overshoot.

In all three strategies, once C_e reached its target of $3.0 \mu\text{g}\cdot\text{mL}^{-1}$, the infusion resumed in standard TCI maintenance mode to maintain this target for the remainder of the simulation. For each constrained strategy, the control parameter (ceiling C_p or ceiling infusion rate) was varied to generate 20 induction trajectories spanning equally spaced target equilibration times from the reference regime (250 s) up to 900 s. For every trajectory, the peak C_p and cumulative propofol dose during the first 15 min were calculated. Concentration and infusion rate-time profiles for the three induction strategies are shown in Fig. 1.

Insert Fig. 1 here.

Results

The relationships between time to Ce target, peak Cp and cumulative 15-min propofol dose for the three induction regimes are shown in Fig. 2. With standard unconstrained effect-site targeting, an initial bolus of 94 mg was delivered at $1200 \text{ mL}\cdot\text{h}^{-1}$ for 28.3 s, achieving the Ce target of $3.0 \text{ }\mu\text{g}\cdot\text{mL}^{-1}$ in 250 s. The corresponding peak propofol Cp was $14.1 \text{ }\mu\text{g}\cdot\text{mL}^{-1}$ and the cumulative propofol dose over the first 15 min was 168 mg.

Augmenting effect-site targeting by limiting either peak Cp or maximum infusion rate slightly increased the time required for Ce to reach its target while significantly reducing the magnitude of the plasma overshoot. For example, prolonging the time to reach the Ce target by 68 s (to 318 s) relative to the standard effect-site targeting regime reduced peak Cp by 32% with infusion-rate limitation and by 52% with peak-Cp limitation, corresponding to peak Cp values of 9.6 and $6.7 \text{ }\mu\text{g}\cdot\text{mL}^{-1}$, respectively. To achieve this trajectory, the infusion-rate-limited regime delivered a constant infusion of $248 \text{ mL}\cdot\text{h}^{-1}$ for 148 s (102 mg) before pausing until 318 s, whereas the peak-Cp-limited regime delivered a reduced bolus of 42 mg to reach the ceiling Cp of $6.7 \text{ }\mu\text{g}\cdot\text{mL}^{-1}$, maintained that ceiling until 196 s and then paused until 318 s (Fig. 1, black traces).

For modest delays in induction time, limiting either peak Cp or infusion rate had minimal impact on the cumulative propofol dose over the first 15 min. In the 318 s examples above, cumulative 15-min doses were 163 mg with infusion-rate limitation and 164 mg with Cp limitation, representing reductions of 3% and 2% from the baseline, respectively.

Insert Fig. 2 here.

Discussion

The principal finding of this simulation study is that limiting either the maximum Cp or the maximum infusion rate during effect-site TCI with the Eleveld model significantly reduces peak propofol Cp with only a modest delay in time to Ce target and minimal change in the total propofol dose over the first 15 min. Both strategies therefore offer the potential to reduce haemodynamic perturbation during induction while maintaining reasonable induction speed.

Standard effect-site targeting is mathematically designed for speed, aiming to reach the Ce target as quickly as possible through a large initial induction bolus. When using the Eleveld model, its relatively slower ke_0 requires a larger Cp overshoot to drive drug into the effect compartment, increasing the likelihood of dose- and rate-related cardiovascular depression. During induction of anaesthesia in elderly or frail patients, haemodynamic stability is generally prioritised over induction speed. A large initial bolus is therefore a particular drawback in these patients. Our results suggest that constraining either the peak

Cp or maximum infusion rate can significantly reduce the size of the initial bolus with little reduction in the induction speed.

Limiting the induction bolus and subsequent plasma overshoot also carries important neurological implications. Rapid propofol inductions and the resulting plasma overshoots promote deep anaesthesia events, including burst suppression, which has been observed more frequently in elderly patients specifically when using the Eleveld model.¹⁰ Conversely, slower inductions preserve frontal alpha oscillations prior to loss of consciousness.^{11,12} The present simulation study provides the pharmacokinetic motivation for future clinical studies examining whether constrained effect-site targeting induction strategies can reduce profound electroencephalographic suppression and the associated risk of postoperative delirium.

Currently, many commercial TCI pumps only implement the Eleveld model in effect-site targeting mode. Pump manufacturers could consider adding functionality that allows clinicians to limit maximum Cp or maximum infusion rate during induction. Displaying the resulting trade-off between time to Ce target and projected peak Cp on the pump interface may help clinicians make more informed decisions on induction, especially for patients with reduced cardiovascular reserve. As a visual and clinical aid, we created a simple progressive web application (tci.propofoldreams.org) that depicts this trade-off and assists clinicians in implementing the constrained induction profiles described in this study.

This study has several limitations. Firstly, it is an *in silico* simulation using the Eleveld model in a single representative patient. Although repeating the simulations across varying elderly demographics (obesity, underweight, and female sex) yielded nearly identical relative trade-off curves (see Supplementary Materials), caution is needed when generalising theoretical findings to clinical practice. Secondly, peak propofol plasma concentration was used strictly as a surrogate marker for haemodynamic perturbation. Because the relationship between a propofol infusion regime and the true *in vivo* cardiovascular response is highly complex, real-world clinical validation studies are required to confirm these findings.

In conclusion, limiting maximum Cp or maximum infusion rate during effect-site targeting effectively reduces the plasma overshoot of the Eleveld model with minimal delay in the time for Ce to reach its target. Implementing either constraint may provide a simple yet effective method to reduce haemodynamic perturbation during induction of anaesthesia in elderly patients.

Declarations

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Ethical considerations

Ethical approval was not required for this study since it involved in silico simulation only.

Conflicts of interest

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

All source code used in the study is freely available and included in the Supplementary Materials.

Artificial intelligence statement

The author used DeepSeek 4.1-Flash to improve efficiency of the MATLAB code as well as formatting, readability and clarity of the manuscript. The MATLAB code and manuscript were cross-checked for errors with both Gemini-4 Argon and ChatGPT-6. The author has reviewed and takes responsibility for the work.

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Figures

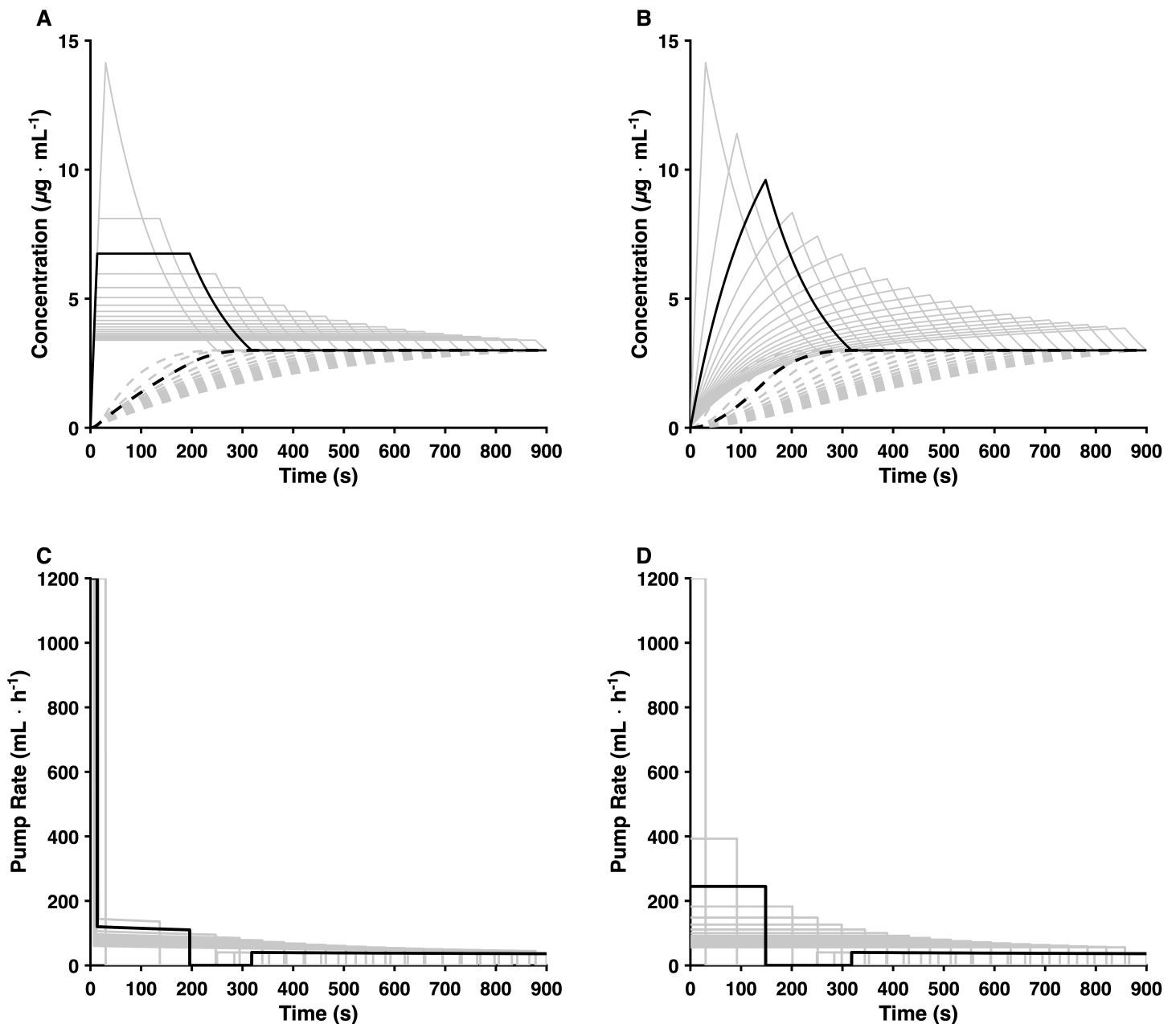


Figure 1

Simulated propofol concentration and infusion rate–time profiles for an 80-year-old, 70 kg, 170 cm male undergoing induction using the arterial Eleveld model (with opioid-present covariate) targeting an effect-site concentration of $3.0 \mu\text{g}\cdot\text{mL}^{-1}$. (A) C_p and C_e profiles for the peak C_p -limiting strategy. (B) C_p and C_e profiles for the maximum infusion rate-limiting strategy. (C) Infusion rate profiles for the peak C_p -limiting strategy. (D) Infusion rate profiles for the maximum infusion rate-limiting strategy. In (A) and (B), solid lines represent plasma concentration (C_p) and dashed lines represent effect-site concentration (C_e). The grey trace with highest C_p overshoot represents standard unconstrained effect-site targeting. Remaining grey traces represent the simulated constrained trajectories across target times up to 900 s. Black traces highlight one representative constrained trajectory with a time to C_e target of 318 s. C_p , plasma propofol concentration; C_e , effect-site propofol concentration.

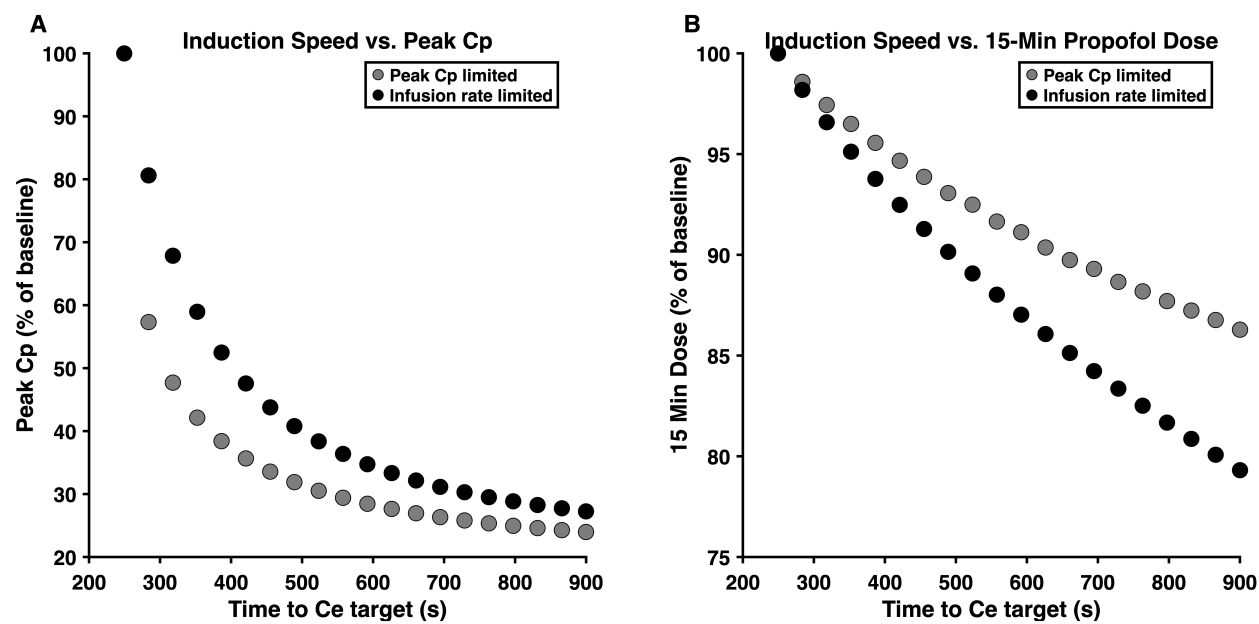


Figure 2

Trade-off between time to C_e target, peak C_p , and cumulative propofol consumption over the first 15 min associated with peak C_p -limiting (grey circles) and maximum infusion rate-limiting (black circles) strategies. (A) Peak C_p expressed as a percentage of the peak C_p during standard unconstrained effect-site targeting ($14.1 \mu\text{g}\cdot\text{mL}^{-1}$). (B) Cumulative propofol dose during the first 15 min expressed as a percentage of the 15-min dose during standard unconstrained effect-site targeting (168 mg). C_p , plasma propofol concentration; C_e , effect-site propofol concentration.

Supplementary Files

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