BJA

British Journal of Anaesthesia, 126 (2): 386–394 (2021)

doi: 10.1016/j.bja.2020.10.027
Advance Access Publication Date: 13 December 2020
Clinical Practice

Prospective clinical validation of the Eleveld propofol pharmacokinetic-pharmacodynamic model in general anaesthesia

Remco Vellinga[1,*], Laura N. Hannivoort[1], Michele Introna[2], Daan J. Touw[3,4], Anthony R. Absalom[1], Douglas J. Eleveld[1] and Michel M. R. F. Struys[1,5]

[1]Department of Anesthesiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands, [2]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy, [3]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands, [4]Department of Pharmaceutical Analysis, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands and [5]Department of Basic and Applied Medical Sciences, Ghent University, Ghent, Belgium

*Corresponding author. E-mail: r.vellinga@umcg.nl

Abstract

Background: Target-controlled infusion (TCI) systems incorporating pharmacokinetic (PK) or PK-pharmacodynamic (PK-PD) models can be used to facilitate drug administration. Existing models were developed using data from select populations, the use of which is, strictly speaking, limited to these populations. Recently a propofol PK-PD model was developed for a broad population range. The aim of the study was to prospectively validate this model in children, adults, older subjects, and obese adults undergoing general anaesthesia.

Methods: The 25 subjects included in each of four groups were stratified by age and weight. Subjects received propofol through TCI with the Eleveld model, titrated to a bispectral index (BIS) of 40–60. Arterial blood samples were collected at 5, 10, 20, 30, 40, and 60 min after the start of propofol infusion, and every 30 min thereafter, to a maximum of 10 samples. BIS was recorded continuously. Predictive performance was assessed using the Varvel criteria.

Results: For PK, the Eleveld model showed a bias < ±20% in children, adults, and obese adults, but a greater bias (−27%) in older subjects. Precision was <30% in all groups. For PD, the bias and wobble were <5 BIS units and the precision was close to 10 BIS units in all groups. Anaesthetists were able to achieve intraoperative BIS values of 40–60 using effect-site target concentrations about 85–140% of the age-adjusted Ce_{50}.

Conclusions: The Eleveld propofol PK-PD model showed predictive precision <30% for arterial plasma concentrations and BIS predictions with a low (population) bias when used in TCI in clinical anaesthesia practice.

Keywords: pharmacodynamics; pharmacokinetic-pharmacodynamic model; pharmacokinetics; plasma concentration; propofol; target-controlled infusion

Editor's key points

- The applicability to broad populations of target-controlled infusion (TCI) systems incorporating pharmacokinetic and pharmacodynamic models used to facilitate anaesthetic drug administration is unknown.
- The authors prospectively evaluated the Eleveld propofol pharmacokinetic-pharmacodynamic model, which was developed for a broad population range, for TCI in children, adults, older subjects, and obese adults undergoing general anaesthesia.
- The Eleveld propofol pharmacokinetic and pharmacodynamic model showed predictive precision <30% for arterial plasma concentrations and bispectral index predictions with a low population bias when used for TCI in clinical practice.

Received: 17 June 2020; **Accepted:** 19 October 2020

Target-controlled infusion (TCI) systems are used to facilitate anaesthetic drug administration, particularly for short-acting drugs used in anaesthesia. TCI systems calculate the drug dose and infusion rate necessary to achieve and maintain a targeted drug concentration in the plasma or an effect-compartment based on a pharmacokinetic (PK) or PK-pharmacodynamic (PK-PD) model. Widespread clinical experience has been gained and TCI is considered a mature technology.[1]

Current TCI systems incorporate PK or PK-PD models developed for specific patient groups, such as adults, children, older patients, and obese adults. Extrapolation of a model developed for one population to a patient from a different population is discouraged because of the uncertainty of whether model predictions and TCI drug administration will be appropriate in the other population. This may result in under- or overdosing, leading to superficial anaesthesia or delayed recovery. Some degree of extrapolation is unavoidable in routine clinical practice because the diversity across patients and clinical conditions exceeds that which was present in the study subjects from which the PK and PK-PD models currently available in TCI systems were developed.

Recently, Eleveld and colleagues[2] developed a propofol PK-PD model that can be incorporated in a TCI system used to administer propofol for general anaesthesia and sedation. This second generation model[3] was developed using PK-PD data from different studies from a broad, diverse, population, including data from neonates, children, adults, and older subjects, and including both volunteers and patients with conditions such as obesity, alcoholism, liver cirrhosis, and cancer, along with varying approaches to concomitant drug administration, such as opioids. In general, greater diversity in the data used to develop a model increases the chance of a match between the model and a given clinical situation,[4] thus reducing the risks associated with extrapolation. The PK predictive performance of the Eleveld model has been evaluated in adults[5] and the underweight.[6]

It is not currently known how accurately the Eleveld PK-PD model predicts plasma propofol concentrations and bispectral index (BIS) values when used by a TCI system for propofol administration to a group of patients with diverse characteristics. The aim of the current study was to validate prospectively the Eleveld propofol PK-PD model in a broad range of patients, from children to older patients, including obese adults, by assessing its predictive performance for arterial plasma concentrations and BIS in routine practice using TCI. Our hypothesis was that its predictive precision is not significantly worse than specialised models and that it is clinically applicable for all subgroups. The secondary objective was to identify effect-site target concentrations for the models that are associated with adequate anaesthesia.

Methods

This investigator-initiated trial was conducted in the Department of Anesthesiology of the University Medical Center Groningen (UMCG), Groningen, The Netherlands. The Medical Ethics Committee of the UMCG approved the study (METc2018/216). The study was registered in The Netherlands Trial Register (NTR7146). All medical devices used in this study are approved for use in clinical research, and all drugs and routes of administration are approved for clinical use.

Subjects

Four groups of 25 subjects each, undergoing an elective surgical procedure, were included. Eligibility criteria were, age of 3 yr or more, an ASA physical status between 1 and 4, and an expected surgery duration of at least 1 h, with a surgery- or patient-related indication for arterial cannulation. Exclusion criteria were use of benzodiazepines preoperatively (chronically or as premedication), contraindications to use of propofol, inclusion in other perioperative interventional studies, or patients admitted to the ICU before surgery, had received propofol in the preceding 24 h, or both. Written informed consent was obtained from all subjects who were ≥16 yr of age. For subjects between 12 and 15 yr of age, consent was obtained from their parents/caregivers, and for subjects <12 yr of age informed consent was obtained from their parents/caregivers.

Study design

We enrolled 25 subjects in each of the following four groups according to age, weight, or both: children (three ≤ age <18 yr), non-obese adults (18 ≤ age <70 yr; BMI < 30 kg m^{-2}), older patients (age ≥70 yr), and obese adults (18 ≤ age <70 yr; BMI≥30 kg m^{-2}). Obese children and older subjects were not excluded.

Arterial blood samples were collected at 5, 10, 20, 30, 40, and 60 min after the start of propofol TCI, and every 30 min thereafter until end of surgery or 10 samples in total had been collected. If the target concentration had been recently increased, sampling was delayed by 3–5 min to reduce the possible influence of possible front-end kinetics on observed concentrations, and sampling times were recorded. All study procedures stopped after the last sample was collected. The TCI system remained connected and in use for the on-going delivery of propofol until the end of the procedure.

Study procedures

All procedures took place in the operation centre of the UMCG. All subjects were fasted according to local adult and paediatric protocols. No sedative premedication was allowed. Upon arrival in the operation theatre, an i.v. cannula was inserted and used for fluid (Ringer's lactate, Baxter, Deerfield, IL, USA) and drug administration, including Propofol (Fresenuis Kabi, Bad Homburg, Germany). Subjects were connected to a Philips IntelliVue MP50 vital signs monitor (Philips Medical Systems, Eindhoven, The Netherlands) using standard monitoring (ECG, noninvasive BP monitoring, pulse oximetry [SpO_2]). A BIS monitor (BIS Vista, Medtronic, Boulder, CO, USA) with bilateral BIS sensor used to record BIS. An arterial catheter was inserted into a radial artery under local anaesthesia before induction, in all subjects except in children and subjects refusing placement before induction. In these subjects, cannulation was performed as soon as possible after the induction of anaesthesia. The arterial line was used for the collection of blood samples to measure the propofol plasma concentration and for arterial BP monitoring. After induction of anaesthesia, the subject's trachea was intubated. Further perioperative care was according to standard care protocols and at the discretion of the anaesthetist. For analysis, recorded data were sampled at 10 s intervals.

An anaesthetic team, consisting of a qualified anaesthetist and a nurse anaesthetist, was responsible for perioperative care as per clinical practice. A research nurse was responsible for drawing the blood samples, and processing and storage of the plasma samples. A research student or PhD student was responsible for controlling RUGLOOP (Rugloop, DEMED, Temse, Belgium) and for other study procedures.

Drug administration

Patients received propofol delivered by a syringe pump (Alaris™ GH syringe pump, Becton Dickinson (BD), Franklin Lakes, NJ, USA) controlled by a computer running RUGLOOP II software (Demed, Temse, Belgium) for Windows (Microsoft, Redmond, WA, USA). The RUGLOOP II software was programmed to deliver propofol by TCI using the Eleveld PK-PD model. As opioids were used in all procedures, 'concomitant opioid use' was selected when subject covariates were entered into RUGLOOP.

Anaesthetists were asked to set the initial target concentrations equal to the age-specific effect-site concentration corresponding with 50% of maximal effect (Ce_{50}, corresponding with a predicted BIS of 47) for the induction of anaesthesia (Fig. 1). This was predicted to result in induction doses close to the recommendations in the propofol product label.[7] Adjustments to the target concentration during the procedure were at the discretion of the anaesthetist, with the advice to maintain BIS values between 40 and 60.

Remifentanil (TCI), sufentanil (TCI), or fentanyl (manual boluses, in some children, <10 yr only) were used for analgesia during the procedure. Inhaled anaesthetics, benzodiazepines and ketamine were not allowed during the study. If the anaesthetist deemed the use of these drugs necessary, then they were administered later in the procedure (at least after 1 h, preferably after the end of the study, 3 h after the start of propofol). PK and PD data from after the time of administration of these drugs were excluded from further analysis.

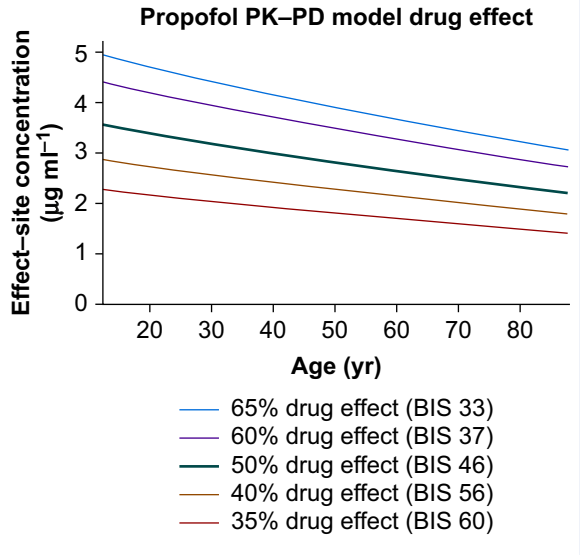

Fig 1. The relationship between target concentration and age for the Eleveld PK-PD model showing the expected drug effect and suppression of BIS values from baseline. BIS, bispectral index; PK-PD, pharmacokinetic-pharmacodynamic.

Measurement of drug effect

The cerebral effect of propofol was measured using bilateral frontal processed EEG monitoring (BIS®, BIS Vista, Medtronic, Dublin, Ireland). A BIS value of 100 represents the awake state and a BIS of 0 defines no detectable electrical brain activity. BIS values between 40 and 60 are considered to be appropriate for general anaesthesia.[8]

Analysis of blood samples

Blood was collected in ethylenediaminetetraacetic acid tubes (EDTA) Becton Dickinson (BD) and stored at room temperature for a maximum of 60 min. Afterwards, samples were centrifuged (Labofuge 400R, Heraeus Holding GmBh, Hanau, Germany) for 5 min at 3200 rpm at 20°C. Plasma was transferred into cryovials and stored at −80°C until analysis. Propofol plasma concentration analysis was performed by the Department of Clinical Pharmacy and Pharmacology of the UMCG using ultra-high-performance liquid chromatography–mass spectrometry **(TSQ-Quantiva, Thermo Scientific,** Waltham, MA, USA**)** in atmospheric pressure chemical ionization mode. The lower and upper limits of quantification were 0.1 and 25 μg L^{-1}, respectively. The method was validated according to European Medicines Agency[9] and Food and Drug Administration[10] regulations and complied with requirements set in these regulations.

Data handling

Recorded BIS values were used for analysis when the signal quality index was >50. BIS signals recorded from the subjects' left and right sides were collected into a single signal and median filtered over 30 s periods to obtain the observed BIS value. Propofol infusion rates and cumulative dose were calculated from the (difference in) infused volume at each 10 s sampled time interval. Model predictions were simulated in NONMEM 7.4 (ICON Development Solutions, Ellicott City, MD, USA) and analysed using R (version 2.14.1; R Foundation for Statistical Computing, Vienna, Austria).

Table 1 Characteristics of the subjects studied. Data are presented as median (range) or as counts.

	Children	Adults	Older subjects	Obese adults
Male/female	12/13	11/14	12/13	14/11
Age (yr)	8 (3–16)	50 (20–69)	79 (72–90)	53 (34–68)
Weight (kg)	32.7 (12.8–68.8)	73 (58.8–101)	75 (52.0–114.5)	105 (82.5–152)
Height (cm)	140 (95.7–171)	172 (159–192)	171 (151–184)	175 (156–186)
BMI (kg m^{-2})	16.5 (14–27.3)	25 (19–29.9)	26.9 (19.6–40.6)	35.8 (30.5–46.8)

Table 2 Predictive Median Performance Error (MdPE), Median Absolute Performance Error (MdAPE), and Wobble of the models considered. Values shown are mean (range). ΔMdAPE and ΔWobble indicate individual differences compared with the Eleveld PK-PD model. The *P*-value was calculated using a one-sided Wilcoxon test for $\Delta MdAPE_i$ and $\Delta Wobble_i$ values <0, indicating better performance than the Eleveld PK-PD model. BIS, bispectral index; PK-PD, pharmacokinetic-pharmacodynamic.

Arterial samples	MdPE (%)	MdAPE (%)	ΔMdAPE (%)	P	Wobble (%)	ΔWobble (%)	P
Eleveld PK-PD							
Children	−4.42 (−35.1–37.6)	16.8 (1.92–37.6)			7.39 (0.77–16.0)		
Adults	−14.1 (−43.3–24.6)	19.5 (4.86–43.3)			7.89 (2.01–17.6)		
Older subjects	−27.0 (−53.9–7.75)	29.5 (6.02–53.9)			7.28 (2.48–24.7)		
Obese adults	−14.1 (−40.7–11.6)	18.3 (4.11–40.7)			6.80 (1.89–14.1)		
Schnider							
Adults	−2.11 (−35.6–61.8)	17.5 (6.04–61.8)	−1.98 (−15.7–37.2)	0.020	8.81 (4.11–22.2)	0.92 (−3.54–5.99)	0.989
Older subjects	−5.13 (−44.0–46.2)	22.2 (5.68–46.2)	−7.28 (−23.7–36.2)	0.043	9.46 (1.74–25.8)	2.18 (−1.65–10.0)	1.000
Obese	5.75 (−30.8–56.2)	22.1 (5.02–56.2)	3.80 (−21.1–46.0)	0.674	8.08 (1.97–24.3)	1.28 (−7.09–12.1)	0.971
Marsh							
Adults	−0.03 (−24.8–53.1)	16.4 (5.82–53.1)	−3.14 (−25.3–29.4)	0.051	9.33 (3.33–19.6)	1.43 (−4.34–8.01)	0.996
Older subjects	3.38 (−45.9–80.4)	26.2 (7.85–80.4)	−3.23 (−32.5–63.2)	0.150	12.0 (4.53–44.4)	4.70 (−1.47–19.8)	1.000
Obese	17.0 (−32.7–71.3)	28.8 (6.48–71.3)	10.5 (−23.1–62.7)	0.965	9.46 (3.43–18.6)	2.66 (−5.20–6.95)	1.000
Marsh (Servin-formula)							
Obese	−10.7 (−46.2–30.9)	20.0 (2.16–46.2)	1.69 (−15.7–22.3)	0.914	7.30 (2.65–14.0)	0.50 (−6.74–4.07)	0.957
Cortinez							
Adults	2.05 (−25.9–58.0)	16.1 (5.37–58.0)	−3.46 (−23.1–33.4)	0.057	9.34 (4.26–21.0)	1.45 (−1.17–5.60)	1.000
Older subjects	0.92 (−40.3–55.9)	23.5 (4.40–55.9)	−5.97 (−27.6–38.6)	0.060	10.0 (2.87–33.9)	2.76 (−0.91–11.4)	1.000
Cortinez (Obese)							
Obese	−7.48 (−47.3–32.0)	20.0 (4.22–47.3)	1.70 (−12.9–23.4)	0.738	7.67 (1.25–18.8)	0.87 (−3.73–5.36)	0.983
Paedfusor							
Children	−3.18 (−27.1–38.1)	15.5 (2.57–38.1)	−1.37 (−13.9–10.2)	0.262	9.89 (2.06–25.0)	2.50 (−10.7–15.9)	0.995
Kataria							
Children	26.2 (−12.9–95.8)	31.1 (7.59–95.8)	14.3 (−16.6–70.1)	0.995	12.6 (0.95–38.1)	5.25 (−5.28–22.1)	0.999
Araujo							
Adults	12.5 (−26.9–51.7)	21.7 (6.82–51.7)	2.13 (−35.6–43.0)	0.489	12.0 (3.72–29.3)	4.13 (−3.40–18.7)	1.000
Older subjects	−20.7 (−51.8–28.0)	25.7 (5.65–51.8)	−3.74 (−25.0–20.7)	0.018	8.47 (2.78–24.9)	1.20 (−2.01–4.29)	1.000
Obese	−5.15 (−47.9–41.9)	26.0 (3.56–47.9)	7.75 (−23.4–35.7)	0.990	8.05 (1.33–16.8)	1.25 (−8.87–10.5)	0.874
BIS	**MdPE (BIS)**	**MdAPE (BIS)**	**ΔMdAPE (BIS)**	**P**	**Wobble (BIS)**	**ΔWobble (BIS)**	**P**
Eleveld PK-PD							
Children	1.95 (−21.7–20.9)	9.10 (3.43–21.7)			4.35 (1.73–8.94)		
Adults	0.29 (−15.2–17.9)	7.88 (1.95–17.9)			3.60 (1.55–7.45)		
Older subjects	1.80 (−11.9–13.1)	7.57 (2.69–13.1)			4.46 (2.18–8.28)		
Obese adults	0.74 (−24.4–31.3)	9.61 (3.17–31.3)			3.50 (1.76–6.03)		
Cortinez (Obese)							
Obese	−12.7 (−40.7–16.9)	17.5 (3.48–40.7)	7.84 (−15.9–25.8)	0.999	3.60 (1.87–6.59)	0.10 (−0.64–1.16)	0.844
Araujo							
Adults	−0.83 (−19.7–22.2)	8.79 (1.97–22.2)	0.91 (−10.2–15.1)	0.573	3.98 (1.59–8.06)	0.38 (−0.46–1.45)	0.999
Older subjects	−0.22 (−23.9–21.1)	9.25 (2.26–23.9)	1.69 (−7.14–16.4)	0.824	4.46 (2.25–9.31)	0.00 (−1.52–1.03)	0.573
Obese	−3.68 (−31.4–35.1)	17.0 (2.10–35.1)	7.39 (−6.76–18.0)	1.000	4.02 (1.73–6.92)	0.52 (−0.67–1.44)	1.000

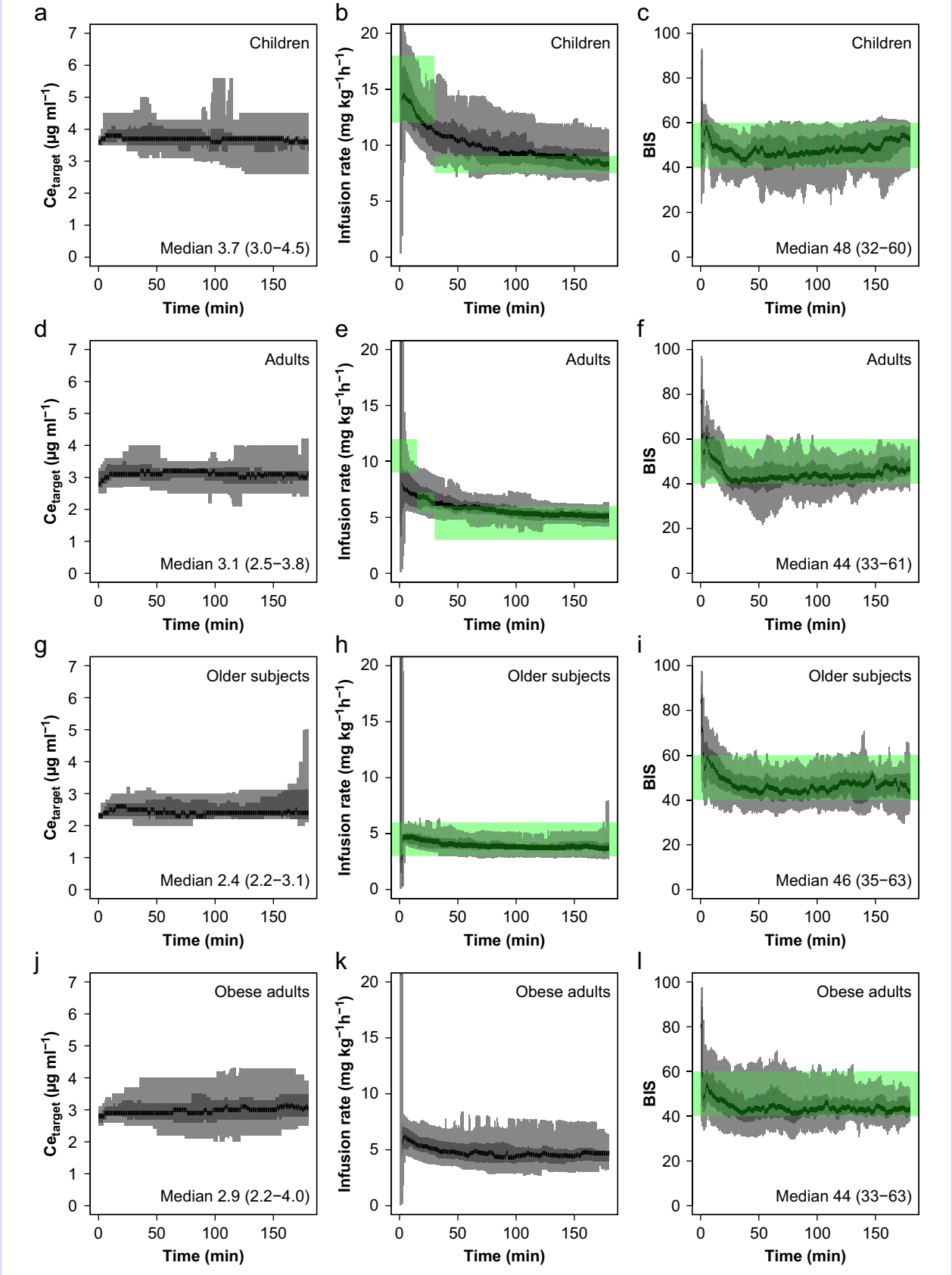

Fig 2. (a, d, g, j) Smoothed distributions of effect-site target concentrations (Ce_{target}), (b, e, h, k) infusion rates, and (c, f, i, l) observed BIS values *vs* time, for children, adults, older subjects, and obese adults. Green shaded infusion rates indicate propofol product label recommendations. Green shaded BIS values indicate the clinical range of 40–60. BIS, bispectral index.

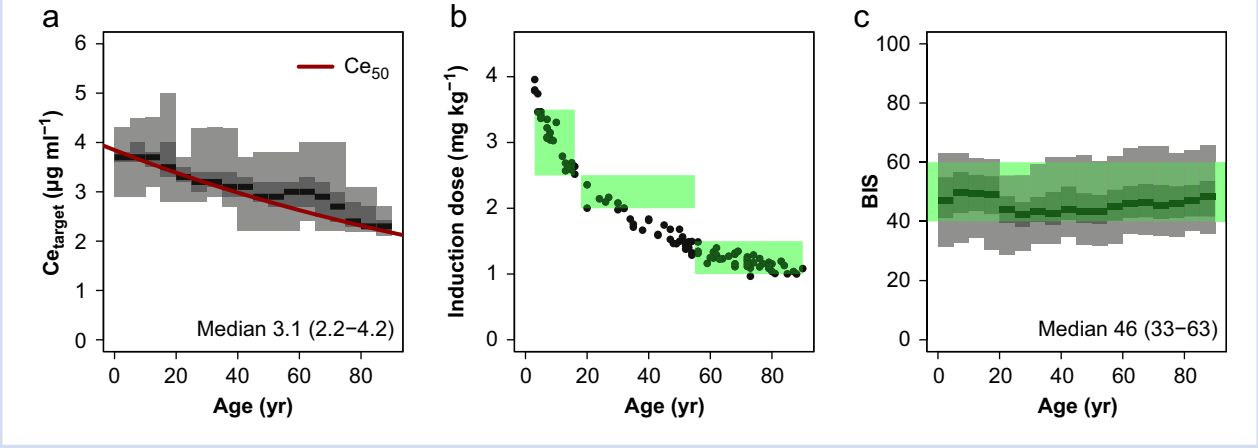

Fig 3. (a) Smoothed distributions of effect-site target concentrations (Ce_{target}), (b) induction dose (cumulative dose over first 2 min), and (c) observed BIS values *vs* age. The red line indicates the Eleveld model age-adjusted Ce_{50}. Green shaded induction doses indicate propofol product label recommendations. Green shaded BIS values indicate the clinical range of 40–60. BIS, bispectral index.

PK-PD predictive performance

The predictive performance of the PK model predicting the time course of the arterial propofol concentrations was evaluated using the Varvel criteria[11] with performance error for observation j in individual i calculated as:

$$PE_{ij} = \frac{Cobserved_{ij} - Cpredicted_{ij}}{Cpredicted_{ij}} \cdot 100\%$$

These are summarised for each individual as $MdPE_i$ and $MdAPE_i$ as:

$$MdPE_i = median\{PE_{ij},\ j = 1, \ldots, N_i\}$$

$$MdAPE_i = median\{|PE_{ij}|, j = 1, \ldots, N_i\}$$

$$Wobble_i = median\{|PE_{ij} - MdPE_i|, j = 1, \ldots, N_i\}$$

These quantify prediction bias, precision, and the variability within an individual, respectively, and we report mean (range) values across the population. An $MdPE$<20% and $MdAPE$<40% have been suggested to indicate clinically acceptable performance.[12,13] Other PK and PK-PD models for comparison (and patient groups) considered were the Schnider model[14] (adults, older subjects, obese) the Marsh model[15] (adults, older subjects, obese), the Marsh model with correction by Servin[16] (obese), the Cortinez model[17] (adults, older subjects, obese) and Cortinez 'obese' model[18] (obese), the Kataria model[19] (children), the Paedfusor model[20,21] (children), and the Araújo model[22] (adults, older subjects, obese). We compared model differences in $MdAPE_i$ and $Wobble_i$ using a one-sided (other model performs better) Wilcoxon signed rank test. We considered P<0.01 as significant to compensate for multiple testing as we compared the Eleveld PK-PD model with two PK models for children, four PK models for adults, four PK models for the older subjects, and five PK models for the obese.

Monte Carlo simulations of the study design were performed including random observation error to obtain an *a priori* estimate of statistical power. With 25 subjects in each subgroup, the simulation median (5–95% percentile) for MdAPE was 19% (15–22) across all groups.

The PD predictive performance was calculated in a similar manner to the PK predictive performance except we used a formula for PE_{ij} more suitable for additive error models:

$$PE_{ij} = BISobserved_{ij} - BISpredicted_{ij}$$

Differences in BIS values <5 were considered clinically irrelevant.[23]

Results

We screened 167 patients for inclusion in the study; the consort diagram is shown in Supplementary Figure S1. Informed consent was obtained from 112 patients, their caregivers, or both. Ten patients were excluded before any study measurements were made for various reasons (i.e. preoperative benzodiazepine usage, not able to obtain i.v. access pre-induction in children). The data from a further two subjects were excluded from analysis. In one subject this was because of a brief leakage from the propofol administration system leading to uncertainty in administered propofol dose, and in the other an event occurred during induction which led to a suspicion of preoperative recreational drug use. Excluded patients were replaced and the data from 100 subjects, 25 in each subgroup, were used for analysis. The characteristics of the population are shown in Table 1. Age, weight, height, and BMI are presented as median (range). The children and older groups include one and three obese patients, respectively. The PK and PD observations are included as Supplementary Digital Content.

Table 2 shows the predictive performance of the Eleveld PK-PD model and other models. The Eleveld model showed bias (MdPE) <20% in children, adults, and obese adults (−4.4%, −14.1%, −14.1%, respectively) but there was a greater bias (−27%) in older subjects. Precision (MdAPE) was <30% for all groups. Some of the other models showed lower average PK MdAPE than the Eleveld PK-PD model, but the differences were not significant at a level of P<0.01. PK predictive performance

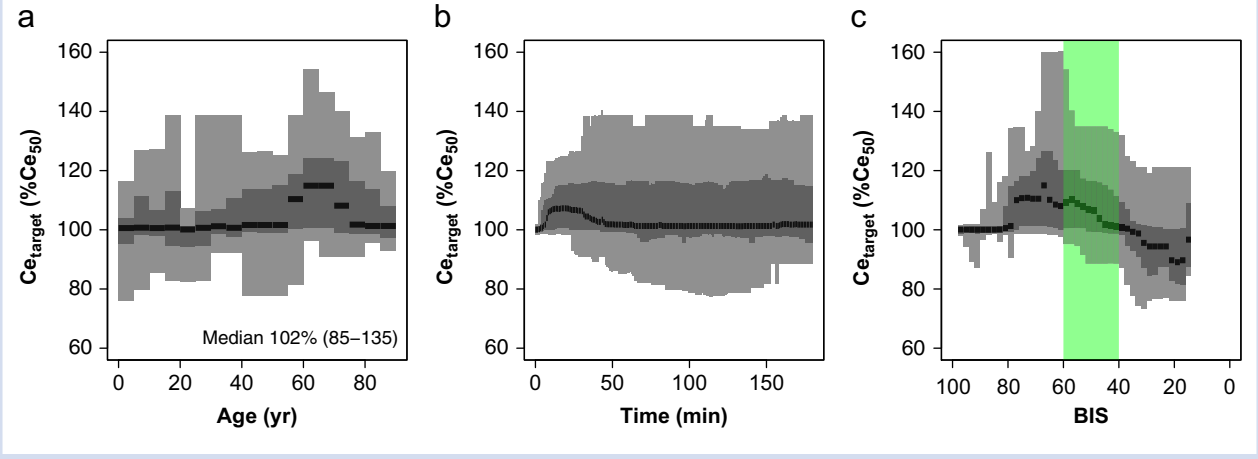

Fig 4. Smoothed distributions of target concentrations relative to the Ce_{50} (%Ce_{50}) *vs* (a) age, (b) time, and (c) observed BIS values. Green shaded BIS values indicate the clinical range of 40–60. BIS, bispectral index.

vs time is shown in Supplementary Figure S2. For BIS predictions, MdPE and wobble were <5 BIS units, which is considered to be clinically irrelevant.[23] MdAPE for BIS was close to 10 BIS units for all groups, suggesting that considerable interindividual variability exists in overall propofol BIS drug effect. BIS predictive performance *vs* time is shown in Supplementary Figure S3.

For Figures 2–4, distributions of study data are shown as percentiles (5–95% light grey; 25–75% dark grey; median black line) for each interval. Smoothing was achieved by including immediately adjacent intervals in each percentile calculation. Green shaded induction doses and infusion rates indicate recommended drug administration for anaesthesia from the propofol product label.[7] These were: children (3 yr < age < 16 yr: induction 2.5–3.5 mg kg^{-1}, maintenance 12–18 mg kg^{-1} h^{-1} for the first 30 min, followed by 7.5–9 mg kg^{-1} h^{-1}), adults (18 < age < 55 yr: induction 2–2.5 mg kg^{-1}, maintenance 9–12 mg kg^{-1} h^{-1} for 15 min, followed by a reduction of 40% until 30 min, followed by 3–6 mg kg^{-1} h^{-1}), and older subjects (age >55 yr: induction 1–1.5 mg kg^{-1}, maintenance 3–6 mg kg^{-1} h^{-1}). Green shaded BIS values indicate the range 40–60 which is considered to be adequate for intraoperative anaesthesia.

Smoothed distributions of the effect-site target concentration selected by the anaesthetists, infusion rates, and achieved BIS values over 1 min intervals for each group are shown in Figure 2. Target concentrations and infusion rates were higher (per kg) in children compared with adults, whereas these were lower in older subjects and obese adults. Despite these differences in target concentration and drug administration between groups, similar BIS values of 40–60 were observed for all groups.

Figure 3 shows the relationship with age for effect-site target concentration, induction dose (cumulative dose over the first 2 min), and BIS values during TCI. The target concentrations selected by the anaesthetist follow a similar decrease with age as predicted by the age-adjusted Ce_{50} of the model. The resulting induction dose matched with the product label recommended doses across the age range.[7] The achieved BIS values were similar for all age groups and showed good agreement with the intended BIS values of 40–60. The median (5–95% percentile) observed BIS during TCI was 46 (33–63).

To gain insight into the selection of effect-site target concentrations by the anaesthetists, we plotted these relative to the Ce_{50} (%Ce_{50}) *vs* age, time, and observed BIS values, shown in Figure 4. When the target concentration was expressed relative to the Ce_{50}, then was no longer a relationship with age, suggesting that the incorporation of the age adjustment to the Ce_{50} resulted in an acceptable depth of anaesthesia during clinical use. Target concentrations are often increased in the early phase of anaesthesia, but tend to be lowered more towards the Ce_{50} value after ~45 min.

Figure 4 also shows dose individualisation or 'titration-to-effect' performed by the anaesthetists. Before the initial onset of drug effect, BIS values of about 90–100 were observed and anaesthetists tended to choose target concentrations close to the Ce_{50}. In this period, the predicted effect-site concentration is still increasing towards the target. When observed BIS values were in the 60–80 range, then target concentrations were typically increased to ~110% of Ce_{50}. In contrast, when observed drug effects were greater than intended, with BIS values <40, target concentrations tended to be lowered, reaching 85% of Ce_{50} for a BIS value of 20. At BIS values around 40, anaesthetists typically selected target concentrations matching the Ce_{50}.

Discussion

We prospectively evaluated the predictive performance of the Eleveld PK-PD model in a TCI system for children, adults, older subjects, and obese adults with regard to propofol concentrations (the PK component) and BIS values (the PD component). For propofol plasma concentrations, precision (MdAPE) <30% was found in all groups. Bias (MdPE) <20% was observed in children, adults, and obese adults, but a greater bias (−27%) was observed in older subjects. Our results are similar to those found by Hüppe and colleagues[5] in adults (bias −18%; precision 22%). Yi and colleagues[6] prospectively validated the propofol PK model from Park and colleagues[24] in underweight Korean patients and also evaluated the Eleveld PK-PD model and found similar results (bias −18.6%; precision 23.1%). This suggests that the PK properties of this special group[25] are similar to the non-obese adults tested here.

Only the Eleveld PK-PD model was applicable over all groups considered: children, adults, older subjects, and obese adults. While some other PK models had a lower MdAPE (i.e. better precision) than the Eleveld PK-PD model, there was considerable interindividual variability in $MdAPE_i$ and the difference did not reach significance. This suggests that the observed lower MdAPE may not be reliably repeatable across investigations.

For BIS observations, the Eleveld PK-PD model showed negligible bias (<5 BIS units) for all groups, whereas precision was about 8–10 BIS units for all groups. This suggests that dose individualisation (titration-to-effect) by adjusting target concentrations will remain an essential part of propofol TCI drug administration. These adjustments are needed to compensate for the biological interindividual PK and PD variability so that an adequate drug effect can be achieved in each patient.

During the study procedures, effect-site target concentrations chosen by the anaesthetist varied between 85% and 140% of the age-adjusted Ce_{50}. Target concentrations exceeded the Ce_{50} in the early phase of anaesthesia and when observed BIS values were in the 60–80 range. These adjustments are possibly in anticipation of stimulation as a result of laryngoscopy and intubation, noxious surgical stimulation, or, in case of a BIS value between 60 and 80, individuals showing insensitivity to propofol drug effects. Target concentrations were sometimes decreased below the Ce_{50} when BIS values were in the 20–40 range. These patients may have greater pharmacodynamic sensitivity to propofol, or variability in pharmacokinetics that resulted in higher than predicted plasma concentrations.

The anaesthetists titrated propofol target concentrations to achieve clinically adequate depth of anaesthesia as assessed by BIS and other clinical monitoring. The practice of defining target concentrations relative to the Ce_{50} is also found in clinical use of inhaled anaesthetics (minimum alveolar concentration) and in drug-interaction research for developing response surface models to predict interactions between two or more drugs on drug effect.[26]

As Eleveld and colleagues[2] indicated in the publication of their PK-PD model, selecting TCI effect-site target concentrations equal to the model age-adjusted Ce_{50} would result in predicted propofol induction doses and maintenance infusion rates close to those recommended in the propofol product label.[7] This was confirmed in the current study as the anaesthetists were able to obtain and maintain adequate anaesthesia using targets close to Ce_{50} in all groups. This is the first study showing that TCI with a single PK-PD model can result in clinically adequate anaesthesia for a diverse group of patients, achieving a BIS between 40 and 60, while drug dosing remains close to product label recommendations.[7]

Dose individualisation or 'titration-to-effect' is likely more difficult when drug response shows intraindividual variability (wobble) compared with predicted values. The Eleveld PK-PD model showed lower PK wobble than other models and wobble for BIS was <5. This suggests that dose individualisation with the Eleveld PK-PD model will be at least as successful compared with other models.

We found that the Eleveld model showed high PK bias in older subjects but a low bias was observed in all groups for prediction of BIS values. It seems likely that the overprediction of arterial concentrations in older subjects is compensated by the age-adjustment in the Ce_{50}, resulting in BIS predictions and clinical effects that are adequate for anaesthesia. The origin of the PK bias in older subjects is not clear. It may be caused by differences in the individuals and studies used to develop the Eleveld PK-PD model compared with the individuals studied here. PK bias may be an issue for future scientific studies using the Eleveld model in older subjects. However, it has little impact for TCI in clinical practice, since during this study clinicians were not aware of PK bias during the execution of the study, and it only became apparent after sample analysis.

This study required an arterial line for sampling and this may bias the study population based on their medical history or surgery indication. We cannot be certain that the subjects included in this study are representative of other groups with different procedures or concomitant drug administration. Also, the Varvel performance measure for arterial samples is asymmetric, having a lower bound of −100% and an upper bound of infinity, and this may influence the comparisons of predictive performance between models.

In conclusion, the Eleveld PK-PD model showed predictive precision <30% for arterial propofol plasma concentrations and BIS predictions with a low (population) bias. None of the other PK models considered were applicable across all of the patient groups tested. The Eleveld model was not inferior in its predictive performance compared with the other models. Anaesthetists used the Eleveld model in TCI to achieve clinically relevant intraoperative BIS values for children, adults, older subjects, and obese adults using effect-site target concentrations of about 85–140% of the age-adjusted Ce_{50}.

Authors' contributions

Study design: LNH, ARA, DJE, MMRFS
Data acquisition: RV, LNH, MI, ARA, MMRFS
Data analysis: RV, LNH, DJT, ARA, DJE, MMRFS
Writing of the manuscript: all authors

Acknowledgements

The authors thank the entire Anaesthesiology staff of the University Medical Center Groningen (UMCG) for participating in this study, with special thanks to all involved paediatric anaesthetists who made it possible to include children in the study. The authors further thank Kai van Amsterdam (data scientist, Department of Anaesthesiology, UMCG, Groningen, The Netherlands) for synchronising the RUGLOOP data with the clinical data, the research nurses of the UMCG for collecting the arterial blood samples, and Tom de Smet (CEO, Demed Medical, Temse, Belgium) for his help with RUGLOOP.

Declarations of interest

ARA: his research group/department received (over the past 3 yr) research grants and consultancy fees from The Medicines Company (Parsippany, NJ, USA), Becton Dickinson (Eysins, Switzerland), Dräger (Lübeck, Germany), Paion (Aachen, Germany), Orion (Espoo, Finland), Rigel (San Francisco, CA, USA), and Janssen Pharmaceutica (Beerse, Belgium). He is an editorial board member and editor for the *British Journal of Anaesthesia*. MMRFS: his research group/department received (over the past 3 yr) research grants and consultancy fees from The Medicines Company (Parsippany, NJ, USA), Masimo (Irvine, CA, USA), Becton Dickinson (Eysins, Switzerland), Fresenius (Bad Homburg, Germany), Dräger (Lübeck, Germany), Paion (Aachen, Germany), Medtronic (Dublin, Ireland). He receives royalties on intellectual property from Demed Medical (Temse, Belgium) and the Ghent University (Gent, Belgium). He is an

editorial board member and director for the *British Journal of Anaesthesia*. The other authors declare that they have no conflicts of interest.

Funding

Department of Anesthesiology, University Medical Center Groningen, The Netherlands. Becton Dickinson, Switzerland.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.10.027.

References

1. Absalom AR, Glen JIB, Zwart GJC, Schnider TW, Struys MMRF. Target-controlled infusion. *Anesth Analg* 2016; **122**: 70–8
2. Eleveld DJ, Colin P, Absalom AR, Struys MMRF. Pharmacokinetic–pharmacodynamic model for propofol for broad application in anaesthesia and sedation. *Br J Anaesth* 2018; **120**: 942–59
3. Shafer Steven L. The evolution of pharmacokinetics. *Br J Anaesth* 2020; **124**: 664–5
4. Short TG, Campbell D, Egan TD. Increasing the utility of target-controlled infusions: one model to rule them all. *Br J Anaesth* 2018; **120**: 877–90
5. Hüppe T, Maurer F, Sessler DI, Volk T, Kreuer S. Retrospective comparison of Eleveld, Marsh, and Schnider propofol pharmacokinetic models in 50 patients. *Br J Anaesth* 2020; **124**: 22–4
6. Yi J-M, Doh I, Lee S-H, et al. Predictive performance of a new pharmacokinetic model for propofol in underweight patients during target-controlled infusion. *Acta Anaesth Scand* 2019; **63**: 448–54
7. Food and Drug Agency. *Product label of propofol* 2017. Available from: www.accessdata.fda.gov/drugsatfda_docs/label/2017/019627s066lbl.pdf. [Accessed 27 September 2017]
8. Medtronic. *Personalize anesthesia, not too deep, not too light, just Right* 2019. Available at: https://www.medtronic.com/content/dam/covidien/library/us/en/product/brain-monitoring/bis-tiva-anesthesia-brochure.pdf. [Accessed 9 June 2020]
9. European Medicines Agency. *Committee for Medicinal Products for Human use (CHMP) uideline on bioanalytical method validation* 2011. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-bioanalytical-method-validation_en.pdf. [Accessed 9 June 2020]
10. Food and Drug Administration. *Bioanalytical method validation guidance for industry biopharmaceutics* 2018. Available from: https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf. [Accessed 9 June 2020]
11. Varvel JR, Donoho DL, Shafer SL. Measuring the predictive performance of computer controlled infusion pumps. *J Pharmacokinet Biopharm* 1992; **20**: 63–94
12. Schuttler J, Kloos S, Schwilden H, Stoeckel H. Total intravenous anaesthesia with propofol and alfentanil by computer-assisted infusion. *Anaesth* 1988; **43**: 2–7
13. Glass PS, Shafer S, Reves JG. Intravenous drug delivery systems. In: Miller RD, editor. *Miller's anesthesia*. Philadelphia, PA, USA: Elsevier (Churchill Livingstone); 2005. p. 439–80
14. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 1998; **88**: 1170–82
15. Marsh B, White M, Morton N, Kenny GN. Pharmacokinetic model driven infusion of propofol in children. *Br J Anaesth* 1991; **67**: 41–8
16. Servin F, Farinotti R, Haberer J-P, Desmonts J-M. Propofol infusion for maintenance of anesthesia in morbidly obese patients receiving nitrous oxide. A clinical and pharmacokinetic study. *Anesthesiology* 1993; **78**: 657–65
17. Cortinez LI, Anderson BJ, Penna A, et al. Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model. *Br J Anaesth* 2010; **105**: 448–56
18. Cortínez LI, Sepúlveda P, Rolle A, Cottin P, Guerrini A, Anderson BJ. Effect-site target-controlled infusion in the obese. *Anesth Analg* 2018; **127**: 865–72
19. Kataria BK, Ved SA, Nicodemus HF, et al. The pharmacokinetics of propofol in children using three different data analysis approaches. *Anesthesiology* 1994; **80**: 104–22
20. Absalom A, Amutike D, Lal A, White M, Kenny GNC. Accuracy of the 'Paedfusor' in children undergoing cardiac surgery or catheterization. *Br J Anaesth* 2003; **91**: 507–13
21. Absalom A, Kenny G. 'Paedfusor' pharmacokinetic data set. *Br J Anaesth* 2005; **95**: 110
22. Araújo AM, Machado H, Pinho PG, Soares-da-Silva P, Falcão A. Population pharmacokinetic-pharmacodynamic modeling for propofol anesthesia guided by the bispectral index (BIS). *J Clin Pharmacol* 2020 May; **60**: 617–28
23. Short TG, Campbell D, Frampton C, et al. Anaesthetic depth and complications after major surgery: an international, randomised controlled trial. *Lancet* 2019; **394**: 1907–14
24. Park JH, Choi SM, Park JH, et al. Population pharmacokinetic analysis of propofol in underweight patients under general anaesthesia. *Br J Anaesth* 2018; **121**: 559–66
25. Eleveld DJ. Target-controlled-infusion for special populations: how different is different enough? *Acta Anaesth Scand* 2019; **63**: 422–3
26. Hannivoort LN, Vereecke HEM, Proost JH, et al. Probability to tolerate laryngoscopy and noxious stimulation response index as general indicators of the anaesthetic potency of sevoflurane, propofol, and remifentanil. *Br J Anaesth* 2016; **116**: 624–31

Handling editor: Hugh C Hemmings Jr