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Pharmacokinetic models for propofol—defining and illuminating the devil in the detail

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The recently introduced open-target-controlled infusion (TCI) systems can be programmed with any pharmacokinetic model, and allow either plasma- or effect-site targeting. With effect-site targeting the goal is to achieve a user-defined target effect-site concentration as rapidly as possible, by manipulating the plasma concentration around the target. Currently systems are pre-programmed with the Marsh and Schnider pharmacokinetic models for propofol. The former is an adapted version of the Gepts model, in which the rate constants are fixed, whereas compartment volumes and clearances are weight proportional. The Schnider model was developed during combined pharmacokinetic−pharmacodynamic modelling studies. It has fixed values for $V1$, $V3$, k_{13}, and k_{31}, adjusts $V2$, k_{12}, and k_{21} for age, and adjusts k_{10} according to total weight, lean body mass (LBM), and height. In plasma targeting mode, the small, fixed $V1$ results in very small initial doses on starting the system or on increasing the target concentration in comparison with the Marsh model. The Schnider model should thus always be used in effect-site targeting mode, in which larger initial doses are administered, albeit still smaller than for the Marsh model. Users of the Schnider model should be aware that in the morbidly obese the LBM equation can generate paradoxical values resulting in excessive increases in maintenance infusion rates. Finally, the two currently available open TCI systems implement different methods of effect-site targeting for the Schnider model, and in a small subset of patients the induction doses generated by the two methods can differ significantly.

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When TCI devices first became commercially available in 1997, the concept was new to clinicians and regulatory authorities, many of whom feared the possible complications arising from use of a device that changed infusion rates automatically. A strong emphasis on safety was thus necessary to ensure regulatory approval and the confidence of clinicians. The systems all contained the Diprifusor® (Astra Zeneca, UK) microprocessor, programmed with the Marsh adult pharmacokinetic model for propofol.[15] The Diprifusor contained two microprocessors—one 16 bit and the other 8 bit (G.N.C. Kenny, personal communication), the former to calculate and implement the required infusion rates, and the latter to monitor the driving motor to calculate the volume of propofol actually being administered and to perform a simple calculation of the estimated plasma concentration from this. The system was designed to shut down if there was a significant discrepancy between the plasma calculations estimated by the two microprocessors.

The first generation systems only allowed the user to target the plasma concentration. At the time of their release the significance of an effect-site anatomically and temporally separate from the plasma was only just being fully appreciated. Early models only displayed the target and estimated plasma concentrations. Later on a k_{eo} value was incorporated allowing an estimate of the effect-site concentration to be made and to be displayed as additional information.

In addition to controlling the user interface, and calculating and implementing the infusion rates required to achieve the target concentration, the Diprifusor microprocessor also controlled a syringe recognition system that only allowed the use of glass pre-filled 50 ml syringes of 1% or 2% propofol (Diprivan 1%™ or Diprivan 2%™, AstraZeneca, UK).

Open TCI systems do not contain the Diprifusor microprocessor and do not have a syringe and drug recognition system. They contain a single processor that the manufacturer can program with any pharmacokinetic model for any drug, and allow the use of a wide variety of syringes of sizes between 10 ml and 50 ml supplied by several different manufacturers. The chief benefit of these systems is that cheaper, generic formulations of propofol can be used for TCI.

At the time of publication, there are two open TCI systems commercially available: the Alaris Asena PK[TM] (Cardinal Health, Alaris Products, Basingstoke, UK) and the Base Primea[TM] (Fresenius, France). These systems provide the user with a potentially confusing range of choices. Generally they are supplied with pre-loaded and activated models for remifentanil (Minto model),[16] [18] sufentanil,[9] and two models for propofol. With the Base Primea system the user has a choice of the modified Marsh[22] and Schnider[19] [20] models, whereas with the Asena PK system, the choice is between the Marsh[15] and Schnider[19] [20] adult models and the Kataria paediatric model.[11] With all these drugs and models both plasma and effect-site targeting are possible (except with the Marsh model implemented in the Asena PK). To further add to the confusion the two systems use two different methods of implementing effect-site targeting with the Schnider model.

Failure to appreciate the differences between the different propofol models and implementation methods may result in administration of excessive or inadequate doses of propofol with potentially harmful results.

Plasma *vs* effect-site targeting

Early TCI systems were designed to achieve a user-defined plasma 'target concentration'. It soon became apparent that there was hysteresis in the relationship between plasma concentration and clinical effect, caused by the temporal delay in equilibration between plasma concentrations and the concentration at the sites of action within the central nervous system, referred to as the 'effect-site'.

The rate of plasma/effect-site equilibration depends on factors that determine the rate of drug delivery to the effect-site (such as cardiac output and cerebral blood flow) and pharmacological properties that determine the rate of drug transfer across the blood–brain barrier (lipid solubility, degree of ionization, etc). The time course of plasma/effect-site equilibration can be mathematically described by a first-order rate constant typically referred to as the k_{eo}. Strictly speaking, this term should be used to describe the rate of removal of drug from the effect-site out of the body, but the effect-site is regarded as having negligible volume, so that there is no need for separate constants describing the rate constants for movement into and out of the effect compartment (the k_{eo} defines the proportional change in each unit of time of the concentration gradient between the plasma and effect-site).

With effect-site targeting, the TCI system manipulates the plasma concentration to achieve the effect-site concentration as rapidly as possible. When the effect-site target concentration is increased, the TCI system briefly increases the plasma concentration to an optimal level above the target effect-site concentration before temporarily stopping the infusion to allow the plasma concentration to decrease to the level of the target effect-site concentration. Most systems use mathematical iterations to determine the magnitude of the optimal plasma concentration overshoot—the peak plasma concentration that generates a gradient sufficient to cause the most rapid increase in effect-site concentration but without an overshoot of the effect-site concentration above its target (Fig. 1).

If the target effect-site concentration is reduced the system stops the infusion, allowing the plasma concentrations to fall, thereby generating a concentration gradient out of the effect-site, until the estimated effect-site concentration has fallen to the new target. At this stage the plasma concentration will be less than the effect-site concentration, and so the system has to administer a small bolus to increase the plasma concentration to the target concentration.

With effect-site targeting, the magnitude of the plasma concentration overshoot estimated by the system depends critically on the k_{eo} and also on the estimated rate of decline in the plasma concentration. If a slower (smaller) k_{eo} is used, a greater overshoot in the peak plasma concentration will be required to produce a larger concentration gradient between the blood and the effect-site and thereby to hasten plasma-effect-site equilibration (Fig. 2).

The estimated rate of decline of the plasma concentration also has an influence on the overshoot. A system that estimates a slower decline in plasma concentrations will administer a lesser plasma overshoot than a system estimating a faster decline, to avoid an eventual effect-site concentration overshoot. After a bolus dose, the rate of decline in plasma concentrations mostly depends on the rate of fast re-distribution, but is also influenced by the rate of drug metabolism and of slow re-distribution. Naturally, the net rate of decline caused by re-distribution depends on the concentration gradients between compartments. If a system estimates that the plasma drug concentration will fall rapidly after a bolus at a given time, then a greater overshoot is necessary to optimize the gradient driving drug into the effect-site, and the flux of drug into the effect-site, than if a slow rate of decline were estimated.

Since the accuracy of the estimated plasma concentration itself and the degree of overshoot required depend on the accuracy of several parameters and assumptions, there are multiple potential sources of error. Model errors resulting in excessively high plasma concentrations may well be tolerated by young fit patients, but in frail, elderly subjects, they may result in significant cardiovascular instability.
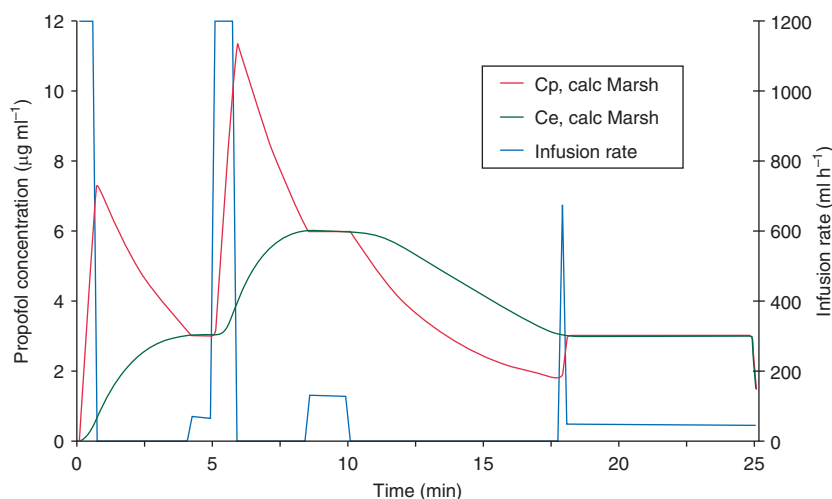
Fig 1 Effect-site targeted TCI. At time zero the target is set at 3 μg ml^{-1}, at 5 min it is increased to 6 μg ml^{-1}, and at 10 min it is reduced to 3 μg ml^{-1}. At each target change the system manipulates the blood concentration to rapidly achieve the target effect-site concentration.

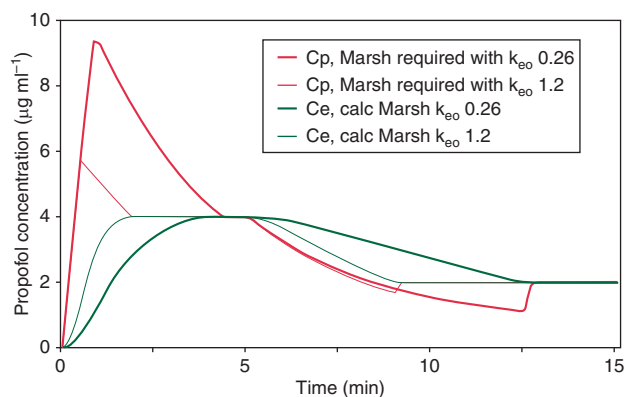**Fig 2** Effect-site targeted TCI for propofol (Marsh model), showing the effect of the choice of k_{eo}. If a slow k_{eo} is used, then a large overshoot in plasma concentration will result when the target concentration is increased.

Methods for estimating k_{eo}

Unlike isoflurane, for which the brain concentration can be estimated with reasonable accuracy by magnetic spectroscopy,[13 14] there are currently no methods of directly estimating the effect-site concentrations of i.v. anaesthetic agents. The time course of changes in effect-site concentration can however be estimated by recording a measure of clinical effect and then used to generate an estimate of the k_{eo}. Ideally, a combined pharmacokinetic–pharmacodynamic (PK/PD) modelling technique should be used, in which concomitant measurements of plasma drug concentrations and clinical effect are performed in a study population during and after administration of a bolus, an infusion, or a combination of the two. The result is a combined model that estimates plasma and effect-site concentrations.

When pharmacodynamic and pharmacokinetic data are not available from the same subject group, then a model-independent parameter called 'Time to peak effect'

(TTPE) can be used to estimate the k_{eo} for a PK model and patient group.[17] After any bolus, maximal clinical effects will occur when the effect-site concentration reaches its maximum. Since transfer of drug between blood and effect-site is gradient-driven, when the plasma concentration is greater than the effect-site concentration, net transfer is from plasma to effect-site and vice versa. When depicted graphically, this peak occurs when the effect-site concentration curve crosses the plasma concentration curve, reaching a local maximum. TTPE is defined as the time delay between a bolus injection and the peak clinical effect. It is considered to be independent of the size of the bolus dose.

The effect-site compartment is assumed to have negligible volume. Hence uptake of drug into the effect-site should have negligible influence on the plasma concentration of a drug, so that the calculated plasma concentration profile following an infusion of drug is identical for any value of k_{eo}. With this assumption, determination of the k_{eo} becomes a simple one-dimensional mathematical minimization problem. This process is illustrated in Figure 3, in which measured or estimated plasma concentrations (following a bolus dose) are plotted over time alongside an observed measure of clinical effect. Different k_{eo} values are then used to estimate the effect-site concentration. Smaller k_{eo} values result in the estimated peak in effect-site concentrations being smaller and occurring later than if faster (larger) k_{eo} is used. In this case, a k_{eo} of 0.38 min^{-1} results in a peak effect-site concentration at 100 s which matches best with the observed maximal clinical effect.

A disadvantage of this approach is that it requires precise observation of TTPE, whereas in real clinical situations noise and other factors make the observation of a single 'peak effect' difficult. Rather than relying mainly on one observation an alternative approach is to plot the relationship between the measure of clinical effect and the estimated effect-site concentrations arising from different
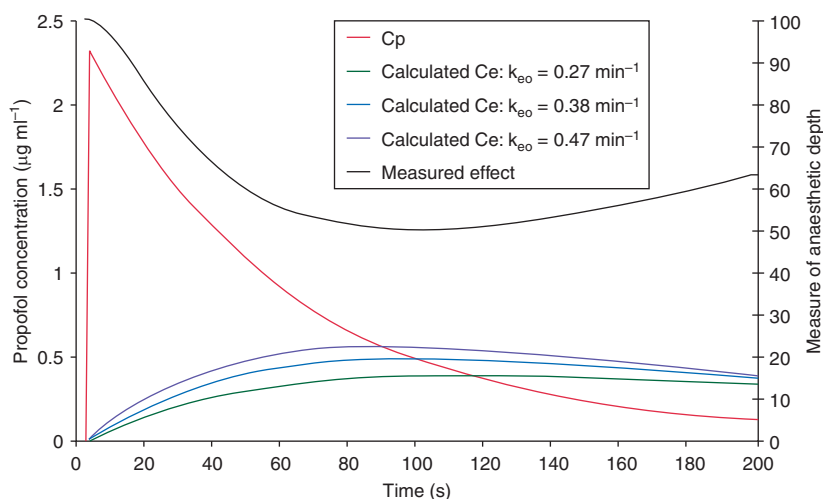
Fig 3 Estimation of k_{eo} using TTPE methodology. Estimated plasma concentrations and a measure of anaesthetic effect are plotted over time. The estimated effect-site concentrations resulting from different k_{eo} values are then calculated and plotted, to determine which k_{eo} value is associated with a peak effect-site concentration that matches the peak clinical effect.
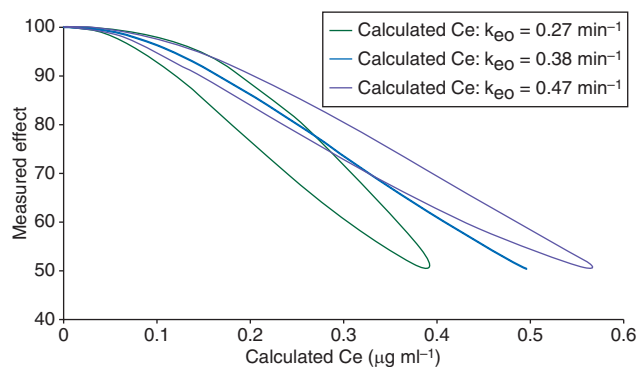

Fig 4 Optimization of k_{eo} value. A measure of anaesthetic effect is recorded continuously after a bolus dose, or during and after an infusion. Estimated effect-site concentrations are calculated from the estimated plasma concentration, and different k_{eo} values. Mathematical techniques are used to determine the k_{eo} value which best collapses the hysteresis curve (i.e. most limits the area between the two limbs of the curve).

Fig 5 Comparison of the cumulative dose of propofol 1% infused when a TCI system uses the Marsh and Schnider models at a target blood concentration of 4 $\mu g\ ml^{-1}$ in a 40-yr-old male patient who weighs 70 kg and is 170 cm tall.

k_{eo} values (Fig. 4). Simple mathematical techniques can then be used to determine the k_{eo} value which limits the area within the loop caused by the hysteresis effect. In this hypothetical example, a k_{eo} of 0.38 min^{-1} is selected since it completely collapses the hysteresis curve. This methodology can also be applied to studies involving infusions.

Difference between Marsh and Schnider models

These models were derived in different ways, have quite different parameters, and when used to determine the infusion rates of a TCI system during effect-site TCI, can r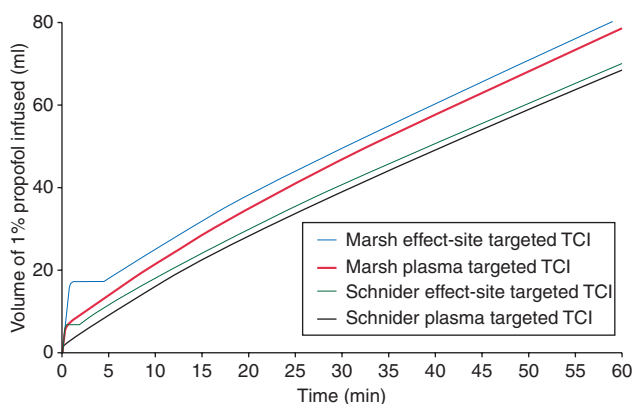esult in significantly different propofol infusion rates. In normal and mildly obese patients, the differences mainly occur within the first 10 min after a target concentration increase (Fig. 5), whereas in more obese patients, the differences can be greater throughout the infusion.

Marsh model

The Marsh model parameters were published with the results of a study of its predictive performance, and that of an adapted model, in children in 1991.[15] Compartmental volumes are proportional to weight, whereas rate constants for slow and fast redistribution are fixed (Table 1). It was pragmatically adapted from the Gepts three-compartmental model,[8] which was developed from a study involving three groups of six patients who each received constant rate infusions of propofol at either 3, 6, or 9 mg kg^{-1} h^{-1}. Although full details were not published it appears that the

Table 1 Adult propofol models

	Marsh[15]		Schnider[19 20]	
	General model	**70 kg**	**General model (LBM calculated using weight, height, gender)**	**70 kg, male height 170 cm**
V1	0.228 litre kg^{-1}	15.9 litre	4.27 litre	4.27 litre
V2	0.463 litre kg^{-1}	32.4 litre	$18.9-0.391\times(age-53)$ litre	24.0 litre
V3	2.893 litre kg^{-1}	202.0 litre	238 litre	238 litre
k_{10} (min^{-1})	0.119	0.119	$0.443+0.0107\times(weight-77)-0.0159\times(LBM-59)+0.0062\times(height-177)$	0.384
k_{12} (min^{-1})	0.112	0.112	$0.302-0.0056\times(age-53)$	0.375
k_{13} (min^{-1})	0.042	0.042	0.196	0.196
k_{21} (min^{-1})	0.055	0.055	$[1.29-0.024\times(age-53)]/[18.9-0.391\times(age-53)]$	0.067
k_{31} (min^{-1})	0.0033	0.0033	0.0035	0.004
k_{eo} (min^{-1})	0.26	0.26	0.456	0.456
TTPE (min)	4.5	4.5	1.69	1.69

study included few elderly or obese patients. The Marsh model is identical to the Gepts model in all respects except that the central compartmental volume was increased to 0.228 litre kg^{-1}. There is no published explanation of the rationale for this adjustment.

Later on, a k_{eo} value of 0.26 min^{-1} came to be used with this model in first generation TCI pumps, to enable effect-site concentration estimations to be made. The data on which this k_{eo} value was based were never published in the peer-reviewed literature, although it is quite similar to the value of 0.2 min^{-1} found by Billard and colleagues.[3]

Struys and colleagues[23] later published evidence that a k_{eo} of 1.2 min^{-1} used in conjunction with the Marsh pharmacokinetic parameters more accurately predicted the time course of clinical effect (as assessed by the Bispectral Index) than the k_{eo} of 0.26 min^{-1}. A k_{eo} of 1.2 min^{-1} used with the Marsh model results in an estimated TTPE of approximately 1.6 min, which is consistent with the findings of other groups.[19] This combination (sometimes referred to as the 'modified Marsh' model) is used in the Base Primea TCI system, and results in more gentle manipulations of the plasma concentration (above and below the target concentration) when effect-site targeting mode is used.

Schnider model

This model was derived during a combined pharmacokinetic and pharmacodynamic study in a single set of 24 volunteers (11 female, 13 male; weight range 44–123 kg; age range 25–81 yr; height range 155–196 cm).[19 20] The co-variates are total body weight, age, height, and lean body mass (LBM) (calculated from total weight, gender, and height) (Table 1).

V1 and V3 (and thus k_{13} and k_{31}) are fixed, whereas the size of V2 (and thus k_{12} and k_{21}) is influenced only by age, being smaller with advancing age. The implications of this are that after a bolus of a given size, the Schnider model will estimate that the same peak plasma concentration is achieved for all patients, irrespective of their age, height, or weight. After the peak, the initial rate of decrease in plasma concentration will depend on the age of the patient. This is in contrast to the Marsh model,

where estimated plasma concentrations after a given bolus are proportional to the patient's weight, whereas the estimated rate of decline of the plasma concentration is the same for all patients.

The elimination rate constant, k_{10}, is the only parameter influenced by body mass. It varies in a complex manner with total body weight, height, and LBM but does not vary with age. Thus, these only influence the rate at which drug metabolism is estimated to occur, and thus the rate at which propofol is infused to replace these losses during the maintenance phase.

The Schnider model incorporates a k_{eo} of 0.456 min^{-1} derived from the combined PK/PD study mentioned earlier, in which a rapidly calculated EEG parameter was used as a measure of clinical effect. This k_{eo}, in conjunction with the PK parameters, predicts a TTPE, after a bolus dose, of 1.69 min.

LBM calculation formula used in Schnider model

In the Schnider model, LBM is calculated using the James formula,[10] which performs satisfactorily in normal and moderately obese patients, but paradoxically in the severely obese.

The James formula calculates LBM as follows:

$$\text{Males}: \text{LBM}=1.1\times weight-128\times(weight/height)^2$$
$$\text{Females}: \text{LBM}=1.07\times weight-148\times(weight/height)^2$$

Figure 6 illustrates the relationship between total body weight, LBM, and ideal body mass (IBM). Note that for males, the calculated LBM increases with total body mass until it reaches a maximum value slightly greater than the ideal body mass [*Males: ideal body weight (kg)=49.9+0.89 x (height in cm−152.4); Females: ideal body weight (kg)=45.4+0.89 x (height in cm−152.4)*].[1] Thereafter [when the body mass index (BMI) is >42 kg m^{-2}], with increasing total body weight, the calculated LBM decreases paradoxically. A similar paradoxical situation exists with females. The calculated LBM increases
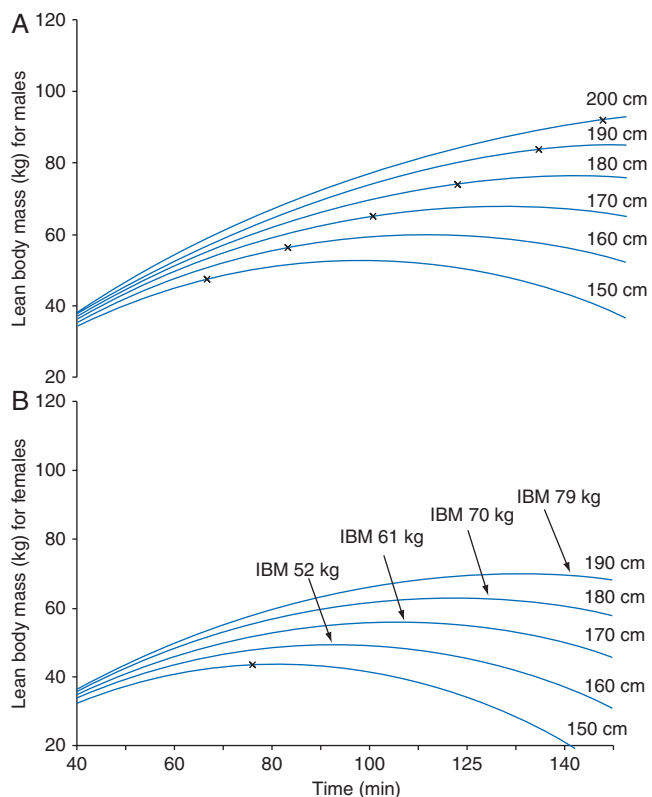
Fig 6 Relationship between body weight, height, and lean body mass (LBM) for males (A) and females (B), as calculated by the James formula. Each line shows the change in LBM for a given height (indicated on the right). Ideal body mass (IBM) for each height is indicated by a cross – read the value off the y-axis – or by text and arrows when the IBM does not fall on the LBM curve.

Fig 7 Relationship between total body weight and k_{10} for males with the Schnider model.

with total body weight, and reaches a peak when the BMI is approximately 37 kg m^{-2}. This maximum LBM value is slightly less than the ideal body mass (for the appropriate height) except in very short females in whom it is similar to ideal body mass.

The effect of the calculated LBM value on the k_{10}, and hence on maintenance infusion rates, is not immediately obvious. As shown in Table 1, increasing total body weight and height tend to increase the k_{10}, whereas increasing LBM will tend to decrease the k_{10}. Thus, total body weight and LBM have opposing effects on the k_{10}, with the LBM value moderating the influence of total body weight on the k_{10}. In severely obese patients, the paradoxically low calculated LBM causes a large *increase* in calculated k_{10}. As a result, as BMI increases beyond 42 kg m^{-2} in males, and 37 kg m^{-2} in females, the infusion rates required (to replace the estimated drug metabolism) increase exponentially. The relationship between total body weight and calculated k_{10} for patients of different heights is illustrated in Figure 7 (solid lines).

The manufacturers of current open TCI systems have implemented compromise solutions that may improve safety. In the Asena PK system, if the user enters a body weight and height com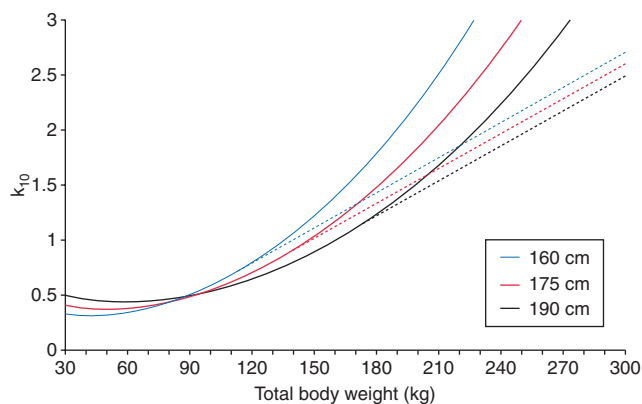bination that falls on the declining portion of the total body weight (TBW) *vs* LBM curve, then the maximal LBM figure for that height is used. A similar solution in implemented in the Base Primea system: for a given height, the system will not accept a TBW figure that falls on the declining portion of the curve, and the user is required to enter a total body mass at or below the value generating the maximum LBM. The influence of increasing total body weight on the calculated k_{10}, when these limits in LBM are applied in the severely obese, are illustrated in Figure 7 (dashed lines).

The influence of total body weight on maintenance infusion rates in the morbidly obese are discussed in greater detail in what follows.

Effect-site targeting implementation with the Schnider model

Schnider used semi-linear canonical correlation to calculate the 'canonical univariate parameter' from EEG data recorded from the volunteers in his study, and used this to track the time course of the pharmacodynamic effect of propofol.[20] The median TTPE of a propofol bolus, determined by this parameter, was 1.69 min. Based on visual inspection of the EEG the TTPE ranged from 1.0 to 2.4 min (median 1.6 min). When a TTPE of 1.6 min was used to calculate the k_{eo} for each of their volunteers, the median k_{eo} was 0.456 min^{-1}. The authors concluded that a k_{eo} of 0.456 min^{-1} used with the pharmacokinetic parameters determined in the same group of volunteers[19] provided the best description of the time course of clinical effect of propofol.

After a standard bolus dose (e.g. 2 mg kg^{-1}), the Marsh model estimates the same peak concentration, and the same rate of decline in plasma concentration, in all subjects, since the compartment volumes and clearances are all weight-proportional. As a result, use of a single k_{eo} value generates the same estimated TTPE in all patients. The converse is also true: if a single TTPE is used, then the calculated k_{eo} will be the same for all patients.

The situation is different with the Schnider model. A weight-adjusted dose will result in different estimated peak plasma concentrations for patients of different weight, since the volume of V1 is the same for all patients. After the peak is reached, the rate of decline in plasma concentrations will vary from patient-to-patient, depending on the age, gender, height, and weight. If a fixed k_{eo} is used to calculate the TTPE in patients who differ in one or more of these parameters, then different TTPE values will result. Likewise, a single TTPE value used to calculate individual k_{eo} values will result in different values in different patients. This latter approach is illustrated in Figure 8, which shows the estimated plasma and effect-site propofol concentrations arising after a 2 mg kg^{-1} propofol bolus in two different male patients, both weighing 70 kg, but one being older and taller than the other. In this example, the k_{eo} has been adjusted in each case to cause the effect-site concentration to reach local maxima at 1.6 min. In the case of the elderly patient a faster (larger) k_{eo} value is required, and results in a greater estimated peak effect-site concentration.

The Asena PK open TCI system incorporates many of the software routines that are used in the Rugloop II software, developed by T.D.S. and M.M.R.F.S.[7] Alternative implementations can be found in Stanpump, developed by Steven L. Shafer, MD at Stanford University.[22] Thus, in common with Rugloop and Stanpump, when implementing effect-site targeting for the Schnider model, the Asena PK uses a fixed time to peak approach to calculate a unique k_{eo} for each patient. The Base Primea system on the other hand uses a fixed k_{eo} (0.456 min^{-1}), and this results in different times to peak effect for different patients.

For non-obese and mildly obese patients, fixed TTPE approach results in a k_{eo} that is in the vicinity of 0.456 min^{-1}. For some severely obese patients this approach can
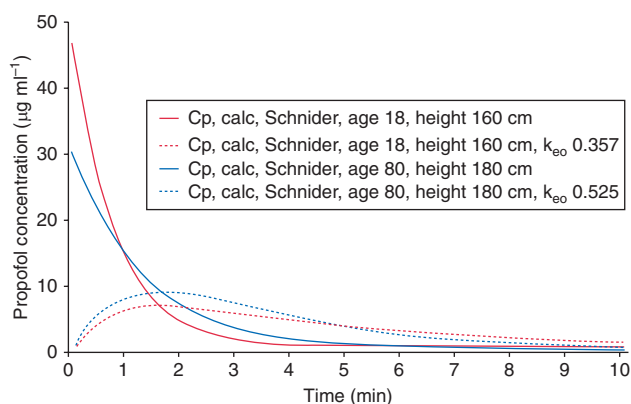

Fig 8 Predicted blood and effect-site concentration profiles, based on the Schnider model and a TTPE of 1.6 min, for two different patients who both weigh 70 kg and who have each received a 2 mg kg^{-1} i.v. bolus dose of propofol. In the older patient, plasma propofol concentrations will fall at a slower rate. To produce an estimated TTPE that is the same as in the younger patient, a faster k_{eo} value is required.

generate a significantly faster (larger) k_{eo}. As mentioned earlier, the choice of k_{eo} will influence the degree of plasma concentration over- and under-shoot when the target concentration is changed, and thus also influences the overall dose.

Practical consequences of differences between the Marsh and Schnider models

Plasma vs *effect-site targeting*

In general, for non-obese or mildly obese patients, the cumulative dose administered by the two models using the two modes of operation will follow a similar pattern. The highest total dose will be given by the Marsh model in effect-site targeting mode (with a k_{eo} of 0.26 min^{-1}), followed by the Marsh model in plasma targeting mode, then the Schnider model in effect-site targeting mode, and finally the lowest dose will be administered by the Schnider model in plasma targeting mode. Figure 5 shows the cumulative dose administered to a 40-yr-old man, who weighs 70 kg and is 170 cm tall, by systems implementing the Marsh and Schnider models in effect-site and plasma targeting mode (target concentration 4 μg ml^{-1}).

The important question is not, of course, which model delivers the largest or smallest dose of drug, but which one produces the most accurate predictions of plasma and effect-site concentration. Plasma concentrations can be measured directly offline using chromatography. While several studies have assessed the predictive performance of the Marsh model,[2 5 6 24] other than the initial study from which the Schnider model was derived, there is a paucity of published data of the ability of the latter model to predict plasma propofol concentrations accurately.

There are very few situations in which use of the Schnider model in plasma targeting mode may be recommended. When a TCI system is used in plasma targeting mode, and the target plasma concentration is increased, the size of the initial bolus dose (in mg) required to increase the plasma concentration to the new target is calculated mathematically as follows:

$$\text{Bolus dose (mg)} = (C_{p,target,new} - C_{p,target,old}) \times V1$$
$$\div \text{drug concentration in syringe}$$

Thus the size of the initial bolus is directly proportional to the value of V1 in the model. In the Marsh model, V1 varies with weight of the patient (15.9 litre for a 70 kg patient), whereas in the Schnider it is fixed at 4.27 litre irrespective of the patient's weight. As a result, when plasma targeting k_{10} mode is used with the Schnider model, the small fixed V1 results in the same initial bolus being given to all patients, for a given plasma target concentration, regardless of their age, weight or height. This is counter-intuitive and contrary to the clinical experience

of anaesthetists, who observe that induction requirements increase with body weight.

In effect-site targeting mode, a system implementing the Schnider model calculates a plasma concentration overshoot. The exact extent of the overshoot will depend on the age, weight, and height of the patient, and will generally be of the order of 300% of the target concentration. In almost all situations where the Schnider model is used, it should be used in effect-site targeting mode.

Few would recommend the use of the Marsh model in effect-site targeting mode with a k_{eo} of 0.26 min^{-1}. Although this k_{eo} value is slower (smaller) than the k_{eo} used with the Schnider model, the degree of overshoot of the estimated plasma concentration is far less than with the Schnider model. This is because the estimated rate of decline of plasma concentrations after a bolus is far slower with the Marsh model than the Schnider model, resulting in a more modest overshoot of ∼150%. Nonetheless, the much larger V1 value in the Marsh model results in much greater initial doses being administered in this mode. For example, for an initial target concentration of 4 μg ml^{-1}, the initial bolus will be 172 mg for a 70 kg patient, whereas for the Schnider model the initial dose will be 77 mg.

The Base Primea system allows effect-site targeting with the Marsh model with a faster k_{eo} value of 1.2 min^{-1}, resulting in smaller overshoots (of the order of 50%). In effect-site targeting mode at an initial target of 4 μg ml^{-1}, it will administer an initial dose of 98 mg to a 70 kg man (age 40 yr, height 170 cm).

In fit, healthy, young patients, the use of the modified Marsh model in effect-site targeting mode may be safe and justifiable. With currently available evidence, in almost all other situations, the safest options, and those most commonly chosen by clinicians are either of the Marsh in plasma mode or the Schnider model in effect-site mode. Thus in the following sections, we will compare the initial and subsequent doses administered with these two options.

Size of the initial dose on starting an infusion

Figure 9 illustrates the influence of choice of model and implementation, total body weight and height on the cumulative dose administered during the first 15 min of a TCI, for males and females aged 20, 40, and 80 yr. The target concentration is 5 μg ml^{-1}, and the figure illustrates the doses administered by the Marsh model in plasma targeting mode and the Schnider model in effect-site targeting mode (both fixed k_{eo} method and fixed TTPE implementation). For the Schnider implementations, the dotted lines indicate the doses administered if the original LBM equations are used in the morbidly obese without the corrections mentioned earlier.

As can be seen in the figure, the dose administered by the Marsh model is unaffected by age or height. For the Schnider model, increasing age decreases the dose, whereas increasing height increases the dose, except in the

morbidly obese in whom shorter patients may sometimes receive larger doses than taller patients of the same weight. In shorter patients, increasing total weight causes the dose administered to increase more steeply.

For the Marsh model (in plasma-targeting mode), the dose administered increases linearly with total body mass, and will be greater than the Schnider model (effect-site-targeting mode) in all patients except those adults with a very low body weight.

For the Schnider model at any given height, the initial dose increases with increasing total body weight. This increase is modest in the normal and mildly obese patient, to whom far less drug would be administered than with the Marsh model. In these patients, the doses resulting from the two different implementations of the Schnider model are very similar. In the severely obese, the increase in total dose is much more rapid, and can be significantly different with the two different implementations of the Schnider model. In particular, in young, tall, obese patients, the fixed TTPE method will result in a greater initial propofol dose (as a result of a slower k_{eo} value, and thus a significantly higher peak plasma concentration for the same effect-site target concentration).

'Maintenance' infusion rates

After the initial dose, the infusion rate administered by a TCI system depends of course on the estimated rates of redistribution and metabolism. As time passes, and the concentrations in the different compartments equilibrate, eventually the infusion rate gradually decreases to that required to replace drug lost by metabolism.

As mentioned before, for the Marsh model, the fast and slow re-distribution rate constants are proportional to the weight of the patient, whereas for the Schnider model, the fast re-distribution rate constant depends only on age, whereas the slow re-distribution rate constant is independent of age, weight, or height. In the Marsh model, the metabolic rate constant varies with weight only, whereas in the Schnider model it varies according to LBM and total body weight.

Figure 10 illustrates the influence of choice of model, age, gender, weight, and height on the total propofol dose that would be administered to patients during the period between 15 min and 60 min after starting an infusion with a target 5 μg ml^{-1}. The dose administered by the Marsh model is unaffected by age or height, and is a linear function of body weight. For the Schnider model, increasing age decreases the dose, whereas increasing height increases the dose (except in morbidly obese patients where shorter patients of the same weight will receive greater doses). Except in very thin patients, increasing weight increases the dose.

Despite these differences, for most patients the choice of model (and effect-site targeting implementation method) does not result in significantly different maintenance infusion rates.
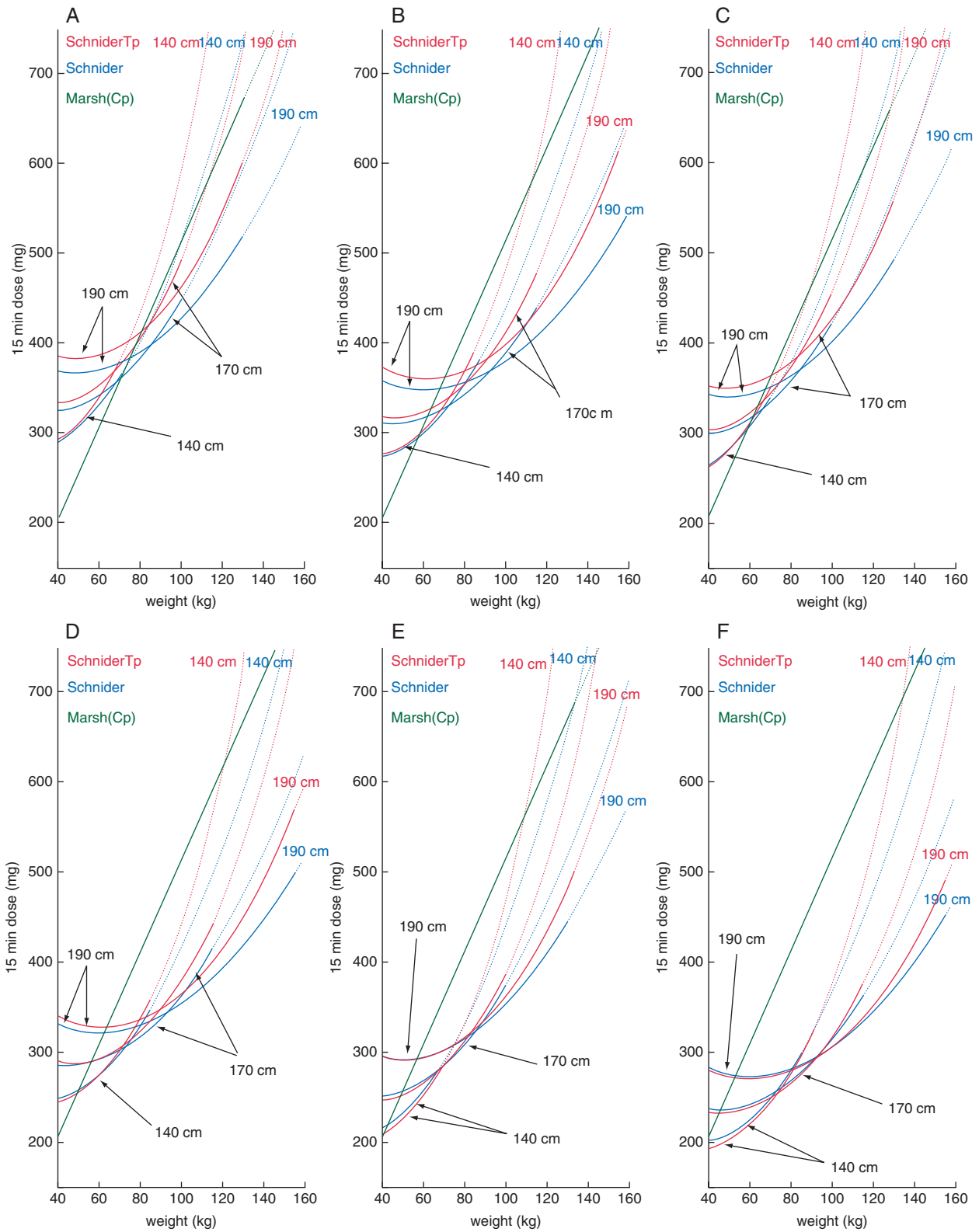
Fig 9 Influence of total body weight, height, age, and gender on the cumulative propofol dose administered during the first 15 min at a target concentration of 5 μg ml^{-1}. The figures illustrate the doses administered by the Marsh model in plasma targeting mode (green) and the Schnider model in effect-site targeting mode (fixed k$_{eo}$ method red, fixed TTPE implementation blue). The solid lines represent the doses implemented by current infusion systems, whereas dashed lines indicate the doses that would be administered to severely obese patients if the systems did not correct for the paradoxical decrease in LBM (see text). (A) Female age 20 yr; (B) Male 20 yr; (C) Female 40 yr; (D) Male 40 yr; (E) Female 80 yr; (F) Male 80 yr.
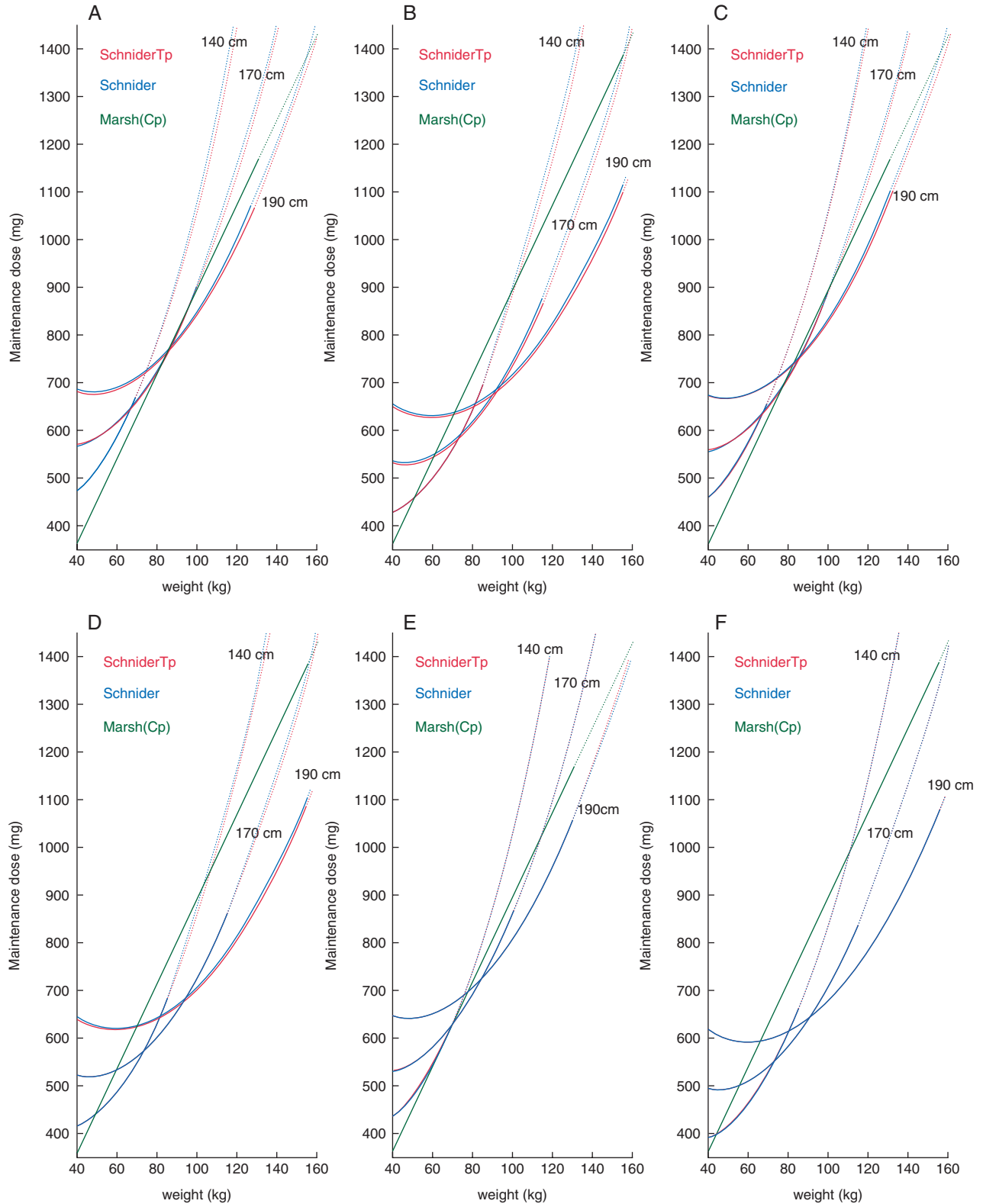
Fig 10 Influence of total body weight, height, age, and gender on the cumulative 'maintenance dose' administered from 15 min to 60 min after starting an infusion of propofol at a target concentration of 5 μg ml^{-1}. The figures illustrate the doses administered by the Marsh model in plasma targeting mode (green) and the Schnider model in effect-site targeting mode (fixed k$_{eo}$ method red, fixed TTPE method blue). The solid lines represent the doses implemented by current infusion systems, whereas dashed lines indicate the doses that would administered to severely obese patients if the systems did not correct for the paradoxical decrease in LBM (see text). (A) Female age 20 yr; (B) Male 20 yr; (C) Female 40 yr; (D) Male 40 yr; (E) Female 80 yr; (F) Male 80 yr.

Comment

With current knowledge, there is little conclusive evidence to demonstrate the superiority of any particular model or method of effect-site targeting implementation. In general, it is best for anaesthetists to use the model and methods with which they are most familiar, and to only use a different model or method of effect-site implementation if they understand the differences of the new model or method. Most experts would agree that if the Schnider model is used it should be used in effect-site targeting mode, whereas if the Marsh model is used it should be used in plasma targeting mode or if it is used in effect-site targeting mode, then it should be used with the faster k_{eo} for propofol recommended by Struys and colleagues[23] (1.2 min^{-1}).

Anaesthetists using the Marsh model in the years after TCI systems were first available quickly learnt by experience that target concentrations appropriate for younger patients were associated with haemodynamic instability in elderly patients. This is because of both pharmacokinetic and pharmacodynamic changes with age. The Marsh model does not make any adjustments for age, and has been shown to under-predict plasma propofol concentrations in the elderly.[24] Advancing age is also associated with increased pharmacodynamic sensitivity to the effects of propofol.

A major benefit of the Schnider model is that it adjusts doses and infusion rates according to patient age. This provides a strong argument for using the Schnider model in elderly and unwell patients, in whom smaller bolus doses will be given after target increases, and this may improve haemodynamic stability and safety.

The situation is less clear for morbidly obese patients. The clinical experience of anaesthetists using TCI systems is that if the total body mass of severely obese patients is used with the Marsh model, the resulting large doses at induction often result in adverse haemodynamic consequences. This observation probably results from the fact that the initial volume of distribution (V1) has been shown not to be significantly increased in obesity,[21] and that induction dose requirements are more closely related to LBM.[4]

The problem for clinicians using the Marsh model is that although induction requirements are more closely related to LBM, maintenance requirements do increase significantly with severe obesity, and are more closely related to total body mass. As a result, for the Marsh model there remains controversy over what value the user should input into the TCI system for patient weight. Most anaesthetists do not input the real total body weight with morbidly obese patients, when using the Marsh model. Many input a weight calculated using a formula recommended by Servin:[21] 'Input weight'=IBM+0.4×(TBW−IBM).

Albertin used this formula with the Marsh model during TCI propofol in obese patients, with IBM calculated using the Lemmens formula.[12] Predictive accuracy was good for the first 20 min, which is not surprising since the input weight is generally closer to the LBM than total body weight. For samples taken after 40 min, however,

measured blood concentrations were significantly lower than predicted concentrations.

The problems for clinicians using the Schnider model in obese patients relate, as indicated earlier, to the problems with the LBM calculation, and the differences between the two methods of effect-site targeting implementation. The equipment manufacturers have implemented a pragmatic solution to the problem of the paradoxical decrease in LBM in the morbidly obese. In the severely obese, maintenance dose requirements do increase with increasing body weight, and the linear increase in k_{10} in the severe obese resulting from the 'fixing' of LBM at the maximum value, seems to be a reasonable and logical solution. Further studies are required to provide the scientific evidence for this.

For most patients, the different methods of Schnider effect-site targeting implemented in the Asena and Base Primea systems result in clinically insignificant differences in dose administered. In a very small subset of the population, the fixed TTPE method will result in significantly higher induction doses. This is because, in these patients, the system will estimate larger values for k_{10} and k_{12} than for older, shorter, thinner patients. As a result, it will estimate more rapid falls in plasma concentration after a bolus dose, which with a fixed k_{eo} results in an earlier TTPE. If the TTPE is fixed, a slower (smaller) k_{eo} is required to delay the TTPE, and this slower k_{eo} then results in the requirement for a greater plasma concentration overshoot and thus a much large initial bolus size. It is not clear at present which method of effect-site targeting implementation is safest and most appropriate.

The studies from which the Marsh and Schnider pharmacokinetic models were developed did not include severely obese patients. Until there is good scientific evidence showing reasonable predictive performance of either of these, or a new pharmacokinetic model, target-controlled infusions should be used with caution in severely obese patients, regardless of which model or effect-site implementation method is used.

Funding

References

1 Abernethy DR, Greenblatt DJ, Divoll M, Harmatz JS, Shader RI. Alterations in drug distribution and clearance due to obesity. *J Pharmacol Exp Ther* 1981; **217**: 681–5

2 Barvais L, Rausin I, Glen JB, *et al.* Administration of propofol by target-controlled infusion in patients undergoing coronary artery surgery. *J Cardiothorac Vasc Anesth* 1996; **10**: 877–83

3 Billard V, Gambus PL, Chamoun N, Stanski DR, Shafer SL. A comparison of spectral edge, delta power, and bispectral index as EEG measures of alfentanil, propofol, and midazolam drug effect. *Clin Pharm Ther* 1997; **61**: 45–58

4 Bouillon T, Shafer SL. Does size matter? *Anesthesiology* 1998; **89**: 557−60

5 Coetzee JF, Glen JB, Wium CA, Boshoff L. Pharmacokinetic model selection for target controlled infusions of propofol. Assessment of three parameter sets. *Anesthesiology* 1995; **82**: 1328−45

6 Davidson JA, Macleod AD, Howie JC, White M, Kenny GN. Effective concentration 50 for propofol with and without 67% nitrous oxide. *Acta Anaesth Scand* 1993; **37**: 458−64

7 De Smet T. Rugloop II. Available from http://www.demed.be (accessed April 27, 2009)

8 Gepts E, Camu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesth Analg* 1987; **66**: 1256−63

9 Gepts E, Shafer SL, Camu F, *et al.* Linearity of pharmacokinetics and model estimation of sufentanil. *Anesthesiology* 1995; **83**: 1194−204

10 James W. *Research on obesity*. London: Her Majesty's Stationary Office, 1976

11 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

12 Lemmens HJ, Brodsky JB, Bernstein DP. Estimating ideal body weight−a new formula. *Obes Surg* 2005; **15**: 1082−3

13 Lockwood GG, Dob DP, Bryant DJ, *et al.* Magnetic resonance spectroscopy of isoflurane kinetics in humans. Part I: Elimination from the head. *Br J Anaesth* 1997; **79**: 581−5

14 Lockwood GG, Dob DP, Bryant DJ, *et al.* Magnetic resonance spectroscopy of isoflurane kinetics in humans. Part II: Functional localization. *Br J Anaesth* 1997; **79**: 586−9

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 Minto CF, Schnider TW, Egan TD, *et al.* Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology* 1997; **86**: 10−21

17 Minto CF, Schnider TW, Gregg KM, Henthorn TK, Shafer SL. Using the time of maximum effect-site concentration to combine pharmacokinetics and pharmacodynamics. *Anesthesiology* 2003; **99**: 324−33

18 Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. *Anesthesiology* 1997; **86**: 24−33

19 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

20 Schnider TW, Minto CF, Shafer SL, *et al.* The influence of age on propofol pharmacodynamics. *Anesthesiology* 1999; **90**: 1502−16

21 Servin F, Farinotti R, Haberer JP, Desmonts JM. Propofol infusion for maintenance of anesthesia in morbidly obese patients receiving nitrous oxide. A clinical and pharmacokinetic study. *Anesthesiology* 1993; **78**: 657−65

22 Shafer S. Stanpump. Available from http://opentci.org/doku.php?id=code:code (accessed April 27, 2009)

23 Struys MM, De Smet T, Depoorter B, *et al.* Comparison of plasma compartment versus two methods for effect compartment−controlled target-controlled infusion for propofol. *Anesthesiology* 2000; **92**: 399−406

24 Swinhoe CF, Peacock JE, Glen JB, Reilly CS. Evaluation of the predictive performance of a 'Diprifusor' TCI system. *Anaesthesia* 1998; **53**: 61−7