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ORIGINAL RESEARCH

Assessment of the clinical validity of an adjusted Marsh pharmacokinetic model using an effect-site rate constant (k_{e0}) of 1.21 min^{-1}

JF Coetzee, A Links, AI Levin

Department of Anaesthesiology and Critical Care, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa
Corresponding author, email: *jfc@sun.ac.za*

Introduction: The first commercially available target-controlled infusion pump, the "Diprifusor", employed a "Marsh" pharmacokinetic-pharmacodynamic parameter set, and this model (the Diprifusor-Marsh model) is also available in several of today's pumps. However, it is unsuited for effect-site, target-controlled infusions (C_e-TCI) because it assumes slow transfer between blood and the effect-site (k_{e0} = 0.26 min^{-1}). We hypothesised that a faster k_{e0} of 1.21 min^{-1} (Adjusted-Marsh model) for C_e-TCI would result in hypnotic effects equivalent to that of the Schnider parameter set (Schnider model).

Methods: We replicated a previously published study that demonstrated the Diprifusor-Marsh model's unsuitability for C_e-TCI. We randomised 40 unpremedicated young adults into two groups to receive C_e-TCI, employing either the Schnider model or the Adjusted-Marsh model. We infused propofol at 3 000 mg.$hour^{-1}$, while running a pharmacokinetic simulation and recording the electroencephalographic bispectral index (BIS) electronically. At loss of consciousness (LOC), indicated by a syringe-drop, we converted the infusion to C_e-TCI, targeting the effect-site concentration (C_e) observed at LOC, for 20 minutes. We regarded a difference of 10 BIS-units as clinically important.

Results: There were no statistically significant differences between the group medians regarding time-to-LOC, induction-dose, BIS at LOC and C_e-target. BIS decreased monotonically in both groups from a median of 78.5 at LOC to a steady-state median (25–27) at 15 minutes. The BIS of the Adjusted-Marsh model group closely followed the BIS of the Schnider model group. At steady state, the median BIS difference (95% CI) was -0.3 (-5.7 to 5.3), which was within the predefined interval for declaring equivalence. The Schnider model group's mean BIS at steady state did not differ from that of the previous study's Schnider model group.

Conclusion: Reasons for the progressive BIS decrease to lower than expected values include delayed response-times by the BIS monitor, C_e overshoot explained by front-end kinetics, neural inertia and the choice of surrogate LOC indicator. We conclude that C_e-TCI using the Adjusted-Marsh parameter set results in equivalent hypnotic effects to those of the Schnider model, with the proviso that this may apply only to young adults of normal body habitus.

Keywords: propofol, drug delivery systems, pharmacokinetic model, pharmacodynamics, bispectral index monitor

Introduction

Target-controlled infusions (TCIs) are universally recognised techniques for administering anaesthetic drugs.[1] These pumps administer drugs according to pharmacokinetic-pharmacodynamic (PK-PD) simulations based upon multicompartment mammillary models, consisting of multi-exponential equations.[2] With regard to propofol, the Marsh[3] and Schnider[4] parameter sets currently feature in TCI pumps which comprise three-compartment models with an added effect-site compartment. TCI pumps provide one or both of two variants of the Marsh model, either (i) the original Diprifusor parameter set[3] that was programmed into the earliest TCI pump (Diprifusor-Marsh) or (ii) an Adjusted-Marsh model.[5] These two parameter sets are identical, except for the k_{e0} rate constant, a parameter that determines the rate of drug transfer between blood and effect-site. The Diprifusor-Marsh model[3] employed a k_{e0} of 0.26 min^{-1}, that specified a relatively slow propofol transfer between blood and effect-site. Thus, a simulated propofol bolus dose using the original model predicts a time-to-peak effect-site concentration at 4.5 minutes. The Diprifusor-Marsh model is mathematically incorrect because it adopted the k_{e0} from a separate study.[6] Subsequent research has demonstrated that the movement of propofol between blood and effect-site occurs faster (a time-to-peak-effect of 1.6 minutes).[4,7,8] A k_{e0} of 1.21 min^{1} results in a peak effect-site concentration of 1.6 minutes (the Adjusted-Marsh model).

A study by Coppens et al.[9] (the Coppens study) compared the time course of the clinical effect of propofol with predicted effect-site concentrations (C_e) after a rapid infusion, using both the Diprifusor-Marsh and the Schnider models. They demonstrated that the slow k_{e0} associated with the Diprifusor-Marsh model is unsuitable for targeting the effect-site (C_e-TCI).

We aimed to replicate the Coppens study, comparing the Adjusted-Marsh and Schnider models. The purpose was to determine whether C_e-TCI using the Adjusted-Marsh model for propofol (using a k_{e0} = 1.21min^{-1}), would result in hypnotic effects equivalent to those produced when using the Schnider model. The hypothesis was that C_e-TCI using the Adjusted-Marsh model results in bispectral index (BIS) values equivalent to C_e-TCI using the Schnider model. The primary outcome was the difference in BIS values and the secondary outcomes were comparisons between results from this study with results from the Coppens study.

Methods

Approval was obtained from the Ethics Committee. Adult participants aged 18–65 years, ASA status I-II, who were scheduled for surgery under general anaesthesia gave informed, written consent. We randomised these participants into two groups: (i) the Adjusted-Marsh model group and (ii) the Schnider model group, according to preprepared random numbers (obtained from https://www.randomizer.org/#randomize). Exclusion criteria included participants < 18 years; weight < 70% or > 130% of ideal body weight; any neurological disorder; cardiac, renal or hepatic dysfunction; myopathies and muscular dystrophies; potential airway problems; recent psychoactive medication; and those who required/requested premedicant drugs (e.g. tranquilisers, sedatives, opioids, beta-blocking drugs).

Our methodology was similar to the method described by Coppens et al.[9] No patient received preoperative medication. Using infiltration local anaesthesia, we placed an 18G intravenous line in a large forearm vein. No fluid load was given. Participants received about 300 ml of crystalloid fluid during the study period; no other drugs, including opioids, were administered. Participants breathed spontaneously via a face mask attached to a circle breathing system delivering 100% of oxygen at 6 $L.min^{-1}$. A GE-Datex-Ohmeda-S5 unit (GE-Healthcare, Helsinki, Finland) monitored the participants' heart rate, non-invasive arterial pressure, arterial oxygen saturation and capnography at one-minute time intervals. We monitored ventilatory frequency and airway patency from a sampling line of a side stream capnometer inserted into the face masks.

We monitored the BIS via frontally-placed electrodes (FPz-FT9 and FP1-FT9) using a BIS-XP monitor (Aspect Medical Systems, Inc., Norwood, MA, USA), with the smoothing time set to 15 s. We captured BIS data to a computer text file at 5-second intervals using proprietary software. TCI software (StelTCI [created by JF Coetzee & P de Kock]) connected via a computer's serial port to an infusion pump (Graseby model 3500 infusion pump [Smiths Medical, Ashford, Kent, UK]) administered propofol intravenously. The StelTCI software adjusted the pump's infusion rate every 10 s. It also recorded data to a computer text file contemporaneously (elapsed time, pump speed, drug dose and the drug concentrations in the model's compartments). A StelTCI utility of specific relevance to this study, was that it permits drug administration to be switched "on the fly" between different regimens, such as between continuous infusion, TCI targeting the plasma concentration (C_p-TCI) and C_e-TCI.

Before propofol administration, the investigator asked the participating patient to relax and close their eyes for 2 minutes, while grasping a fluid-filled 20 ml syringe between their thumb and forefinger from a supported, outstretched arm. Meanwhile, the investigator verified the electroencephalograph (EEG) signal quality and electrode impedance, and confirmed successful data capture. He then induced unconsciousness by administering propofol 1% at a constant rate of 300 $ml.h^{-1}$. Simultaneously, the StelTCI simulation software calculated the corresponding effect-site concentrations, in real time, using either the Schnider model or the Adjusted-Marsh model. We considered loss of consciousness (LOC) to be the instant of syringe-drop. Thereafter, the investigator changed the infusion regimen from constant-rate to C_e-TCI for a further 20 minutes. The C_e target was the calculated C_e that he observed at syringe-drop. Afterwards we administered appropriate opioid and muscle relaxant drugs, secured the patient's airway by laryngeal mask or tracheal intubation, and permitted surgery to proceed.

With sample size calculation, we regarded a difference of 10 BIS units as clinically relevant. The null hypothesis for this equivalence study was that there would be a difference between mean/median BIS values greater than 10 units. Thus:

$H0: (\mu_{Schnider} - \mu_{Marsh}) \leq -10$ or $(\mu_{Schnider} - \mu_{Marsh}) \geq 10$

Where $\mu_{Schnider}$ and μ_{Marsh} are mean/median BIS values achieved at steady state by the Schnider model and Marsh model groups, respectively. A minimal sample size of 17 participants per group has 90% power to demonstrate equivalent BIS values if alpha is 0.05 (Appendix A). Therefore, we decided to recruit 40 participants.

Data analysis

We imported the electronic text files into a Microsoft Excel spreadsheet and prepared the data for graphing and statistical analysis. The 5-second interval BIS values that were recorded were averaged to a single BIS value for each minute of the study. We analysed the data using MedCalc® Statistical Software (version 19.5.3 [MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020]). We compared groups using two-sided t-tests for independent samples. If data did not meet the requirements for parametric tests (Shapiro–Wilk test for normal distribution and F-test for equal variances), we performed a distribution-free nonparametric test (Mann–Whitney test for independent samples). For this test, the MedCalc® software calculates the Hodges–Lehmann median difference and its 95% confidence interval.[10] Using the Statpages website (https://statpages.info/anova1sm.html), we used a one-way analysis of variance (ANOVA) to compare our results with those of the Coppens study.[9] We regarded an alpha value < 0.05 as indicating statistical significance. We estimated effect sizes by calculating Cohen's *d*, using the Psychometrica website (https://www.psychometrica.de/effektstaerke.html). See Table AI in Appendix A for an interpretation of Cohen's *d* effect sizes.

Results

Twenty participants per group completed this study. Demographics indicate that there was a preponderance of males in the Adjusted-Marsh group (Table I). Table II displays the results of the comparison between the two model groups. There were no statistically significant differences regarding awake BIS values, times to LOC, propofol induction doses (mg/kg) and BIS at LOC. Accompanying effect sizes were small (Cohen's $d = 0.01$ to 0.41). The mean (standard deviation [SD]) C_e targets for the Schnider model group and Adjusted-Marsh model group were 6.8 (1.3) µg/ml and 6.1 (1.2) µg/ml, respectively. These did not differ significantly, despite the moderate effect size (Cohen's $d = 0.56$).

During C_e-TCI, BIS values decreased monotonically over time to reach steady state after approximately 12 minutes (Figure 1). We visually judged steady state to have been established in both groups at 15 minutes. At each one-minute interval, there were no statistically significant differences between the median BIS values of the two model groups. At 15 minutes the median difference was 0.3 BIS units (95% CI from -5.7 to 5.3). Mean total doses over the 15-minute period did not differ significantly despite a moderate effect size (Cohen's $d = 0.53$).

Table III displays the comparison with the Coppens study. Target C_e's and resulting BIS values at steady state differed significantly between the Diprifusor-Marsh model and Adjusted-Marsh model groups. The accompanying effect sizes were large (Cohen's $d = -4.3$ for targeted C_e and $d = 6.0$ for BIS at steady state). Steady state BIS values did not differ between the three groups: our Schnider model group, the Coppens Schnider model group and our Adjusted-Marsh model group; mean ± SD being 31.0 ±10.3, 29.0 ± 6 and 30.5 ± 10.2, respectively. The 99% CIs of the differences between these three means ranged from -8.7 to 9.3.

Table I: Demographic details

		Schnider	Adjusted-Marsh
Age (years)	Median	38.5	30.5
	95% CI	27.0–30.5	23.8–32.0
	Range	21.0–68.0	18.0–51.0
Weight (kg)	Median	68.5	63.0
	95% CI	56.5–72.0	60.0–67.5
	Range	47.0–106.0	47.0–92.0
Height (m)	Median	1.69	1.70
	95% CI	1.63–1.72	1.64–1.73
	Range	1.19–1.82	1.56–1.88
M/F		10/10	17/3

* 95% CI – 95% confidence Interval of the median value

Discussion

The different propofol k_{e0} rate constants have created confusion and controversy,[6,11] as several TCI pumps implement both the Diprifusor-Marsh and Adjusted-Marsh models, while others provide only the original, "slower" k_{e0}. Furthermore, the correct k_{e0} is critical for patient care, both to avoid under- or overdosing, and to prevent deleterious haemodynamic effects or awareness. We, therefore, investigated the suitability of the faster k_{e0} by targeting C_e-LOC using either the Adjusted-Marsh model or the Schnider model.

Our study mirrored the Coppens study. Both studies induced unconsciousness using the same dose rate to all participants. At LOC, the effect on the BIS should theoretically be the same in all groups. However, it was likely that the different models would calculate different effect-site concentrations, because they use different parameter sets. If the faster k_{e0} was indeed suitable for C_e-TCI, then targeting C_e-LOC should produce equivalent BIS values in both the Adjusted-Marsh model and the Schnider model groups. In our study, all Adjusted-Marsh model group participants remained clinically unconscious and the BIS values

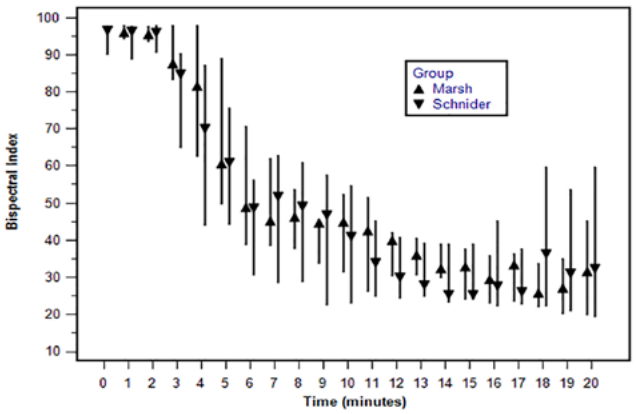

Figure 1: BIS values at one-minute intervals
* Error bars depict 95% confidence intervals of the median values.

Table II: Results of the infusion study

Variable	Group	N	Mean/Median	SD/IQR	P	Difference (95% CI)	Effect size (Cohen's *d*)
Baseline BIS	Schnider	20	97.5	95.0–98.0	0.199	-1.1 (-3.2–0.2)	0.41
	Marsh	20	95.2	91.8–97.9			
Time to LOC (min)	Schnider	20	3.0	2.5–4.0	0.190	0.5 (0.0–1.0)	0.41
	Marsh	20	3.75	3.0–4.0			
Induction dose (mg)	Schnider	20	162	38	0.486	14 (-8–37)	0.41
	Marsh	20	176	32			
Induction dose (mg/kg)	Schnider	20	2.4	0.7	0.120	0.3 (-0.1–0.7)	0.15
	Marsh	20	2.5	0.6			
BIS at LOC	Schnider	20	78.5	72.7–83.0	0.808	-1.0 (-13.0–7.0)	0.08
	Marsh	20	78.5	55.5–83.0			
Target Ce (µg/ml)	Schnider	20	6.8	1.3	0.118	-0.7 (-1.5–0.2)	0.56
	Marsh	20	6.1	1.2			
15 min BIS	Schnider	19	25.3	24.0–38.3	0.966	-0.3 (-5.7–5.3)	0.01
	Marsh	20	27.2	24.1–34.3			
15 min Dose (mg)	Schnider	19	421	77.0	0.102	-36 (-80– 8)	0.53
	Marsh	20	385	56.4			

#SD – standard deviation, IQR – interquartile range, 95% CI – 95% confidence interval, Difference – difference between the mean values or median difference

Table III: Between study comparisons

	Schnider model		Marsh model		Cohen's *d*	Significant differences*
	Present study (Group 1)	Coppens et al.[9] (Group 2)	Present study (Group 3)	Coppens et al.[9] (Group 4)		
Time to LOC (s)	204 (59)	163 (25)	222 (5)	163 (59)	-0.8 -0.7 3.2 -1.4	1 vs 2 1 vs 4 2 vs 3 3 vs 4
BIS at LOC	74 (18)	59 (14)	72 (19)	59 (12)	-0.9 -1.0	1 vs 2 1 vs 4
BIS at steady state	31.0 (10.3)	29 (6)	30.5 (10.2)	77 (4)	5.9 9.4 6.0	1vs 4 2 vs 4 3 vs 4
Target C_e ($\mu g/ml^{-1}$)	6.8 (1.3)	5.5 (0.8)	6.1 (1.2)	2.0 (0.6)	-1.2 -4.7 -5.0 -4.3	1 vs 2 1 vs 4 2 vs 4 3 vs 4

#Data are mean (standard deviation)
*Analysis of variance: Tukey HSD post hoc test

closely matched that of our Schnider model group over time (Figure 1). At 15 minutes the median difference was negligible (0.3 BIS units; 95% CI from -5.7 to 5.3). This interval falls well within the prespecified acceptable 95% CI difference for accepting equivalence (-10 to 10 BIS units). (See the supplementary file for a graphical depiction of the concept.) Thus, although the two PK-PD models were targeting slightly different C_e's, the hypnotic effects, as reflected by the BIS monitor, were equivalent. Interestingly, the groups' C_e targets (mean (SD) 6.8 (1.3) versus 6.1 (1.2) $\mu g.ml^{-1}$) did not achieve statistical significance. Nonetheless, the effect size (Cohen's d = 0.56) indicated that a moderate difference did exist. Thus, it is possible that our study was inadequately powered to demonstrate a statistically significant significance between mean C_e targets.

Conversely, in the Coppens study,[9] all 20 participants in the Diprifusor-Marsh model group regained consciousness after a mean elapsed time of 6.7 (SD 1.7) minutes. At 11 minutes, the awakened Diprifusor-Marsh model group exhibited a mean BIS of 77 (SD 4). This was the consequence of a much lower C_e target than that of the Schnider model group; 2.0 $\mu g.ml^{-1}$ (SD 0.6) versus 5.5 $\mu g.ml^{-1}$ (SD 0.8). The low C_e target had resulted from the assumption of slower transfer between blood and effect-site.

Another interesting finding is that, similar to the Coppens' Schnider model group, targeting the C_e-LOC did not result in stable hypnosis. Indeed C_e-TCI to both our Schnider model and Adjusted-Marsh model groups resulted in a monotonic decrease in the BIS. The mean steady state BIS values of our two groups and the Coppens' Schnider model group were remarkably similar, albeit lower than expected (see Table III).

The progressive BIS decreases after changing to C_e-LOC, were probably caused by high blood concentrations. These excessive concentrations were likely caused by multiple factors, including (i) the BIS monitor's response time, (ii) the PK-PD model misspecification (front-end kinetics), (iii) the differing C_e requirements for induction and maintenance of the unconscious state, and (iv) the choice of LOC surrogate.

Response-time delay of the BIS monitor

The actual response time of the BIS monitor may be considerably greater than the manufacturer's specified 5–10 seconds. Ferreira et al.[12] compared, measured and predicted BIS values in the 3 minutes after BIS decreased below 80 during propofol induction of anaesthesia. They based their predictions on the Schnider PK-PD model as well as the PD parameters of Bruhn et al.[13] They demonstrated a mean delay of 30.09 s (95% CI 24.62 s to 35.56 s) between measured and predicted values. Pilge et al.[14] determined the response times of three EEG monitors, including the BIS, using simulated EEG signals. They tested abrupt EEG changes between an awake state (BIS = 98), anaesthesia (BIS = 52) and iso-electricity; as well as between smaller intermittent steps (BIS: 9, 21, 38, 52, 63, 74 and 86). Time delays were inconstant, ranging from 14–66 seconds for abrupt changes from awake to anaesthesia, and from 15–66 seconds during smaller steps. The same group later verified their findings using recorded EEG signals from patients undergoing surgery.[15]

Model misspecification (front-end kinetics)

The algorithms used by target-controlled infusion pumps are based on two- or three-compartment mammillary PK-PD models. These models assume that a drug is injected into a central compartment from where the drug is distributed and redistributed between one or more peripheral compartments. The central compartment is supposed to contain the blood volume and unspecified "organs with a rapid blood supply". The peripheral compartments include other organs to which the drug is distributed and redistributed more slowly. In the PK-PD model, the effect compartment is attached to the central compartment and has a negligible volume of distribution. When programmed into TCI pumps, these models can achieve and maintain targeted blood concentrations, and also predict C_e with clinically acceptable precision.[16] They have even been used successfully to provide closed-loop anaesthesia.[16] However, the models err regarding the fate of injected drugs during the initial few minutes of infusion.[17] This weakness results from treating the central compartment as a well-stirred "black box", within

which the drug is distributed instantaneously upon injection (Figure 2A). In reality, it is the "front-end kinetics",[18] a chain of physiological and anatomical events, from the site of entry to the cerebral circulation, that determine the time course of arterial concentrations and, ultimately, the effect-site concentrations.[17,19] Firstly, drug is mixed in the venous flow before entering the lungs, through which it must undergo a first-pass before arriving in the systemic circulation. The lungs delay the passage of drugs and may even remove some.[20-22] The systemic circulation distributes the drug to various organs (including the brain) which also subjects it to first-pass processes. Thereafter, a portion is returned to the venous side of the circulation and is recirculated. Figure 2B illustrates that much more takes place within the central "black box".

Ludbrook and Upton[23,24] described propofol's front-end kinetics by compiling and verifying a 6-compartment physiological sheep model that describes propofol's front-end kinetics. Their model includes first-pass events and recirculatory phenomena. They performed a sensitivity analysis[23] in which they demonstrated the roles played by various model components. Simulating a short, rapid propofol infusion, they showed that including drug recirculation into the model resulted in increases in the following: time-to-peak-effect (20%), peak arterial concentration (51%), peak brain concentration (32%) and increased duration of effect (108%). One simulation may be relevant to both our and the Coppens studies. A simulated rapid propofol infusion (200 $mg.min^{-1}$) just until LOC, resulted in significant "overshoot", with propofol brain concentrations continuing to rise for 3 minutes, to reach a peak concentration 2–3 times greater than when the infusion had been stopped.

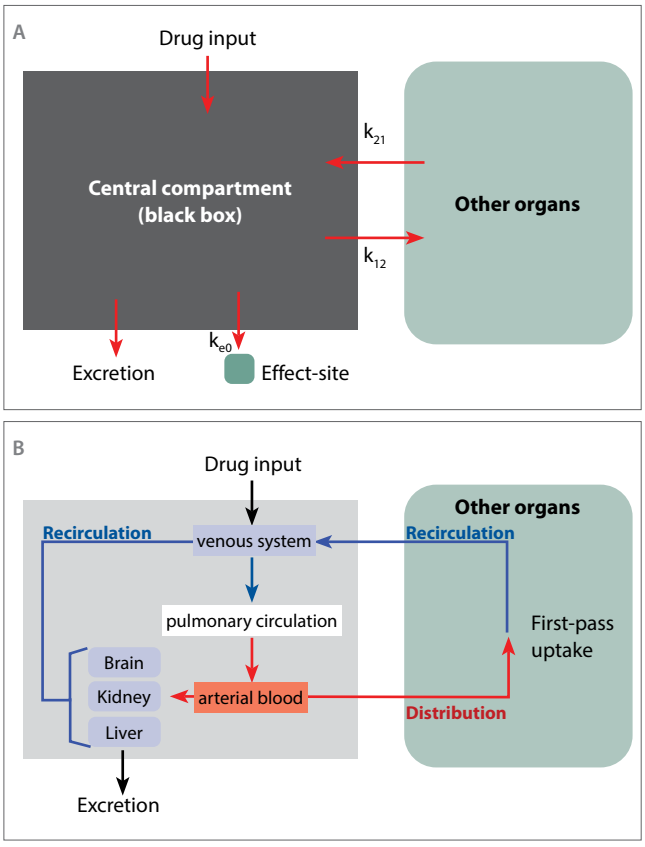

Figure 2: Differences between a 2-compartment mammillary pharmacokinetic model and a recirculatory pharmacokinetic model

A – Concept diagram of a two-compartment mammillary pharmacokinetic model. Drug is injected into the central compartment, within which it is instantaneously distributed. Drug is distributed and redistributed to a peripheral compartment at rates determined by the rate constants, k_{12} and k_{21}. The effect compartment has a volume of distribution of negligible size. The rate constant k_{e0}, determines the rate of drug transfer between the central compartment and the effect compartment.
B – Concept diagram of a recirculatory pharmacokinetic model.
Drug is injected into the venous circulation. There is a delay as drug passes through the lungs. The arterial system distributes drug to various organs within which there is first-pass uptake. A portion of drug is recirculated via the venous system.

Different C_e requirements for induction and maintenance of the unconscious state (neural inertia)

PK-PD models assume that the hysteresis that occurs between changing drug blood concentrations and changing effect, is solely due to the time taken for the drug to move between the blood and the effect-site. This assumes a single C_e versus effect curve. On observing that targeting the C_e-LOC resulted in progressively decreasing BIS and deeper levels of hypnosis, Coppens et al.[9] postulated that greater propofol concentrations may be required to cause LOC than to maintain the unconscious state. Several studies support this hypothesis. Martin-Mateos et al.[25] administered propofol by manually-controlled infusions to 42 patients undergoing surgery, while keeping BIS values between 40–60. They simultaneously recorded BIS values and employed a Schnider PK-PD simulation to estimate C_e. By fitting pharmacodynamic C_e versus response, E_{max} equations,[2] they demonstrated that greater propofol concentrations were required during induction than maintenance to achieve similar BIS values. The mean (95% CI) C_{e50} were 3.35 (2.79–3.91) $\mu g.ml^{-1}$ and 2.23 (1.95–2.51) $\mu g.ml^{-1}$, respectively. There were separate sigmoid C_e versus response curves for induction and maintenance. The slope of the curve was steeper during maintenance, implying greater responsivity to changes in C_e during maintenance; again, supporting the hypothesis of Coppens et al.[9] Animal experiments in fruit flies[26] and mice[27,28] also indicate that higher anaesthetic drug concentrations are required for induction than for emergence.

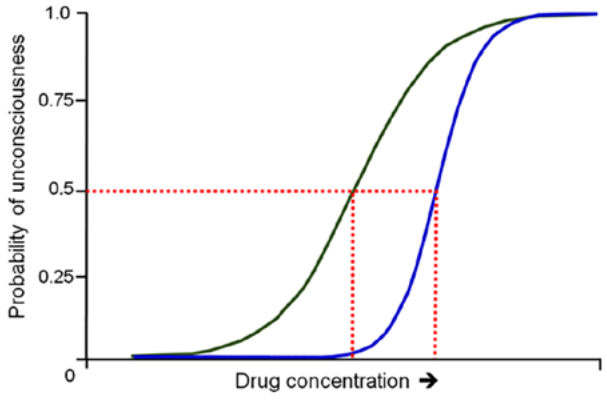

Figure 3: Effect-site concentration versus response curves for induction of unconsciousness and for recovery from an unconscious state

The concept of two separate effect-site concentration versus response curves for induction of unconsciousness (blue) and for recovery from unconsciousness to wakefulness (green). The red dotted lines indicate the different C_{e50}'s. Between the two curves there are drug concentrations at which a subject may be either unconscious or awake, depending on whether they are transitioning from wakefulness to unconsciousness or from unconsciousness to wakefulness.

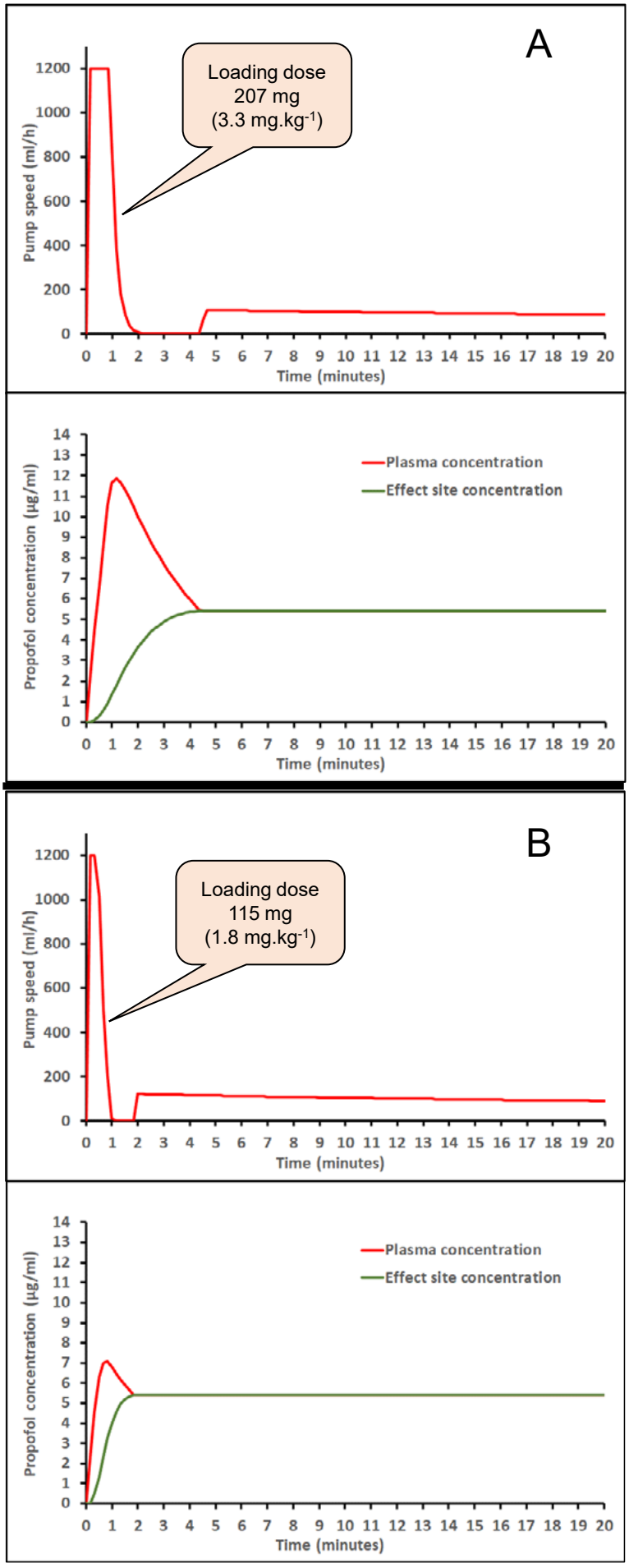

Figure 4: (Left) Simulations of effect-site target controlled infusions, to a patient weighing 63 kg, comparing (A) the Diprifusor-Marsh model (k_{e0} = 0.26 min^{-1}) and (B) the Adjusted-Marsh model (k_{e0} = 1.21 min^{-1})

The upper portions of Graphs A and B depict the infusion pump speed, the lower portions depict plasma and effect-site propofol concentrations. Targeted effect-site concentration 5.4 µg.ml^{-1}.

Graph A (k_{e0} = 0.26 min^{-1}) – The TCI pump administers an initial loading dose, then stops and waits. Meanwhile the plasma propofol concentrations decrease and the effect-site concentrations increase. The magnitude of the loading dose is such that the plasma and effect-site concentrations will meet at the set target. When this happens, the pump restarts and maintains the propofol concentrations at the specified target. The slow k_{e0} results in a slowly increasing simulated effect-site concentration. While the effect-site concentration is slowly increasing, propofol is escaping from the central compartment via distribution and excretion. The pump compensates by administering a large initial loading dose, in order to maintain a concentration gradient between the central compartment and the effect-site. This occurs at the cost of several minutes during which there are high plasma propofol concentrations.

Graph B (k_{e0} = 1.21 min^{-1}) – Simulated effect-site concentrations increase more rapidly. The pump's waiting period is shorter, during which time less drugs escapes from the central compartment. Thus, a smaller loading dose is required, resulting in lower initial plasma concentrations.
Simulations were performed using StelSim pharmacokinetic simulation software (Creators JF Coetzee and P de Kock, Stellenbosch 2007).

These findings appear to negate the usual PK-PD model's explanation for hysteresis. Recently, attention has been drawn to the phenomenon of *neural inertia*[29,30] as a partial explanation for anaesthetic hysteresis. Neural inertia describes the propensity of the brain to resist transitions between the states of consciousness and unconsciousness. According to this hypothesis, the response to changing concentrations depends on the brain's previous state. This implies that there are two different C_e versus response curves for induction and emergence from anaesthesia (Figure 3). A corollary of the neural inertia concept is that at a particular C_e, it is possible to be either awake or unconscious.[31] Unfortunately, confirming or refuting neural inertia in humans has proved difficult,[32-34] mainly because we cannot directly measure drug concentrations within human brains.[30] The effect-site PK-PD model remains a convenient mathematical concept by which we can predict anaesthetic hysteresis by employing a rate constant (k_{e0}).[2,8] However, evidence from animal experiments does suggest that anaesthetic hysteresis results at least partially from neural inertia.[31]

Choice of surrogates for loss of consciousness

Our times to LOC and our C_e targets differed from those of the Coppens study (Table III), possibly because of different LOC surrogates. Whereas the Coppens study used loss of response to name calling (LORNC), we employed the syringe-drop technique used by several previous anaesthetic induction studies.[35-38] We preferred the syringe-drop method because South Africans speak several different languages and an interpreter was not always available

to participate in the LORNC procedure. However, it is possible that neither surrogates precisely indicate the instant of LOC. For example, in isolated forearm experiments,[39] responses to verbal commands are not necessarily associated with explicit recall.[40] Regarding syringe-drop, loss of muscle tone may happen after LOC, resulting in errors in identifying the exact moment of LOC. Furthermore, neural inertia may well occur at spinal level.

We replicated Coppens' study in order to demonstrate equivalence of C_e-TCI when using the Schnider and Adjusted-Marsh pharmacokinetic parameter sets. Our targets were calculated C_e observed at LOC. However, our methodology may have not been entirely suitable. We could perhaps have made a more direct comparison by simply targeting a set C_e for all three models and recording BIS. Struys et al.[5] administered C_e-TCI using the two versions of the Marsh model. The C_e target was 5.4 $\mu g.ml^{-1}$. The induction dose administered to their Diprifusor-Marsh model group was 204 mg, SD 36; (3.3 mg/kg). This resulted in a greater and more precipitous blood pressure decrease in the Diprifusor-Marsh model group than in the Adjusted-Marsh model group. Thus, targeting the effect-site using the original Marsh slow k_{e0}, could have resulted in adverse haemodynamic effects, resulting from a large induction dose (Figure 4). C_e-TCI begins with a rapidly-infused loading dose that produces high initial C_p, much higher than the desired C_e target. After administering the loading dose, the pump pauses, and Cp decreases exponentially. When the Cp declines to reach targeted C_e, the pump restarts to maintain C_e target. The Diprifusor-Marsh model has a large central volume of distribution and a slow k_{e0}. The initial loading dose is deliberately large, with the intention of filling the central compartment and also to compensate for distribution and elimination that cause loss of propofol out of the central compartment. Thus, we considered it prudent to target the C_e-LOC. Our approach also enabled us to make historical comparisons with the Coppens study. (For a further explanation as to why the Diprifusor-Marsh model overdoses during TCI and underdosed in the Coppens study, see the supplementary file.)

A weakness of our study is that results and conclusions likely apply only to young adults. The reason for this is that the Schnider model adjusts pharmacokinetic parameters according to weight, age and gender.[8] For a certain C_e target, the model administers reduced doses in elderly patients. On the other hand, the Marsh model assumes a fully linear model, dependent only on weight, and its application to elderly patients may involve risk of overdosage.

Conclusion

We conclude that propofol effect-site target-controlled infusions using either the Schnider or the Adjusted-Marsh pharmacokinetic parameter sets produce similar EEG changes as measured by the BIS in healthy young adults. Secondary findings illustrate the inability of the BIS monitor to track rapid EEG changes as well as the inability of traditional multicompartment mamillary models to predict front-end kinetics. Pharmacodynamic hysteresis may be partly explained by the neural inertia phenomenon.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

This study was approved by The Health Research Ethics Committee, Faculty of Medicine and Health Sciences, Stellenbosch University (Reference No: N10/07/228).

ORCID

JF Coetzee https://orcid.org/0000-0002-9925-7767
A Links https://orcid.org/0000-0002-4262-3754
AI Levin https://orcid.org/0000-0001-7638-2840

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Appendix A

Calculation of sample size

The null hypothesis for this equivalence study was that there would be a difference between the mean values greater than 10 BIS units. Thus,

H0: $(\mu_{Schnider} - \mu_{Marsh}) \leq -10$ or $(\mu_{Schnider} - \mu_{Marsh}) \geq 10$

Where $\mu_{Schnider}$ and μ_{Marsh} are the mean BIS values achieved at steady state by the Schnider model and Marsh model groups, respectively.

Otherwise stated, the null hypothesis was that the 95% confidence interval of the difference between the means would include -10 or 10 BIS units or would include both. The alternative hypothesis was that the lower and upper limits of the 95% confidence interval of the difference between the mean values would lie somewhere between > (-10) and < 10 BIS units, respectively. The formula for calculating the sample size (*n*) is:[41]

$$n = 2 * \left\{ \frac{z_{(1-\alpha)} + z_{(1-\frac{\beta}{2})}}{Standarised\ mean\ difference} \right\}^2$$

Where the

$$Standardised\ mean\ difference = \frac{Clinically\ relevant\ difference}{Standard\ deviation\ of\ the\ outcome}$$

From the 2-sided z-table, $z_{(1-\alpha)} = 1.96$, for alpha = 0.05 and $z_{(1-\beta/2)} = 1.65$ for $\beta = 0.1$

We assumed that at steady state the standard deviation of the mean BIS values would be similar to that in the study by Coppens et al.[9], namely 8 BIS units. Thus, the estimated standardised mean difference for our sample size calculation was 10/8 = 1.25. The sample size is, therefore:

$$n = 2 * \left\{ \frac{1.96 + 1.65}{1.25} \right\}^2$$

Resulting in a sample size of 16.7 (rounded to 17) per group.

Table AI: Interpretation of Cohen's *d* effect sizes

d	Interpretation
0.0 0.1	No effect
0.2 0.3 0.4	Small effect
0.5 0.6 0.7	Moderate effect
0.8 0.9 ≥1.0	Large effect

Table AII: The Marsh and Schnider pharmacokinetic parameter sets

Model parameters	Marsh[3]	Schnider[4,8]
V1	0.228 Litre.kg^{-1}	4.27 litre
V2	0.463 Litre.kg^{-1}	18.9 - 0.391x(age-53) litre
V3	2.893 Litre.kg^{-1}	238 litre
k_{10} (min^{-1})	0.119	0.443+0.0107 x (weight-77) -0.0159 x (LBM-59) + 0.0062 x (height-177)
k_{12} (min^{-1})	0.112	0.302 - 0.0056 x (age-53)
k_{13} (min^{-1})	0.042	0.196
k_{21} (min^{-1})	0.055	[1.29–0.024 x (age-53)] / [18.9–0.391 x (age-53)]
k_{31} (min^{-1})	0.0033	0.0035
k_{e0} (min^{-1})	0.26[§]	0.456
TTPE* (min)	4.5	1.6

[§] For the Adjusted Marsh model k_{e0} = 1.21 min^{-1}
* TTPE – Time-to-peak-effect

Supplement

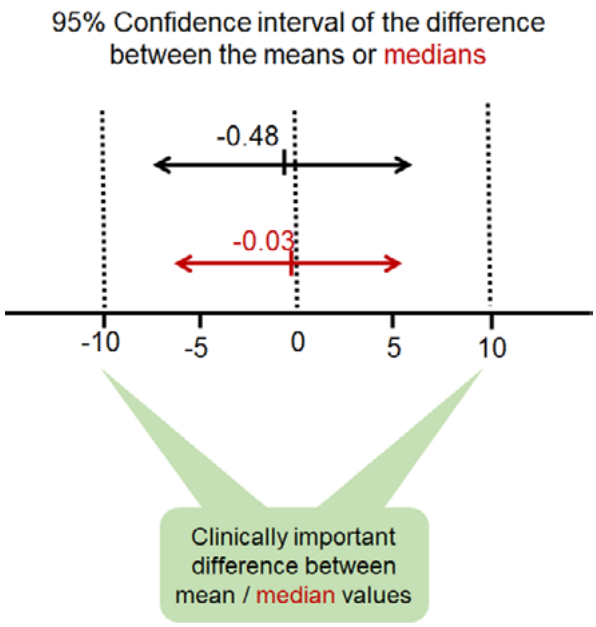

Figure S1: Concept diagram illustrating how the BIS values at 15 minutes elapsed time (i.e. at steady state), met the requirements for declaring equivalence between the Adjusted-Marsh group and the Schnider group.
The horizontal scale indicates differences between mean or median BIS values. Vertical dotted lines indicate plus or minus minimal clinically important differences between BIS values. Double-headed arrows indicate 95% confidence intervals of the differences.
The null hypothesis was that the 95% confidence interval would extend beyond one or both of the vertical dotted boundary lines. The alternative hypothesis was that the 95% confidence intervals would be within the boundaries.

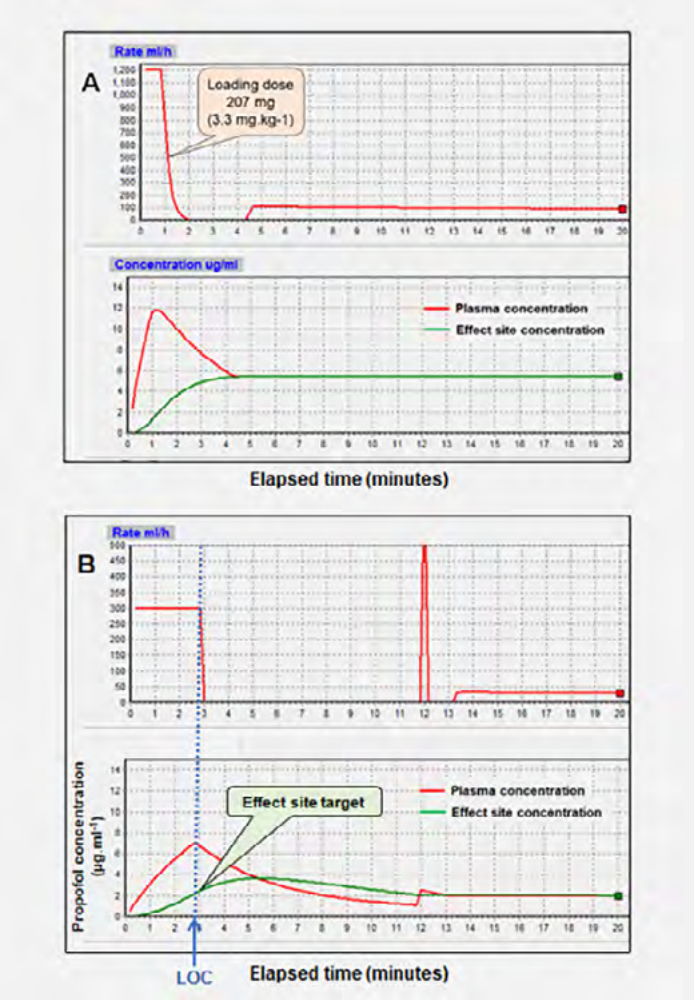

Figure S2: Graphs illustrating how C_e-TCI using the Diprifusor-Marsh model results in overdose (Graph A) and how in the Coppens study it resulted in underdose.
LOC – loss of consciousness
Graph A: The effect-site TCI is begun at the start of the procedure. The pump delivers a large loading dose (3.3 $mg.kg^{-1}$) by means of a short, rapid infusion, in order to compensate for loss of propofol via excretion and distribution while the effect-site concentration slowly increases towards the target of 5.4 $\mu g.ml^{-1}$.
Graph B: The effect-site TCI is begun only after LOC is achieved by delivering a smaller dose (2.2 $mg.kg^{-1}$) over a longer period. The effect-site target is taken as the simulated effect-site concentration at the time of LOC. This is a low concentration because of the simulated slow increase in effect-site concentration during the initial constant-rate infusion. Note the lower peak plasma propofol concentration, compared with Graph A.