How low can you go? Examining Pharmacokinetically Defined Minimum Safety Bounds for Propofol During Closed-Loop Control of Anesthesia

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Background: In closed-loop control of anesthesia, drug infusion rates are automatically adjusted using continuous feedback from a measure of clinical effect[1]. This personalized approach allows appropriate drug delivery for each individual based on the level of stimulation during the procedure. The design of a closed-loop system needs to include a safety system to ensure the safety of the patient [2]. Our current system includes safety constraints based on propofol's known therapeutic window[3]. By default the propofol predicted effect site concentration (Ce) is limited to a of range of 1.5 mcg/mL to 8 mcg/mL, based on the Schnider pharmacokinetic (PK) model[4]. While these constraints reduce the risk of under- or overdosing for most patients, the bounds are expected to be reached for outliers, indicating that such a patient may not be well represented by the PK model. All population-based PK models have their shortcomings; and a recently published general purpose PK model for propofol[5] suggests that the Schnider model underestimates drug concentrations. Thus, we examine the incidence of reaching the lower safety bound for propofol with our current system, and compare the predicted plasma concentrations (Cp) of the Schnider model to the general purpose PK model.

Methods: Following Health Canada and local Research Ethics Board approval, and written informed consent, subjects were recruited from a population of ASA I-III adults undergoing routine, elective surgery. Our closed-loop control system, iControl-RP, receives processed electroencephalography (pEEG) feedback from the NeuroSENSE DOH measure (WAV_{CNS}) [NeuroWave, Cleveland, USA[6]], and controls two infusion pumps for propofol and remifentanil administrated during both induction and maintenance of anesthesia.

Results: Data from 82 cases (all with propofol in closed-loop; 51 with remifentanil by target controlled infusion, 31 with remifentanil in closed-loop) were collected. The minimum safety lower bound for propofol was reached in 62 % cases. (**Table 1**).
Compared to the Schnider model used in our system, the general purpose PK model for propofol[5] estimates the median [range] Cp during maintenance 0.84 [0.26-2.3].mcg/mL higher (**Figure 1**). Thus, the minimum safety bound may not have been reached as frequently, and as a result propofol infusion may have gone lower in some cases, had we defined our safety bounds with this general purpose model[5].

Table 1.
Summary of data when the WAV_{CNS} set point was ≤55:

Minimum safety bound for propofol reached at least once	51 cases (62%)
Median propofol dose (mcg/kg/min)	65 [56-85]
% of case at min bound	17 [5.8-33]
WAV_{CNS}	45 [43-48]
MAP (mmHg)	87 [74-94]
HR (bpm)	67 [55-73]

*minimum safety bound for propofol reached when predicted Ce<1.51mcg/mL; data are median [IQR].

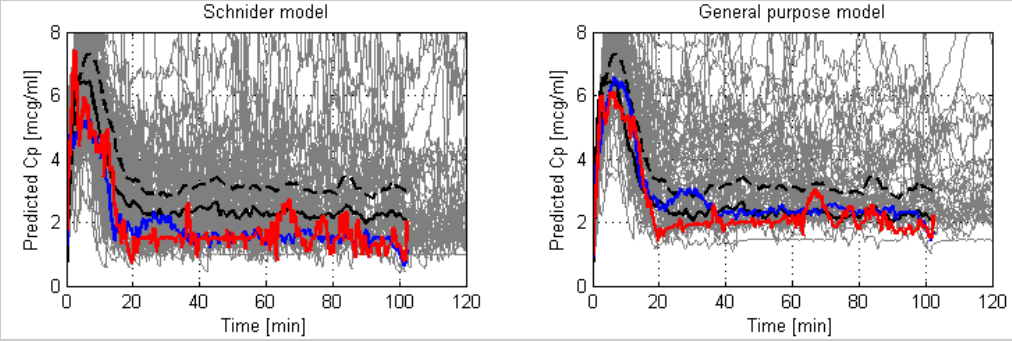

Figure 1. Predicted plasma concentrations of propofol for each of the 82 cases shown in grey, calculated using either the Schnider model[4] (left) or the General purpose model[5] (right). In both plots median Cp value from Schnider model in solid black, General purpose in dashed black. Example case from phase 1 (propofol in closed loop) in red; phase 2 (propofol and remifentanil in closed loop) in blue.

Conclusion: The considerable interpatient variability in propofol requirements emphasizes the utility of a closed-loop system which can administer low doses of propofol when needed. However, the minimum safety bound for propofol was reached in the majority of our cases. The median propofol predicted effect site concentration was relatively low in these cases, however the WAV index was also consistently low, and the vital signs were within normal clinical range. The original safety bounds we defined were conservative based previously published data. The high degree of variability between and within patients highlights the challenges of using a population based prediction model for safety bounds. This brings to question which PK model should be used to define the safety bounds for propofol delivered in closed loop. To reduce the number of threshold violations we propose to make it easy for the user to manually adjust the safety threshold to reflect the accuracy of the model, and to consider using the stability in the WAV index to permit automated adjustments to the threshold.

References: [1] J Clin Monit Comput. 2014;28(1):5-11; [2] Anesth Analg 2013;117:1130–8 [3] Anesthesiology. 1997;87(6):1549–62; [4] Anesthesiology, 88(5):1170 – 1182, 1998; [5] Anesth Analg 2014;118:1221–37; [6] J Clin Monit Comput. 2011;25(1):81-7.