Eleveld, Marsh, and Schnider propofol pharmacokinetic models in 50 patients

Tobias Hüppe1,*, Felix Maurer1, Daniel I. Sessler2, Thomas Volk1 and Sascha Kreuer1

1Homburg (Saar), Germany and 2Cleveland, OH, USA

*Corresponding author. E-mail: tobias.hueppe@uks.eu

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Editor—Numerous pharmacokinetic models have been developed to dose propofol administration accurately during anaesthesia.1 Pharmacokinetic models developed by Marsh and colleagues2 (n=20) and Schnider and colleagues3 (n=24) have been applied in commercial propofol target-controlled infusion (TCI) syringe pumps. Recently, Eleveld and colleagues4 used a large diverse population to develop a pharmacokinetic–pharmacodynamic model for predicting propofol concentrations and the bispectral index. Specifically, they used data from 1033 patients in the Open TCI Initiative which combines data from many investigators. However, the Eleveld model5 has yet to be validated in an independent patient population. It is unclear whether this pharmacokinetic model provides better predictive performance of measured plasma propofol concentrations than conventional models such as those of Marsh and colleagues6 and Schnider and colleagues.7 We therefore evaluated plasma concentrations in 50 patients who were not included in the population used by Eleveld and colleagues8 for model development. Specifically, we tested the hypothesis that the Eleveld model provides better predictions (smaller median absolute performance error [MDAPE] and smaller median performance error [MDPE]) of arterial propofol plasma concentration than either the Marsh or Schnider models.

After approval from the responsible ethics committee (Identification number 39/2016, March 22, 2016, Ärztekammer Saarland, Saarbrücken, Germany) and written informed consent, we enrolled 50 patients who were undergoing visceral or trauma surgery. All had total i.v. general anaesthesia and an arterial catheter. Data were obtained from a previous study related to development of an exhaled propofol monitor.9 Anaesthesia was provided with propofol using TCI with the Minto model10 and remifentanil using TCI with the Minto model.10,11 Quantification of propofol in plasma was performed by liquid chromatography (Agilent 1260 Infinity series, Agilent Technologies, Waldbronn, Germany). We calculated propofol plasma concentrations using automatically recorded perfusor flow rates with respective pharmacokinetic data sets of Eleveld and colleagues,4 Marsh and colleagues,7 and Schnider and colleagues.3 Specifically, we used transfer constants of the respective pharmacokinetic models and the propofol supply to the central distribution compartment (Microsoft Excel 2011, Microsoft Corporation, Redmond, WA, USA) for calculations. To compare measured and corresponding estimated plasma concentrations and the precision of different pharmacokinetic models, we calculated the MDAPE as a measure of accuracy. The MDAPE of individual patients were compared between different pharmacokinetic models using analysis of variance on ranks (ANOVA). The MDPE was estimated as a measure of bias. Post hoc power analysis was performed using one-way ANOVA with fixed effects in three groups with a total sample size of 150 and alpha-error 0.05.

We analysed 488 arterial blood samples. Post hoc power analysis revealed an effect size of 0.11 with a power of 0.21. The MDAPE with the Eleveld model for individual patients was 22 (4–50)%; 25 (6–58)% with the Marsh model; and 26 (2–54)% with the Schnider model. Individual patient MDAPE values did not differ significantly among the three models, and did not depend on age, weight, or gender. MDPE values were –18% for the Eleveld model, 9% for the Marsh model, and –20% for the Schnider model. When using the Marsh model, measured propofol plasma concentrations were a mean of 0.25 μg ml⁻¹ above estimated concentrations. The Schnider and Eleveld models overestimated measured concentrations by 0.64 and 0.53 μg ml⁻¹, respectively. Using the Marsh model, individual ratios of measured-to-calculated concentrations indicated that measured propofol plasma concentrations were underestimated, especially after induction of anaesthesia. The Schnider and Eleveld models tended to overestimate measured plasma concentration throughout anaesthesia (Fig. 1). In our patients, prediction of actual measured propofol plasma concentration was slightly better with the Eleveld model than with either the Marsh or Schnider models. Presumably performance was better because Eleveld was able to incorporate more than 15 000 propofol concentrations from more than 1000 patients from 30 studies, making the results both robust and generalisable.4 The Eleveld model included covariates such as age, weight, height, and sex to predict arterial propofol concentrations. Nevertheless, the MDAPE of –22% was only slightly below those of the previous models. The clinical relevance of this small difference is likely to be low. Complexities specific to our patient population might possibly have led to increased MDAPE in our validation study. It seems unlikely that it will be possible to develop a pharmacokinetic model for propofol with MDAPE <20% using currently available covariates, largely because of time-varying distribution volumes and metabolic differences between individuals. The metabolism of propofol occurs predominantly via cytochrome P450 2B6, and is subject to individual genetic influence, alcohol consumption, and use of various medications, none of which is adequately included in current pharmacokinetic models. However,
Eleveld’s model is based on the largest data set and, as we have shown, has the lowest prediction error so far. Furthermore, Eleveld improved model performance at the extremes of age and in the obese. This model brings a significant gain in predicting plasma concentrations, especially in these patient groups. Thus, it should be integrated into commercial syringe pumps for TCI. The major limitation of our study is the low power with only a very small effect size. Small differences in the outcome parameter MDAPE between the three pharmacokinetic models would require a case number of nearly 700 patients to get a power of 0.8. In conclusion, the Eleveld pharmacokinetic model showed a slightly better predictive performance for measured propofol plasma concentrations compared with those of the Marsh and Schnider models. Further studies with significantly more patients must confirm these preliminary data to clarify whether this small difference from other pharmacokinetic models is clinically relevant.

**Authors’ contributions**

Performed the intraoperative measurements and wrote the manuscript: TH
Measured and evaluated the blood plasma samples: FM
Carried out the conceptualisation, formal analysis, data correction, and manuscript preparation: DIS
Reviewed and edited the manuscript: TV
Designed the manuscript and performed the pharmacokinetic calculations: SK

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**Declaration of interest**

The authors declare that they have no conflicts of interest.

**References**

Comment on ‘Cutaneous innervation of the hand: clinical testing in volunteers shows high intra- and inter-individual variability’ (Br J Anaesth 2018; 120: 836–45)

Sheng-Hao Cheng1, Min Cheol Chang2, Mathieu Boudier-Revéret3,* and Ming-Yen Hsiao1

1Taipei, Taiwan, 2Taegu, Republic of Korea and 3Montreal, Canada
*Corresponding author. E-mail: mathieu.boudier-reveret@umontreal.ca

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Editor—We read with great interest the article entitled ‘Cutaneous innervation of the hand: clinical testing in volunteers shows high intra- and inter-individual variability’ by Keplinger and colleagues.1 They defined the cutaneous sensory supply of the hand by blocks of median, ulnar, and radial nerves in 12 volunteers under ultrasound (US) guidance, which was followed by a comment by Edwards and Power2 and the authors’ response.3 Inspired by the study and comment2 mentioning that the lateral antebrachial cutaneous nerve (LACN) might be involved in cutaneous innervation of the hand, we describe a relevant case of Wartenberg’s syndrome caused by LACN entrapment.

A 48-yr-old woman with no past medical history presented with a complex wound on the lateral side of the left forearm after a dog bite a week before (she consented to this description of her case). She complained of progressive thumb, second and third finger dorsal-sided numbness with incidental tingling sensations, although the wound was gradually healing. The wound was clean and dry with no signs of infection or palpable mass. There was no muscle weakness, but hypoaesthesia and allodynia were noted on the lateral side of the left wrist and thumb, and Tinel’s sign was positive in the left superficial radial nerve (SRN). Based on the clinical symptoms and area of sensory deficit, the tentative diagnosis was SRN entrapment, also anatomic variation.4 This patient had a variant in which the LACN replaced the SRN, which was absent. We diagnosed entrapment of the left distal LACN within scar tissue, and administered triamcinolone 10 mg, xylocaine 3 ml, and normal saline 6 ml via a US-guided perineural injection at the entrapment site of the left LACN. The tingling sensation completely disappeared 30 min after the injection and was not present at the 1 month follow-up. Although the mechanism is not clear, injecting corticosteroids and local anaesthetics blocks nerve transmission in C-fibre nociceptors, reduces ectopic discharge, and facilitates recovery of nerve conduction after nerve injuries.5 However, in a recent randomised controlled study, addition of...