Clinical validation of pharmacokinetic/pharmacodynamic models for propofol infusion. Response to Br J Anaesth 2021

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The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.03.018.

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Clinical validation of pharmacokinetic/pharmacodynamic models for propofol infusion. Response to *Br J Anaesth* 2021: 126: e172-4

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Editor—We thank Schnider and colleagues[1] for commenting on our publication,[2] and appreciate the opportunity to respond to a few selected points they raise. We described the results of a validation study of the Eleveld propofol model[3] that showed its unique applicability for target-controlled-infusion (TCI) in children, adults, older subjects, and the obese. Schnider and colleagues[1] suggest an 'alternative approach' where TCI systems are programmed with several subgroup-specific models and the systems select a model based on the patient covariates. We have two concerns with this approach.

First, such a system has complex edge-cases that are also unaddressed in the literature. If the patient is 70 yr old and has a BMI of 35 kg m^{-2}, should the system then select the best 'eldery' model or the best 'obese' model? Recently, a propofol

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model was developed for an 'underweight Korean' population.[4] Which TCI model should be selected for a normal weight Korean, or an underweight Caucasian? The design of such an 'alternative' system would be very complex and would require a large number of models (most of which do not yet exist) to be able to cover the range of permutations. Specialised models are not always an improvement in TCI performance. Colin and collegues[5] showed that for vancomycin there is no advantage in using vancomycin pharmacokinetic models specifically tailored to obese patients over the general purpose model. For propofol, we suggest that broad application of our model is a better choice, not only for 'edge-cases' but also for specialised populations for which models are available[6] since there is currently no evidence that specialised models obtain a clinically meaningful improvement in TCI system performance.

Second, selecting the best model based on the patient covariates entails a risk of clinician unfamiliarity with the TCI model and incorrect usage. For example, 'adult' and 'obese' models developed independently will not match characteristics at the boundary BMI of 30 kg m^{-2}. Clinicians would be rightfully surprised if TCI targets appropriate for patients with a BMI of 29.5 kg m^{-2} would be significantly different to those with a BMI of 30.5 kg m^{-2}, and this may lead to misunderstandings and dosing errors. This is a real issue with current models at every boundary in the system: child-adult, adult-elderly, adult-obese, elderly-obese, etc. Biology does not support hard boundaries between patient groups so why should our TCI systems? Models developed for broad populations enforce smooth predictable behaviours across the range of patient covariates. The benefit for clinicians is a reduced burden of knowledge to correctly use a TCI system and improved predictability.

There is no evidence for inadequate bipsectral index (BIS) titration in our study. If this were an issue then excess variability would be present. We found BIS varied between 33 and 63 (5–95% percentiles, all samples, children, adults, older patients, and obese). This is similar to a recent study of the Schnider model[7] where BIS varied between 32 and 61 (2.5–97.5% percentiles, time=30 min, adults BMI<35 kg m^{-2}). Because BIS variability in our study was similar to other studies we conclude BIS titration was not an issue. Our analysis did not require 'tight' BIS titration and our model performance measures are uninfluenced by the 'titration paradox'.[8]

The closed-loop performance measures described by Soltesz and colleagues[9] are not ideal measures of TCI performance because 1) they are single-variable measures and clinical anaesthesia is multivariate, 2) TCI systems are open-loop[10] and closed-loop measures are confounded by clinician skill and intent, and 3) achieving a pre-specified BIS is not synonymous with adequate anaesthesia. While the Varvel criteria[11] do have drawbacks, they are well known and despite these drawbacks, they are widely applied.

We did not examine the prediction accuracy of the Eleveld model in the 3–5 min after a change in target concentrations because this was beyond the scope of our study. Divergence was not reported because we do not consider it an essential descriptor of TCI system performance. If divergence was an issue in the pharmacokinetic measures or BIS, this would be visible as increasing absolute prediction error (APE) in (APE_{PK} and APE_{BIS} over time). However, we do not see such an effect.

Schnider and colleagues[1] suggest that after induction, the infusion pump will stop for longer with the Eleveld model compared with the Schnider model. This is not correct if equal doses are considered. Consider a male patient, 35 yr old, 70 kg, and 170 cm tall. With the Eleveld model at an effect-site target of 3.08 μg ml^{-1} (the predicted concentration for 50% drug effect), the induction dose is 1.88 mg kg^{-1}, and once delivered the pump will stop infusing until 3.33 min. Thereafter, the steady-state infusion rate will be 4.99 mg min^{-1}. To achieve a similar induction dose (and thus similar drug effects), the Schnider model requires a target of 7.4 μg ml^{-1}, which would then need to be subsequently lowered to 3 μg ml^{-1} to achieve a similar steady-state infusion rate (4.91 mg min^{-1}). When the Schnider model is targeted in this way, propofol administration will be paused for 5.17 min after induction (longer than for the Eleveld model), while the effect-site concentration decays from 7.4 to 3 μg ml^{-1}.

The important practical benefit of the Eleveld model is that it reduces the burden on clinicians. Training requirements can be simplified because they do not have to take into account the arbitrary boundaries in age, weight, BMI, etc, that are imposed by multiple TCI models.

Declarations of interest

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Metabolic outcomes in patients with diabetes mellitus administered SGLT2 inhibitors immediately before emergency or elective surgery: single centre experience and recommendations

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Editor—The cardio-renal benefits[1] of sodium–glucose cotransporter-2 inhibitors (SGLT2i) in people with diabetes mellitus have led to their widespread use. SGLT2i predispose to perioperative diabetic ketoacidosis (DKA),[2] including euglycaemic DKA. To minimise perioperative DKA risk, current guidelines recommend withholding SGLT2i for 48 h before surgery (where fasting and anaesthesia are required)[3,4]; otherwise, postponement should be considered.[5] Further research is required to understand the optimal management approach, where SGLT2i has been administered within 48 h before surgery. We report metabolic outcomes in a case series of patients treated with SGLT2i immediately before emergency or elective surgery.

The series was assembled from cases where SGLT2i were used in the 48 h before surgery during 2018–20. DKA was defined as the presence of ketosis (capillary beta-hydroxybutyrate [BOHB] >0.6 mM) and acidosis (blood pH <7.30: mild 7.25–7.29; moderate 7.00–7.24; severe <7.00).[6] Ketone screening was performed in the perioperative period if a patient was identified to have used SGLT2i, or if SGLT2i use was not recognised in the perioperative period, then ketones were measured if the patient became unwell with acidosis in the postoperative period. Fisher's exact test statistical analysis was performed, and results should be regarded as hypothesis generating. The study was approved by the Human Research and Ethics Committee of Melbourne Health (QA2019038).

We identified 23 patients who underwent surgery despite SGLT2i administration (empagliflozin: n=15; dapagliflozin: n=8) in the 48 h prior. Of these, 17 were male and six were female with median age 69 yr (range: 46–79 yr). Median Charlson Comorbidity Index was 5.0 (inter-quartile range [IQR]: 4.5–6.0). There were 21 with type 2 diabetes (T2D), two with type 1 diabetes (T1D) with off-label SGLT2i use, seven were insulin requiring pre-admission, and median glycosylated haemoglobin was 7.8% (IQR: 7.0–8.7%) or 62 mmol mol^{-1} (IQR: 53–72). Seventeen patients underwent emergency surgery; six patients who underwent elective surgery had inadvertently not withheld their SGLT2i, as recommended. The SGLT2i dose was last administered a median 24 h before surgery (IQR: 24–29), median preoperative fasting time was 12 h (IQR: 9–17), and median procedure duration was 2.5 h (IQR: 1.8–4.0). Seven patients underwent high-risk cardiac or vascular surgery, 13 intermediate-risk and two low-risk surgery (American College of Cardiology/American Heart Association classification),[7] and 15 patients were managed in the ICU after surgery.

Overall, 20 of 23 patients (87%) developed ketosis, with 13 (57%) having ketosis without acidosis and seven (30%) having DKA (mild, n=5; moderate, n=2; severe, n=0) (Table 1). Three patients with DKA were euglycaemic at the time of peak ketosis. Median initial BOHB was 2.1 mM (IQR: 0.7–3.6) and median peak BOHB was 2.7 mM (IQR: 1.2–4.6). For patients with ketosis without acidosis, the median ketosis duration was 16 h (IQR: