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Review Article

Anomalies in target-controlled infusion: an analysis after 20 years of clinical use

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Summary

Although target-controlled infusion has been in use for more than two decades, its benefits are being obscured by anomalies in clinical practice caused by a number of important problems. These include: a variety of pharmacokinetic models available in open target-controlled infusion systems, which often confuse the user; the extrapolation of anthropomorphic data which provokes anomalous adjustments of dosing by such systems; and the uncertainty of regulatory requirements for the application of target-controlled infusion which causes uncontrolled exploitation of drugs and pharmacokinetic models in target-controlled infusion devices. Comparison of performance of pharmacokinetic models is complex and mostly inconclusive. However, a specific behaviour of a model in a target-controlled infusion system that is neither intended nor supported by scientific data can be considered an artefact or anomaly. Several of these anomalies can be identified in the current commercially available target-controlled infusion systems and are discussed in this review.

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Introduction

Target-controlled infusion (TCI) is a particular implementation of automated intravenous drug administration in which specifically-designed software adjusts the rate of drug delivery to achieve an anticipated and user-adjustable target concentration of the drug in blood (TCI_B) or at the effect-site (TCI_E). The infusion rates are calculated by means of a pharmacokinetic (PK) model of the drug, supplemented with the blood effect-site equilibration rate constant (ke0). Target-controlled infusion has been around for more than two decades [1, 2]. Initially intended for creating stable blood concentrations and, consequently, stable conditions for research purposes [3], it soon became a useful and appreciated clinical tool for the administration of propofol for anaesthesia. The first commercial release of a TCI device (Diprifusor™) and corresponding tagged, single-use, pre-filled syringes of propofol came to the market under the responsibility of ICI (now AstraZeneca). The Diprifusor is a closed hardware module suited for the administration of propofol with only one PK model that is an intrinsic part of the commercially available infusion pumps [4]. Soon thereafter, so called 'open TCI' systems became available. These were capable of administering multiple drugs in TCI mode with different PK models derived from a variety of studies. In contrast to the Diprifusor, the pump manufacturers of open TCI systems (rather than the pharmaceutical companies) were responsible for the selection and application of PK models. Most of these PK models are parameterised with specific patient characteristics such as weight, height, age and sex. Since each PK model is

based on a specific patient population, these models are only valid for parameter values within the limits of the studied population, such as age and weight. However, open TCI systems do not take these limits into account. Although in a recent publication the use of TCI in clinical practice was considered mature, safe and practical [5], blind extrapolation of research data (i.e. the various PK models) into clinical practice may lead to anomalies with significant clinical impact. In this review, we will discuss anomalies that have been recognised and corrected in the past as well as issues that continue to distort the benefits of current open TCI systems. Although some open TCI systems allow administration of a large variety of drugs, this review will focus on propofol, remifentanil and sufentanil, as these three drugs are available in all open TCI systems.

Propofol

Four distinct PK models are available in open TCI systems for adults: the Marsh model (the original PK model implemented in the Diprifusor) [6]; the Schnider model [7] with a fixed ke0 ($Schnider_K$); the Schnider model with variable blood effect-site equilibration constants but fixed time to peak effect (TPE) ($Schnider_T$); and the modified Marsh model with a shorter ke0 based on a published TPE (MMarsh) [8]. We will discuss several issues which, in our view, potentially affect the use of these models in clinical practice.

Lean body mass

The Marsh model was derived from venous blood samples from 200 patients. The single influencing parameter is patient weight which affects the model in a linear fashion (i.e. a 120-kg patient will receive twice the amount of propofol of a 60-kg patient at any point in time during TCI). The linearity is related to the rather simple parameterisation of the model; it is expressed in rate constants (with units.$time^{-1}$) and clearance is expressed as volume per weight and time units ($ml.kg^{-1}.h^{-1}$). For further explanation on how the model descriptors affect the PK components see Appendix 1.

The parameterisation of the Schnider model is more complex. It has a central compartment with a fixed small volume and clearance is dependent on weight, lean body mass and height. Additionally, the fast distribution is age dependent. The model was derived from 10 younger and 10 older patients. The objective of the study was to assess whether the method of drug administration (bolus or infusion), age and the addition of a preservative to the propofol would affect PK model estimates. After implementation of the PK model into open TCI systems, an error was discovered in the formula used for the calculation of lean body mass [9]. At increasing weights and heights, lean body mass reaches a maximum after which it decreases and may even become negative (Fig. 1). Consequently, since in this model clearance is inversely related to lean body mass but positively related to weight and height, clearance increases to irrationally high values in obese individuals. (Fig. 2).

After recognition of the erroneous lean body mass calculation, the pump manufacturers adapted the algorithm in such a way that lean body mass cannot decrease beyond its maximum. However, in practice, this adaptation works out differently in individual open TCI systems. In some systems from manufacturers Fresenius Kabi (Fresenius, Brezins, France) and Arcomed (Acomed Medical Systems, Regensdorf, Switzerland), patient data are entered before drug and model selection. If the calculated lean body mass exceeds a limit (a pre-set maximum), selection of the Schnider model (or the Minto model for remifentanil) is disabled. Enabling is only possible by returning to previous settings and by entering a different weight for lean body mass (below the limit). In other systems from manufacturers Alaris (Alaris Medical later BD, Berkshire, UK) and B Braun (B.Braun Melsungen AG, Melsungen, Germany), drug and model selection precede selection of weight and height. Since potential values for both parameters are limited to prevent lean body mass values exceeding its maximum, the user will have to decide how to use the model despite its misfit in patient data input. Not all clinicians are aware of this issue and some will be left wondering why, during induction of anaesthesia, specific inputs to the model are not accepted by the TCI system. The work-around solutions are to input (incorrect) values within the default limits of the system or to induce the patient manually. This will certainly distract the anaesthesia care giver in a critical phase of anaesthesia and potentially jeopardise patient safety. In Table 1, an overview

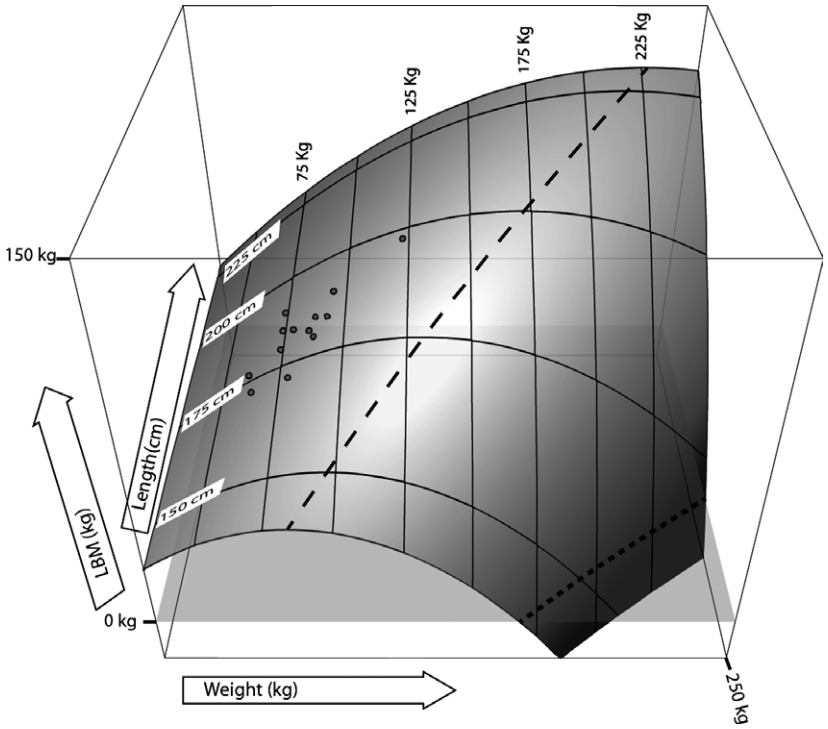

Figure 1 Lean body mass (LBM) calculated with the James formula: $LBM_{male} = 1.1 \times \text{weight-}128 \times (\text{weight/height})^2$. Dots: 10 male patients in the Schnider study; Dashed line: Maximum LBM; Dotted line: LBM = 0.

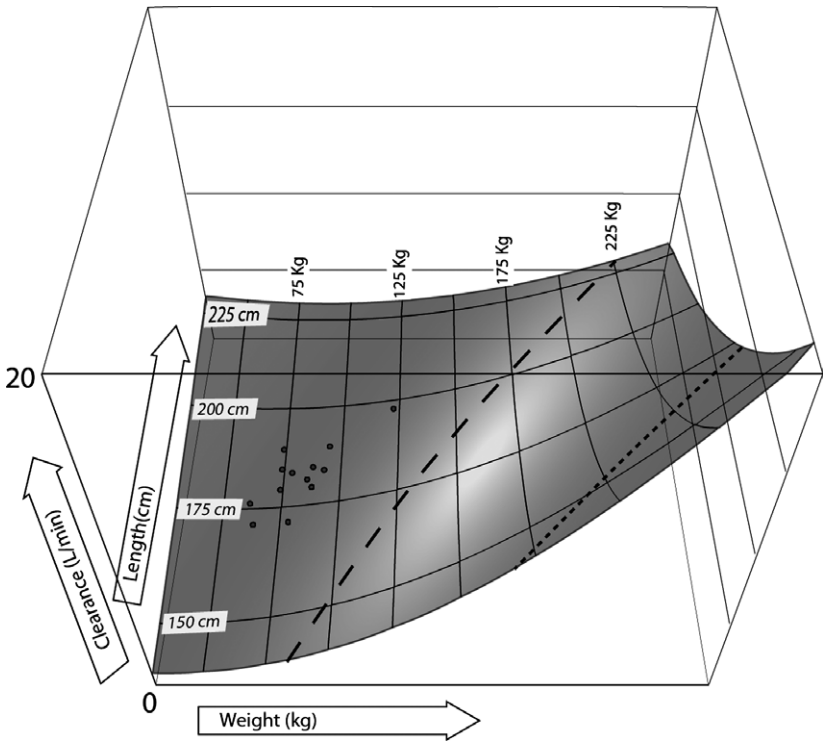

Figure 2 Relationship between weight, length and clearance in the Schnider PK model. Dots: 10 male patients in the Schnider study; dashed line: maximum LBM; dotted line: LBM = zero (see appendix for formula).

of the patient data input limits of respective open TCI systems is given.

Blood effect-site equilibration constant (ke0)

Since the central compartment in the Schnider models ($Schnider_K$ and $Schnider_T$) is relatively small and fixed to 4.5 l, the loading dose for the central compartment will be small and independent of patient characteristics when using TCI_B. Some experts, therefore, recommend use of the Schnider models in TCI_E mode only [10]. In the TCI_E mode, an overshoot in blood concentration will be created to increase the concentration gradient between blood and brain and, thereby, reach the desired effect-site concentration more quickly. The speed at which the effect-site concentration increases is dependent on ke0 and the magnitude of the difference between blood and effect-site (brain) concentration. At the correct, maximal peak of the blood concentration overshoot, the infusion is stopped and blood concentration will drop towards effect-site concentration while the effect-site concentration still increases. The decrease in blood concentration is dependent on fast distribution and clearance. In the Schnider models, fast distribution is dependent on age, whereas clearance is dependent on weight, lean body mass and height (see above). Consequently, various factors influence both the overshoot in blood concentration as well as its decrease upon the termination of infusion. Larger values of ke0 (equivalent to a fast equilibration between blood and effect-site) will result in less overshoot in blood concentration, while the reverse is true for small ke0 values (slow equilibration). Similarly, a faster distribution and/or higher clearance will lead to higher blood concentrations as the faster decrease will allow more time for drug delivery in the loading phase and vice versa (Fig. 3). In contrast, in TCI_B there is no influence of ke0 on the propofol dose delivered to reach a specific blood target concentration; ke0 here only predicts the time at which the expected effect-site concentration (asymptotically) reaches blood concentration.

Time to peak effect (TPE)

The determination of the 'induction dose' with TCI_E is obvious (in contrast to TCI_B), as this is the amount of

Table 1 Input limits, propofol models and maximum infusion rates for different target-controlled infusion (TCI) systems.

	Diprifusor[a] Module	Alaris[b] PK	Fresenius Kabi Base Primea[c]	Arcomed[d]	B Braun Infusor space[e]
Patient parameters					
Weight; kg	150	207	200	150	220
	30	30[g]	30	10	30
Length; cm	–	220	200	220	220
	–	100	60	50	130
Age; year	–	94	100	100	100
	16	16	15	12	16
Propofol models					
Marsh					
TCI_B	Y	Y	Y	Y	Y
TCI_E	N	N	N	N	N
Marsh short ke0					
TCI_E	N	Y/N[f]	Y	Y	N
Schnider					
TCI_B	N	Y	Y	Y	Y
TCI_E	N	TPE	Ke0	TPE	Ke0
Max rate; $ml.h^{-1}$	1200	1200	1200	1500	1500

[a]'Diprifusor™' TCI, Zeneca Pharmaceuticals, Macclesfield, UK.
[b]Alaris Pk, Cardinal Health, Runcorn, UK.
[c]Fresenius Base Primea, Fresenius Kabi, Brezins, France.
[d]Arcomed Syramed USP6000, Arcomed, Regensdorf, Switzerland.
[e]Braun Infusor Space, B. Braun AG, Melsungen, Germany.
[f]On request.
[g]With Sufentanil: 1 kg.
PK, pharmacokinetics.

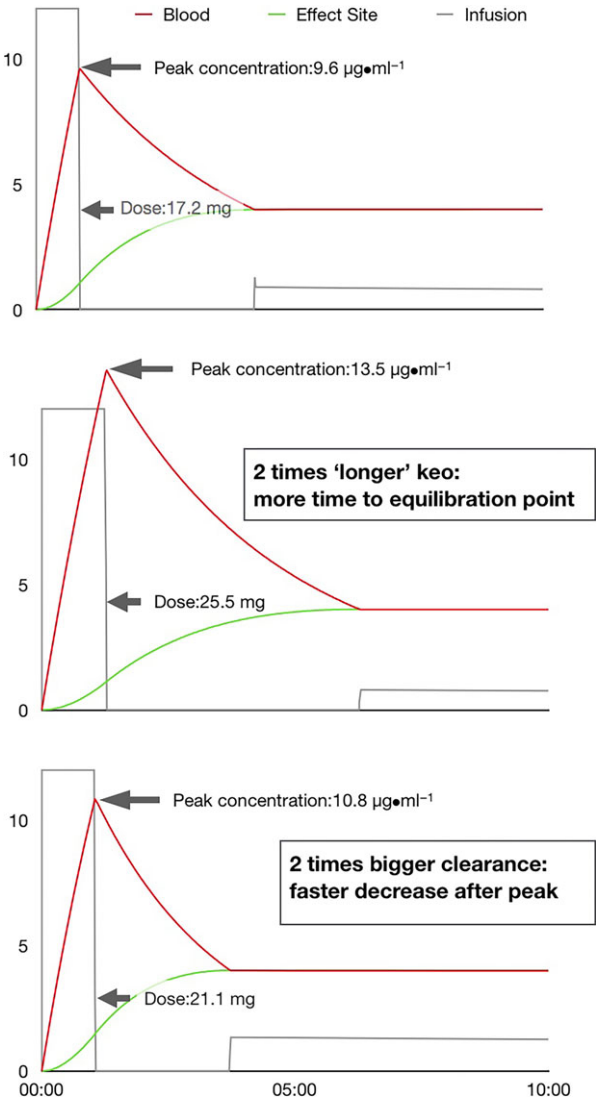

Figure 3 Upper panel: TCI_E using a hypothetical drug. Middle panel: two times smaller ke0-> more time for equilibration-> larger dose and increase peak blood concentration. Lower panel: two times larger clearance-> faster decrease-> moderate larger dose and increase peak blood concentration.

drug delivered until the infusion stops. When blood and effect-site concentration are equilibrated, the hypothetical effect is at the target value. It is often incorrectly assumed that time to reach the target effect with TCI_E on the one hand and time to peak effect on the other hand are equivalent. The time to peak effect is determined by observing the maximum effect of a continuous measurement of a surrogate effect parameter such as processed electroencephalography (EEG), for example, bispectral index (BIS™), auditory evoked potential or any other equivalent parameter after a bolus administration. Being model independent, it is incorrectly assumed that such time to peak effect can be used to determine the ke0 value that connects a pharmacokinetic (PK) model to the effect and, therefore, can be used for TCI_E [11]. This assumption erroneously originates from the suggestion that the three compartment model that is used for TCI_E warrants immediate homogenous mixing of drug in the central compartment to the effect that, after a bolus, the concentration in the central compartment is immediately equal to dose/(volume of the central compartment). Various studies [12, 13], however, show that this is incorrect since mode of administration, bolus or infusion, will influence the PK parameters and hence infusion-PK is not bolus-PK. When time to peak effect is calculated in a PK model after a bolus, its value is affected by ke0 and the decay in blood concentration from peak concentration (determined by fast distribution and clearance). Obviously, a faster equilibration time will shorten time to peak effect and so will a higher clearance and faster distribution. Assuming that time to peak effect is identical among patients, while clearance is different (as it is dependent on weight, height and lean body mass in the Schnider models), ke0 has to differ among patients to satisfy this condition of a fixed, patient-independent time to peak effect

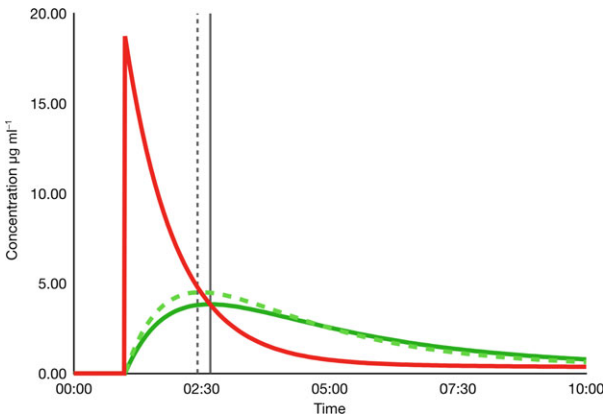

Figure 4 Fixed ke0 (time to peak effect variable) or variable ke0 (time to peak effect fixed). Red line: blood concentration after bolus of 1 $mg.kg^{-1}$. Green dashed line: effect concentration with ke0 fixed to 0.456 and time to peak effect 1.48 min. Green solid line: effect concentration with time to peak effect fixed to 1.6 min and ke0 0.3565 min^{-1}.

(Schnider$_T$ model). However, when ke0 is assumed to be constant among patients, time to peak effect will differ as a result of varying clearances among patients (Schnider$_K$ model; Fig. 4).

Unfortunately, some manufacturers of open TCI systems use the Schnider$_K$ model with the ke0 fixed to the published value. Consequently, the time to peak effect varies among patients. Other TCI systems use the Schnider$_T$ model with the time to peak effect fixed which will cause a varying ke0. As explained above, the induction dose for a specific target concentration is dependent on the combination of PK parameter values and magnitude of ke0. Consequently, the application of different models will lead to different induction doses for the same target concentration in TCI$_E$. The variability in the induction dose among patients with different anthropometric characteristics will increase when the ke0 is not fixed (Fig. 5). The applied fixes to deal with the erroneous lean body mass calculation and the varying approaches to deal with time to peak effect, introduce an undesirable and incomprehensible level of complexity in the use of TCI$_E$ and especially in the analysis of the consequences of these issues on the induction doses [10, 14].

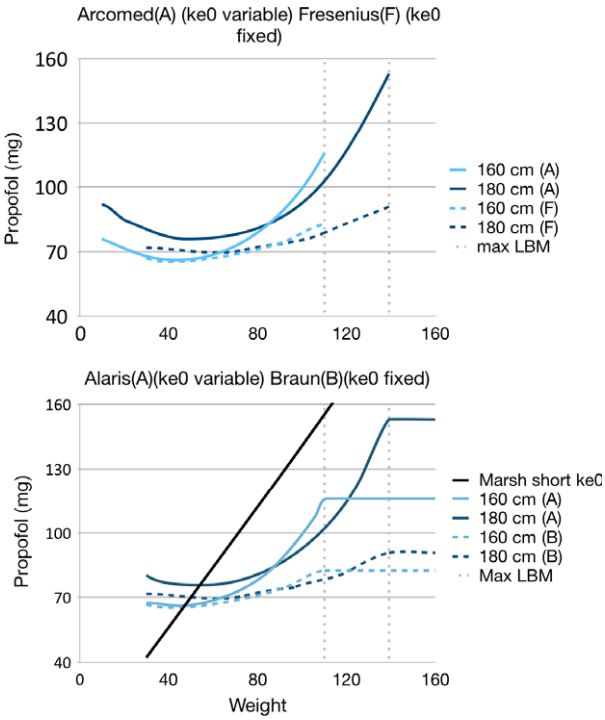

Figure 5 Induction dose in mg for a target of 4 μg.ml^{-1} in TCI$_E$ mode for male patients. Solid lines: the Schnider$_T$ model (time to peak effect 1.6 min, ke0 varies). Dashed lines: Schnider$_K$ model (ke0 is fixed to 0.459 min, time to peak effect varies). Upper panel: Arcomed and Fresenius Kabi will not be used above the maximum lean body mass. Lower panel: Alaris and B Braun could be used if the weight entry that corresponds with maximum lean body mass is accepted as input. In the modified Marsh (Marsh short ke0: 0.57 min^{-1}, time to peak effect 1.6 min) induction dose has a linear relationship with weight, independent of height.

Both Schnider models predict a faster equilibration (larger values of ke0) between blood and effect-site than most other models for propofol. Consequently, even in the TCI$_E$ mode, the induction dose is relatively small, especially when the Schnider$_K$ model is used. Possible causes for a large ke0 are the use of the particular surrogate end-point, the canonical univariate parameter derived from the EEG (the selection of the surrogate effect parameter may influence estimated time to peak effect values and derived ke0's [15]) and the study setup: a bolus followed by an infusion. Other studies that used the Schnider PK model for pharmacodynamic analysis in fact suggest the use of smaller (longer) ke0 values [16–18]. According to the findings in these studies, both Schnider models will overpredict the effect-site concentration, thereby, giving the clinician incorrect information on the effect-site concentration at loss of consciousness (erroneously high) and, hence, the selected target for maintenance which may result in overdosing [19].

Sex and age

Although in the original study no effect of sex was observed, sex has been introduced indirectly (through lean body mass) in the PK of propofol in open TCI systems using the Schnider model. Similar to the effect of other anthropomorphic data, the sex effect is largest in the Schnider$_T$ model. A female subject of 90 kg will, in this case, receive 30% more propofol than a male patient of the same weight. Overall, the sex effect is an anomaly that makes TCI use with the Schnider model unpredictable (Fig. 6). The fast distribution is dependent on age and older patients will receive reduced induction doses. This has been proposed as an advantage of the Schnider models over the Marsh model. There is, however, a remarkable difference between the

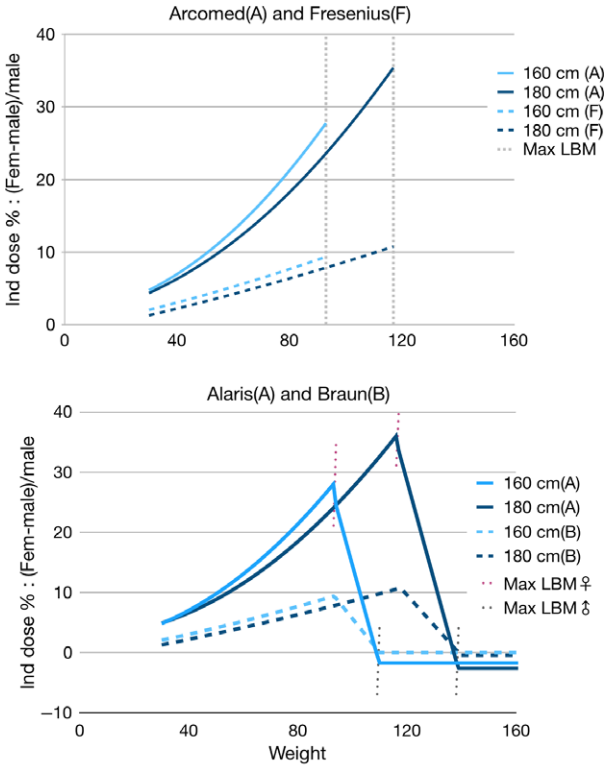

Figure 6 Percentage difference in induction dose for a target of 4 μg.ml^{-1} between male and female subjects in TCI_E mode. Calculation of lean body mass is different for male and female subjects. Upper panel: Arcomed and Fresenius Kabi will not be used above the maximum lean body mass. Lower panel: Alaris and B Braun could be used if the weight entry that corresponds with maximum lean body mass is accepted as input. Note the irrational differences in the induction dose above the maximum lean body mass in women.

$Schnider_T$ and $Schnider_K$ models. Akin to the effect of sex, the $Schnider_T$ model implementation shows an increased age effect. For example, a patient aged 80 years will receive 20% less propofol compared with a 20-year-old patient (both 80 kg, target concentration 4 μg.ml^{-1}) using the $Schnider_K$ model. The difference in dose can mount to 38% when using the $Schnider_T$ implementation (Fig 7).

The Marsh model(s)

In open TCI systems there are also two variations of the Marsh model. They are usually referred to as the (original) Marsh and modified Marsh (MMarsh) models. These models are similar in pharmacokinetic properties but differ with regard to the ke0. At the time the

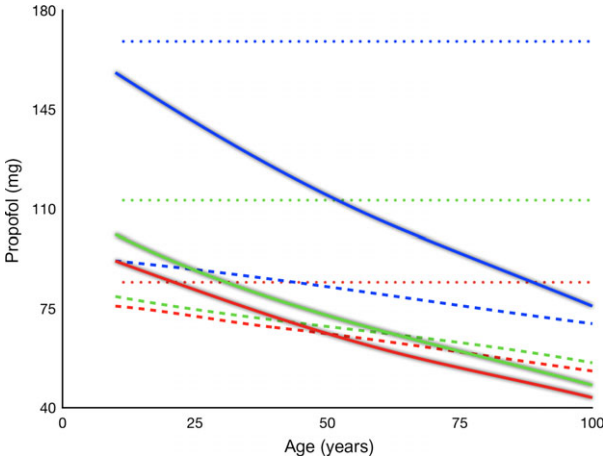

Figure 7 Induction dose for target 4 μg.ml^{-1} TCI_E relation with age. Patient weight: blue, 120 kg; green, 80 kg; red, 60 kg. Dotted lines: Modified Marsh, small (short) ke0. Dashed lines: $Schnider_K$ model (variable time to peak effect fixed Ke0). Continuous lines: $Schnider_T$ model (fixed time to peak effect variable Ke0).

Diprifusor was launched, no effect-site concentration was available for the Marsh model. Display of the effect-site was added at a later stage, based on preliminary study data from 20 male patients to whom a continuous infusion was administered, while the auditory evoked potential was used as a surrogate effect measure [20]. As explained above there is a strong relationship between the value of ke0 and induction dose in TCI_E [21]. The small (slow) Ke0 in the Marsh model will produce a large induction dose when the (original) Marsh model is used for TCI_E (for a target effect concentration of 4 μg.ml^{-1} in an 80-kg patient the induction dose would be 198 mg: about 2.5 mg.kg^{-1}). As a result, no commercially available TCI system applies TCI_E for the (original) Marsh model for which only TCI_B is available. The TCI_E pump manufacturers did apply a faster ke0 based on the concept of a published TPE, which is, however, a disputed approach [8]. This resulted in the modified Marsh (MMarsh) model. Based on evidence from literature [18, 21–23], one may conclude that the ke0 in the original Marsh is too small (or slow), whereas the ke0 in the modified Marsh is too large (or fast). Regardless of the current dispute on the correct ke0, we observe that the original Marsh with the small ke0 correlates well when case effect-site concentration is compared with sedation end-points [24] and concentrations at

loss of consciousness relate closely to the concentrations at regaining consciousness [25].

Sufentanil

In countries where sufentanil is available, it is usually available for both TCI_B and TCI_E. However, dosing information for TCI is not available in any of the summaries of product characteristics (SPC). The PK model implemented in both TCI systems is from Gepts et al. [26], whereas the blood effect-site equilibration constant is based on data from Shafer and Varvel [27] using the time to peak effect principle. The objective of the PK study of Gepts et al. was not to develop a model for TCI but to compare the linearity of applied pharmacokinetics while using different analysis techniques for the measurement of propofol. The Gepts model is based on 23 patients and no influence of anthropomorphic data on the model parameters was found. Consequently, sufentanil administration in open TCI systems is based on population data without allowing adaptations based on weight, height or sex. The authors did recognise a potential issue when applying their PK model in clinical practice where weight-based dosing is accepted as a standard dosing strategy, by explicitly observing: "*Thus, for the population studied, the data did not support adjusting sufentanil pharmacokinetics on the basis of weight or lean body mass. However, our results also do not suggest that such an adjustment would be detrimental to the pharmacokinetic parameter estimates*".

Although TCI applying the Gepts model has been used in obese patients with reasonable performance, they will be underdosed (i.e. there is a negative bias) [28]. This is not surprising, as a 40-kg patient will receive the same dose as a 140-kg patient when setting the same TCI targets. An additional issue is that one manufacturer allows the weight to be set as low as 1 kg (although the lower age limit is 12 years in this system). Consequently, a clinician supposing that weight but not age is a parameter in the PK model may decide to use this system in a neonate. Massive overdosing would then occur, not only due to the absence of appropriate weight scaling but also due to limited sufentanil clearance capacity in the neonate due to the immaturity of the enzyme system responsible for metabolism [29].

Concerning TCI_E, it may be reasoned that, similar to propofol, the TPE dosing of sufentanil derived from bolus administration will produce an induction dose that is too small for the predicted effect on spectral edge frequency of the EEG, that was used to measure the TPE.

Remifentanil

Not dissimilar to the Schnider PK model for propofol, the Minto [30] model for remifentanil uses the same erroneous equation for lean body mass. The implementation in the Minto model is different, however. Although propofol clearance increases when lean body mass surpasses its maximum, the opposite is true for remifentanil. Target-controlled infusion applying the Minto model will, therefore, cause underdosing when used in overweight patients. This was confirmed in a study with a corrected estimate of lean body mass [31]; the negative bias decreased from −53% to −19% in a population of obese patients. Since the recognition of this lean body mass calculation error, these TCI systems are not allowed to be used in patients with a lean body mass greater than the lean body mass maximum in the original equation. However, the lower limits of weight and height are set by the pump manufacturer and are not based on data from the Minto study. The youngest subject in the study of Minto et al. was 20 years with a weight of 47 kg and height of 156 cm. The lower limits set in the Arcomed TCI pump (12 years, 10 kg and 50 cm) reflect anomalous model extrapolations. It is very unlikely that these values will correlate with an actual individual considering that a 12-year-old boy would have a median length of 149 cm, a median BMI of 17.5 $kg.m^{-2}$ and, therefore, on average, a weight of about 39 kg [32]. The estimated clearance in this (average) 12-year old using the Minto model would be 2.65 $l.min^{-1}$. Models specifically derived from paediatric data, however, calculate clearances for this individual of 2.03 $l.min^{-1}$ [33], 1.8 $l.min^{-1}$ [34] and 1.5 $l.min^{-1}$ [35]. The extrapolation of the Minto model will lead to the administration of about 30–75% more remifentanil than required. An overdose is even more manifest if the age limit is ignored and the characteristics of an actual patient of 10 kg and 77 cm are entered in this TCI system. The Minto model would deliver 1.6–4.5 times more drug than the specific paediatric models predict.

In the Minto model [36], ke0 is age dependent in the sense that older patients will have slower equilibration times, which results in greater induction doses if no other PK parameter estimate is changed. Fortunately, clearance decreases with age and both effects counteract within the age range studied (20–85 years) and only a minimal effect of age on induction dose will be observed in TCI_E. However, as the upper age limit in all commercial TCI systems is 100 years, an anomalous increase in induction dose of about 10% will occur in the age range 85–100 years.

Discussion

Originally, the TCI concept was to supply the anaesthetist with a control device that would make drug administration time independent with proportional and reproducible modifications in estimated drug concentrations in plasma. A number of current TCI systems appear to be flawed as a result of the use of models in clinical practice which are derived from studies that were not intended for this purpose, the extrapolation of patient data beyond the limits of the original data, and last, but not least, the failure to validate the models and their use in clinical practice. Various studies show that adequate modelling based on clinically-valid parameters is capable of allowing accurate prediction of the individual effect-site concentration at awakening from the concentration at loss of consciousness [16, 22, 25, 37]. This valuable information, however, is presently still mostly lost in the turmoil of model differences and non-uniformity of TCI systems.

A recent study was the first to construct a PK model from all available propofol data in a population with age range from birth to 100 years [38]. We strongly recommend validation of this model in the light of the above-discussed anomalies in current TCI systems as well as a clinically sensible approach when a ke0 is to be connected to this model for TCI_E [21].

Considering regulatory issues: dosing advice using TCI in the SPC for propofol can presently only be found using the Marsh model and remifentanil using the Minto model. The European Medicines Agency upon consultation on the requirements for TCI observed: "*To support a marketing authorisation of the intravenous drug using TCI as a mode of administration, relevant clinical studies would need to be conducted with the drug and the applicable mode of administration (e.g. infusion pump for TCI) to demonstrate its safety and efficacy. When the intravenous drug receives marketing authorisation, the relevant sections of the SmPC would describe the mode of administration (e.g. the use of an infusion pump for TCI). The infusion pump would be assessed separately … to receive a CE mark for its intended use*". (European Medicines Agency, personal communications, 26 April 2016, quotation authorised 19 September 2017). Considering that dosing is model dependent, the use of a model based on dosing advice in the SPC for another model should, in our view, be strictly abandoned.

Finally, we conclude that the following steps are required to reduce the anomalies identified in this review, to mitigate the potentially damaging effects thereof and to make application of TCI systems the preferred market standard for the benefit of both patients and clinicians;

1 Pump devices for TCI_B and TCI_E must be individually validated for the application of each drug.
2 For each drug, only one model should be available. If different models are required for different patient groups, then the selection should be done automatically by the device. Selection of the appropriate model should not be the responsibility of the manufacturer of the infusion device.
3 Commercial TCI systems must apply patient data (limits) and models in a uniform and validated way.
4 Dosing advices for TCI_B and TCI_E, must be explicitly included in the summary of product licences (SPC) for each individual drug.

Dosing advice for use with TCI is, to the knowledge of the authors, for all SPCs derived from the original SPC from Zeneca for the use of the Diprifusor [39]. As the PK model used in the Diprifusor is the Marsh model, dosing advices are only applicable for the Marsh model. For good practice we, therefore, recommend the use of the Marsh model.

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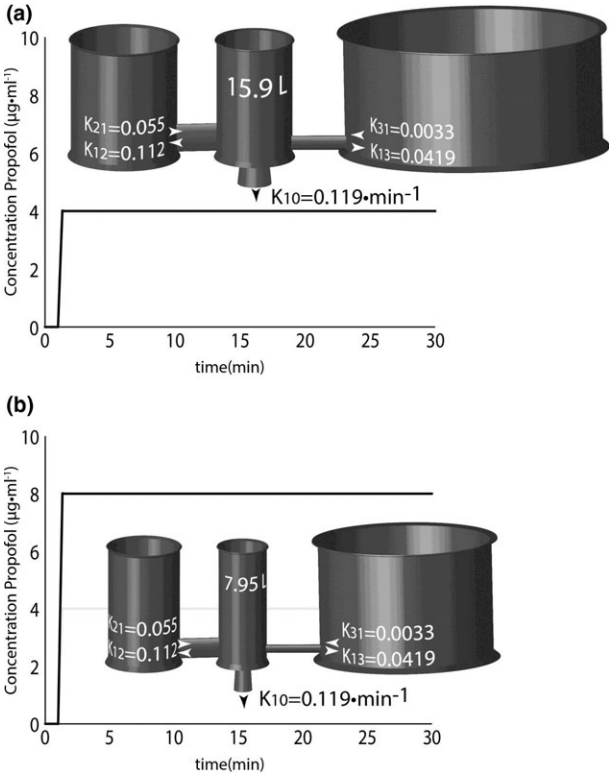
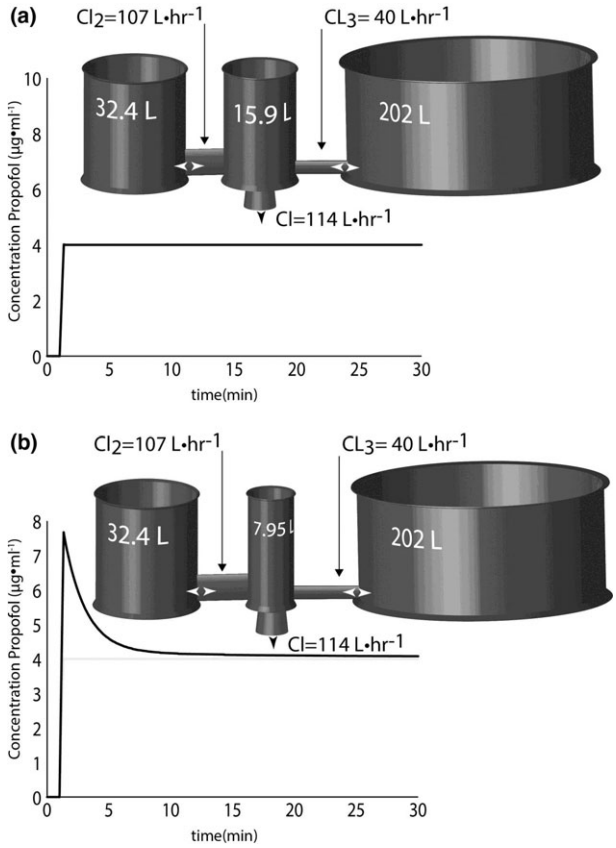
Appendix



Appendix Figure 1 If models are expressed as central volume and time constants (min^{-1}) while central clearance (=V1 × k10) is expressed in $ml.kg.min^{-1}$ like in the Marsh model, all the model parameters become linearly related to weight. If the central volume (V1) is halved, then the volumes of the other compartments are also halved as are the intercompartmental clearances. Therefore, the amount given by TCI in A for a concentration of 4 $\mu g.ml^{-1}$ will produce 8 $\mu g.ml^{-1}$ continuously in situation B.



Appendix Figure 2 Models expressed as volumes and intercompartmental clearances like in the Schnider model. When the central volume is halved then the other volumes will not automatically change. Hence, only the loading dose from model A will produce the double concentration in B but thereafter the concentration will converge back to the target of 4 $\mu g.ml^{-1}$ because distribution and clearance are not different from A.

