Adequacy of open-loop Target Controlled Infusion devices: Is there room for a closed-loop control to improve automated propofol delivery during anesthesia?

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Introduction & Objectives

- Propofol is a short-time acting hypnotic drug largely used for anesthesia induction and maintenance.
- Open-loop Target Controlled Infusion (TCI) devices are widely used to control propofol intravenous administration.
- Propofol pharmacokinetics (PK): 3-compartment model + 1 effect site compartment (brain).

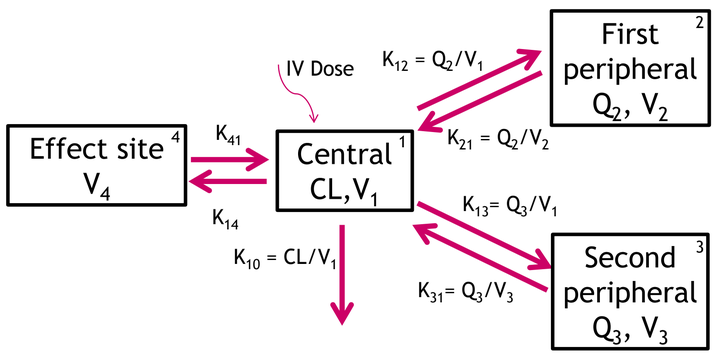

Figure1: Schematic representation of the propofol structural PK model. CL, clearance; V_1, V_2, V_3, and V_4, volume of distribution of central, first and second peripheral and effect site compartments; Q_2 and Q_3, intercompartmental clearances of peripheral compartments; K_{ij}, first-order transfer rate from compartment *i* to *j*; IV, intravenous.

- Schnider *et al.*[1]:
  - model developed on 24 healthy volunteers;
  - propofol PK depends on patient's age, weight, height and lean body mass;
  - low inter-individual variability.
- Eleveld *et al.*[2]:
  - model developed on 660 individuals (volunteers and children, adults, elderly, and obese patients);
  - propofol PK depends on body weight, development, age and gender as well as on individual status (volunteers *vs.* patients);
  - important inter-individual variability.
- The current algorithms driving TCI pumps are based on published PK models neglecting drug inter-individual variability: propofol infusion rates are adjusted aiming to a defined target according to model-predicted plasma or brain concentration. The model of Schnider *et al.*[1] is recommended in many hospitals.

Problem: Clinical conditions may markedly alter propofol PK and actual propofol levels could significantly differ from predicted ones, leading to important drug over- or under-exposures.

Study aim: To assess the adequacy of TCI-predicted propofol dosages and to evaluate whether there would be room for a closed-loop control in anesthesia delivery to optimize drug dosages based on concentration measurements.

Methods

Experiment[3]

- An Orchestra BasePrimea pump (Fresenius Kabi, Germany) was configured with the characteristics of a virtual male patient (70 kg, 170 cm and 36 years).

- Changing propofol target brain concentration during a 15 min operation was set to 6 → 4 → 5 mg/L.
- Propofol dosage scheme to achieve these targets were obtained with the model of Schnider *et al.* as implemented in the BasePrimea pump.
- The equilibration time between brain and plasma concentrations at target achievement was extracted.

Simulations

- The virtual subject was simulated 10000 times under the estimated TCI dosage scheme using the comprehensive model with inter-individual variability developed by Eleveld *et al.*[2].
- Median plasma concentration with 90% prediction interval ($PI_{90\%}$) were calculated and compared to the target brain concentrations at equilibrium according to TCI prediction.
- The percentage of virtual patients with propofol levels above 15 mg/L (maximum allowed in current TCI) was estimated.

Results

- According to Schnider *et al.*[1] model, plasma and effect site concentration were equilibrated maximum 2 min after target change.
- Figure 2 shows median with $PI_{90\%}$ of the Eleveld *et al.*[2] model and TCI predicted plasma concentrations along with the aimed target and TCI predicted brain levels. The TCI dosage scheme is also shown.
- Comparison of simulated median ($PI_{90\%}$) plasma and target brain concentrations at equilibrium according to TCI predictions:

Target levels (mg/L)	Median ($PI_{90\%}$) (mg/L)
6	5.9 (3.7-8.6)
4	4.1 (2.8-5.8)
5	5.0 (3.5-7.0)

- 9% of virtual patients had concentrations exceeding 15mg/L within the first minute of propofol infusion.

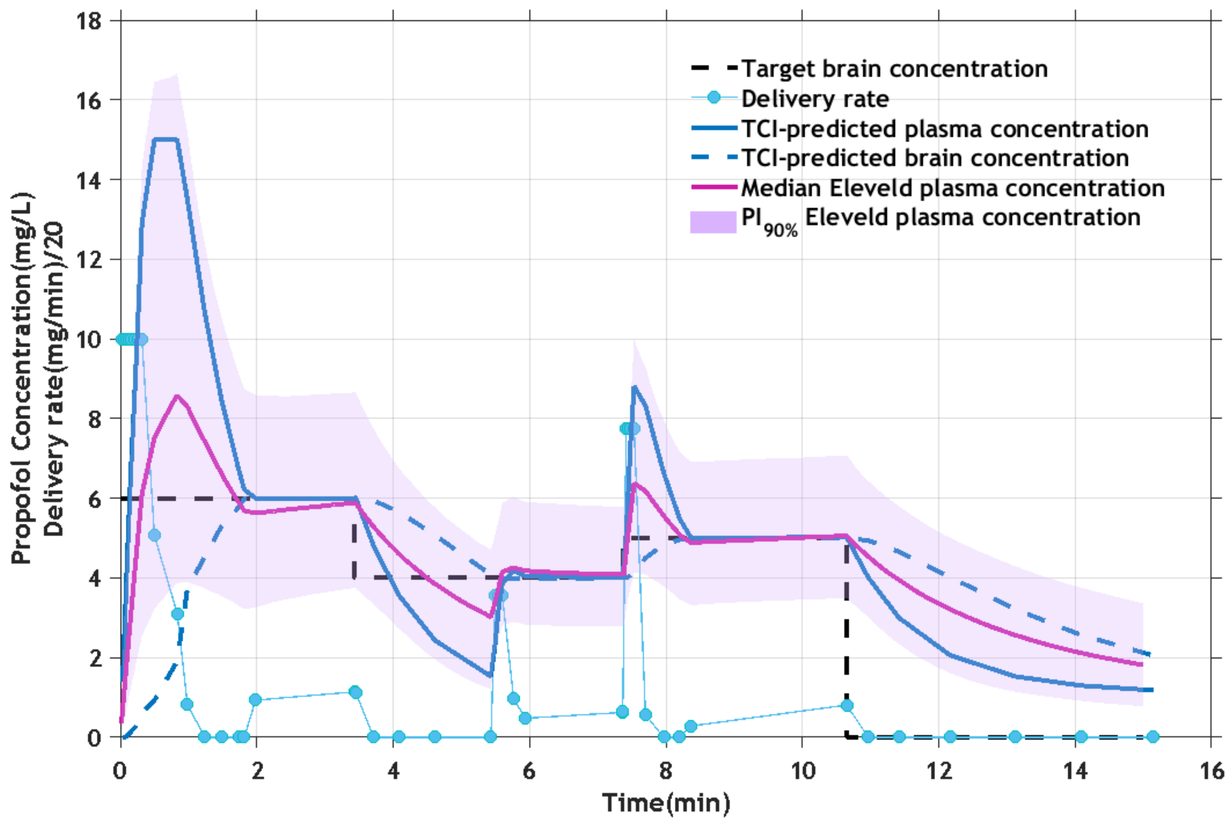

Figure2: Median with $PI_{90\%}$ concentration-time profile of propofol obtained by simulating 10000 times the virtual subject under the estimated TCI dosage scheme using the Eleveld *et al.*[2] model.

Conclusions

- Due to inter-patient variability, current TCI pumps probably deliver inadequate propofol dosages to a significant fraction of patients with possible clinical consequences.
- Our simulations show a potential for a closed-loop control of propofol administration based on real-time concentration measurement to improve automated anesthesia delivery.
- Controllers based on Kalman filter and Bayesian minimization incorporating real-time propofol measurements to optimize infusion rate are currently under development.

References

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3. A. Simalatsar, M. Guidi, and T. Buclin. *38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 533–536, Aug 2016.

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