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TCI : Target Controlled Infusion, or Totally Confused Infusion? Call for an Optimised Population Based Pharmacokinetic Model for Propofol.

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Abstract

Different pharmacokinetic models for target controlled infusion (TCI) of propofol are available in the recently launched open TCI systems. There is also a compelling choice to work with either plasma- or effect-site targets. Knowledge about the clinical consequences of different alternatives is of importance. We aimed to illustrate the potential differences in the actual drug delivery/output between three present commercially available and clinically used pharmacokinetic models: the original Marsh model, which is also implemented in the Diprifusor®, the "modified Marsh-" and the Schnider models.

Simulations were made in the TivaTrainer program (eurosiva.com). Firstly, our standard plasma target regimen was simulated, and secondly an effect-site target of 3.5 µg/mL was chosen. Thirdly, real infusors were used for measuring the time to reach defined predicted effect-site concentrations when aiming at a plasma target of 6 µg/mL. Identical patient characteristics were used in all simulations: male, 170 cm, 70 kg, 40 years of age. Resulting predicted effect-site peak concentrations, and used bolus doses were recorded, as were the resulting plasma over-shoot, and time frames.

The plasma target regimen gave predicted effect-site peaks in the different models ranging from 3.6 to 7.2 µg/mL, reached after 2¾ to 4 minutes. To reach the same effect-site target, the three models used bolus doses ranging from 68 to 150 mg given during 22 to 46 seconds. The predicted plasma concentration over-shoots varied from 5.0 to 13.4 µg/mL. There were obvious differences between the models in the time taken to reach defined effect-site concentrations.

We observed clinically significant different results between the models. The choice of model will make a difference for the patient. To eliminate confusion – not necessarily to improve precision – we call for an optimised population based pharmacokinetic model for propofol – a consensus model!

Introduction

Target controlled infusion (TCI) of propofol was introduced with the Diprifusor in Europe in 1996 and made propofol based anaesthesia easier to perform (1). The Diprifusor algorithm seems to work well in clinical practice, although the underlying population based pharmacokinetic model relied upon two small populations, 18 and 20 patients, with a quite narrow range of ages and weights (2,3). In 2003 so called open TCI became available, making TCI remifentanil feasible and making TCI propofol possible to perform with generic alternatives. Additionally, alterna-

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tive pharmacokinetic models for propofol were offered (4,5). A new feature was also that the effect-site, i.e. the CNS, could be chosen as the target, in contrast to plasma target only with the Diprifusor. Effect-site targeting is more logical to use, and it should decrease the time needed for achieving the desired effect when concentration adjustments are made.

The first model by Marsh (Marsh I) for plasma targeting, included in the Diprifusor, was replaced by a "modified Marsh" model (Marsh II) for effect-site targeting in the commercially available open TCI systems (4). Also, a propofol model from Schnider was included in these systems (5). The values of important pharmacokinetic/pharmacodynamic (Pk/Pd) parameters vary a lot between the three models (Table 1). Different alternatives increase the need of pharmacokinetic knowledge.

The lower k_{eo} and thus the higher $t_{½}k_{eo}$ in the Diprifusor, compared with the other two models, demand a higher concentration gradient between plasma and effect-site to achieve a certain effect-site target concentration, i.e. the dose must be relatively higher. This is a drawback for the elderly and fragile patients leading to a pronounced over-dosing, especially if Marsh I would be used for effect-site targeting. Ways to come around this problem are to take time and titrate to the optimum target, or to modify the model, or to do both. On the other hand, young fit patients need higher effect site target concentrations, otherwise they receive too little of the drug and will not become unconscious within a reasonable time.

The potential clinical differences between the three models were investigated in this study by performing two types of simulations in the TivaTrainer program (eurosiva.com). Also, the time frames, with which the three models display a predicted effect-site concentration during plasma target mode, were simulated in different infusors.

Methods

The pharmacokinetic parameters listed in Table 1 (read V_c and $t_{½}k_{eo}$) were used in the TivaTrainer simulation program. Two different situations were simulated. We used identical patient variables in all simulations, including a third simulation for evaluating the time to reach certain effect-site concentrations with the three models in real infusors: male 170 cm, 70 kg, 40 years of age.

1. Plasma target, "The way we use the Diprifusor"

The starting point was the way we use the plasma target controlled Diprifusor. The procedure may be described as effect-site targeting with the anaesthetist as an inter-face, cf.: Appendix. Identical output was programmed in the TivaTrainer for the three different models, i.e. the same bolus dose and the same infusion flow profile of propofol. The predicted effect-site concentration peak, the time to reach the peak, and the predicted plasma concentration over-shoot were noted.

Table 1. Values of some pharmacokinetic- and pharmacodynamic parameters used in the original Marsh-, the modified Marsh-, and the Schnider models for target controlled infusion of propofol.

Pk/Pd-parameters	Marsh (Diprifusor)	Modified Marsh (Open TCI)	Schnider (Open TCI)
V_c	0.228 L · kg^{-1}	0.228 L · kg^{-1}	4.27 L
k_{eo} (min^{-1})	0.26	1.21	0.456
$T_{½}k_{eo}$ (min)	2.6	0.57	1.8 [1.51]
TTPE (min)	4.5* (3.87)	1.60** (1.60)	1.60** (1.64)

V_c = Volume of the Central compartment
k_{eo} = Rate constant for drug elimination from effect site
$t_{½}k_{eo}$= Half-time for the rate constant for drug elimination from effect site
TTPE = Time To Peak Effect
* from reference 4
** from reference 5
Note: The TivaTrainer simulation program suggests the $t_{½}k_{eo}$ value within bracket, but the number used in the simulation was the one given in Table without bracket. Values for TTPE within parentheses are suggested and used by the TivaTrainer simulation program. See text for further clarification.

2. Effect-site target

Simply, in the second type of simulation an effect-site target concentration of 3.5 µg/mL was set in the three different propofol models. The calculated bolus dose used by the model, the time for delivering it, and the predicted plasma over-shoot were noted.

3. Time to reach a displayed predicted effect-site target in infusors

A syringe containing propofol (Diprivan 10 mg/mL pre-filled 50 mL syringe, AstraZeneca, Södertälje, Sweden) was connected to either a Diprifusor (Fresenius Vial S.A., Brezins, France) for testing the Marsh I model, or a Base Primea (Fresenius Vial S.A., Brezins, France) for testing the Marsh II-, and the Schnider models. The infusors were programmed for a plasma target of 6 µg/mL and started. The time point, at which different predicted effect-site concentrations (0.1, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 µg/mL) were displayed, was recorded.

Statistics

No statistical evaluation was made. Purely clinical considerations were made when comparing the outcome variables.

Results

1. Plasma target, "The way we use the Diprifusor", Fig. 1a-c

The predicted plasma- and effect-site concentration peaks ranged from 6.0 to 17.5 µg/mL and from 3.6 to 7.2 µg/mL, respectively, when the same infusion profile was simulated. The time to reach the predicted effect-site peak concentration ranged from 2¾ to 4 min.

2. Effect-site target, Table 2

The bolus dose given, the extent of plasma over-shoot, and the time to reach a predicted effect-site concentration of 3.5 µg/mL differed more than twofold between the three pharmacokinetic models. The models used bolus doses ranging from 68 to 150 mg infused during 22 to 46 seconds. The predicted plasma over-shoot concentrations varied from 5.0 to 13.4 µg/mL.

3. Time to reach a displayed predicted effect-site target in infusors, Fig. 2

The infusor with the Schnider- and Marsh II models started to indicate an increasing effect-site concentration sooner than the Diprifusor with the Marsh I model. E.g. after 30 seconds of infusion the predicted effect-site concentration displayed by the Diprifusor was less than 0.4 µg/mL, while the Schnider- and the Marsh II models in the Base Primea displayed 1.0 and 1.5 µg/mL, respectively. A predicted effect-site concentration of 1.0 µg/mL was displayed after almost 60 seconds with the Marsh I model.

Table 2. Values of some measured variables and estimated parameters after simulations with the original Marsh-, the modified Marsh-, and the Schnider models for target controlled infusion of propofol. An effect-site target of 3.5 µg/mL was set in each model (male, 40 years, 170 cm, 70 kg).

Variables/ parameters	Marsh (Diprifusor)	Modified Marsh (Open TCI)	Schnider (Open TCI)
Bolus dose (mg)	150	85	68
Time to deliver dose (sec)	46	28	22
Plasma over-shoot (µg/mL)	8.5	5.0	13.4
Time to reach target (min)	3.75	1.5	1.5

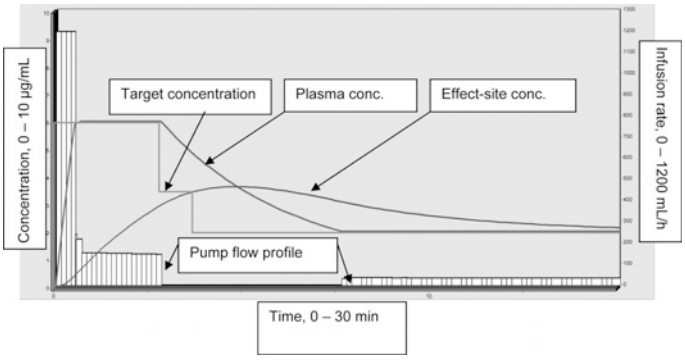

Figure 1a. A simulation of plasma target directed propofol infusion with the original Marsh model with an initial plasma target of 6 µg/mL, reduced to 3 µg/mL just before the predicted effect-site concentration reached 3 µg/mL, cf.: Appendix. A predicted effect-site peak concentration of 3.6 µg/mL was reached after 4 min. (Male 170 cm, 70 kg, 40 years of age; TivaTrainer, eurosiva.com)

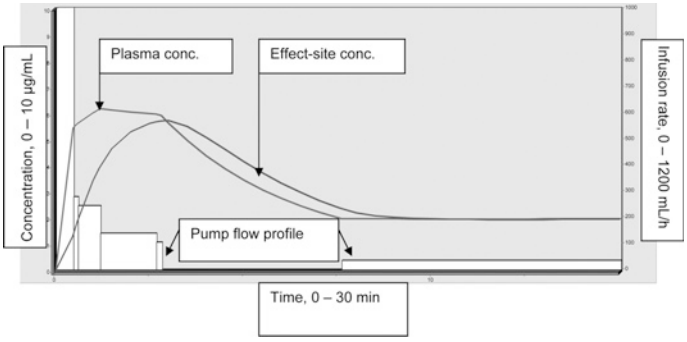

Figure 1b. A simulation of plasma target directed propofol infusion with the modified Marsh model. The bolus dose and the flow rate profile were identical with those used in Figure 1a. The model predicted the plasma peak concentration to 6.2 µg/mL, which was reached after a bit more than 1 min. A predicted effect-site peak concentration of 5.8 µg/mL was reached after approx. 2¾ min. (Male 170 cm, 70 kg, 40 years of age; TivaTrainer, eurosiva.com)

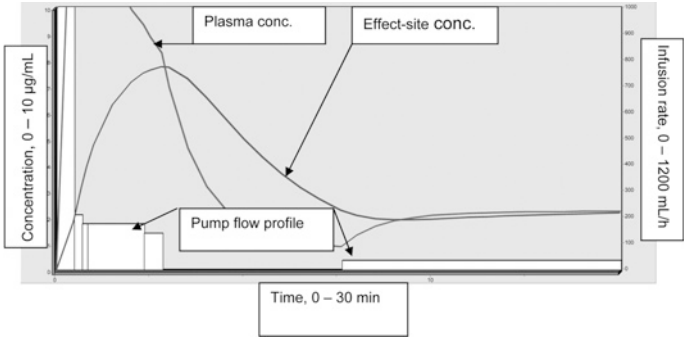

Figure 1c. A simulation of plasma target directed propofol infusion with the Schnider model. The bolus dose and the flow rate profile were identical with those used in Figure 1a. The model predicted the plasma peak concentration to (out of scale) 17.5 µg/mL, which was reached after approx. 30 sec. A predicted effect-site peak concentration of 7.2 µg/mL was reached after approx. 2¾ min. (Male 170 cm, 70 kg, 40 years of age; TivaTrainer, eurosiva.com)

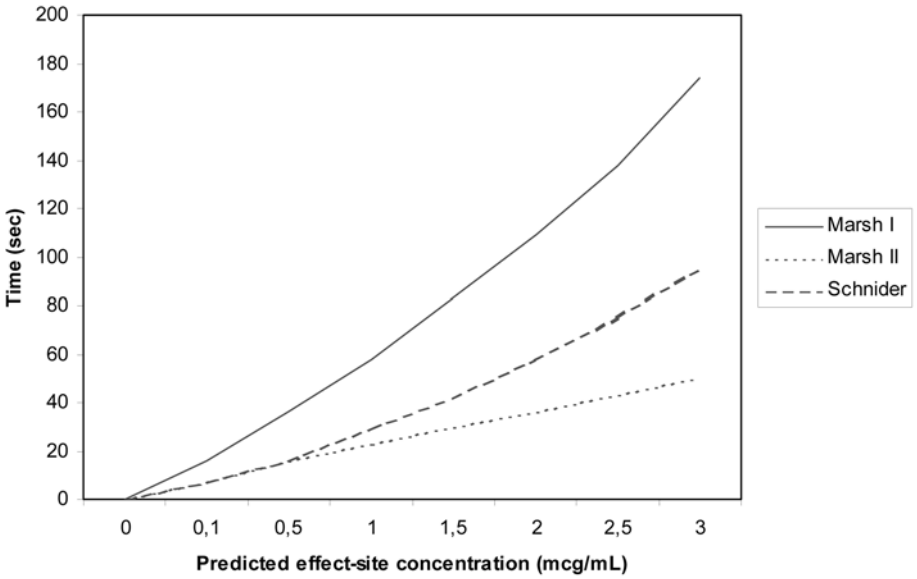

Figure 2. Approximate time frames for respectively: the original Marsh- (Marsh I), the modified Marsh- (Marsh II), and the Schnider models of displayed predicted effect-site concentrations (0.1-3 µg/mL) in infusors, when aiming at a plasma target of 6 µg/mL to a male 170 cm, 70 kg, 40 years of age. (See text for type of syringe and types of infusors).

Discussion

The three population Pk-models for target controlled infusion of propofol differ considerably in critical Pk-parameters (Table 1). These differences had apparent effects in the simulations, to an extent that must be considered of major clinical importance (Fig 1a-c, Table 2, Fig 2). E.g. the maximum predicted effect-site concentrations varied twofold with an identical infusion regimen (Fig 1a-c). Likewise, the initial dose used to reach the same effect-site target (3.5 µg/mL) varied more than twofold (Table 2). Thus, the choice of model in a clinical situation may make a difference for the patient.

Of important pharmacological factors only drug plasma or blood concentrations (at intervals) and the time to peak effect (TTPE) can be measured, while information on the actual drug dose is easily accessible. All other factors (= parameters) are calculated based on these values. TTPE for propofol has to be measured by introducing surrogate endpoints, like processed EEG, introducing additional physiological variability. TTPE was not measured for the Marsh I model (3). The value of 4.5 min was estimated in later simulations (4). Obviously, the Marsh I model comprises a much longer TTPE than the other two models (Table 1). Which TTPE is the most accurate one? As observed in the infusor simulation, the Marsh II- or the Schnider models indicated a small, increasing predicted effect-site concentration already after a few seconds of infusion. This is a well-known and essential model simplification. Pk-modelling assumes that the central compartment is well mixed.

This leads to the false indication of a concentration gradient between the plasma and the effect-site already after a few seconds of infusion. If considering an arm-brain circulation time of 30-40 seconds and an undetermined time for transfer of the drug across the blood-brain-barrier for further transport to the regions of interest, no drug should have had time to reach the effect-site until a minimum of 40 seconds. After 30 seconds the predicted effect-site concentration displayed by the Diprifusor was less than 0.4 μg/mL, while the Schnider- and the Marsh II models in the Base Primea displayed 1.0 and 1.5 μg/mL, respectively (Fig 2). This may be interpreted as an over-estimation of the effect-site concentration and an under-estimation of TTPE in the latter models. In a recent clinical trial, changes in the sedation score and Bispectral index correlated better with effect site concentration predictions by the original Marsh model than with the Schnider model (6). Additionally, when comparing with the k_{eo} and $t_{½}k_{eo}$ reported for sevoflurane (with clinical on- and off set similar to propofol), the Marsh I model harmonised better (7,8).

On the other hand, the Marsh II- and Schnider models seem to have a stronger scientific base of Pk/Pd-modelling with the use of EEG measurements and actual measurement of TTPE (4,5). However, the presumption that different EEG responses reflect clinically purposeful measures is not unchallenged (9). The median effective concentration (EC_{50}) of propofol for loss of consciousness (LOC) differs significantly from EC_{50} for immobility, indicating that different effects are mediated at different levels of the central nervous system (10). This supports the discussed clinical finding. Anatomically, EEG reflects the electrical activity in superficial cortical structures, and from a functional point of view EEG reflects LOC rather than immobility. It may be that the defined TTPE of 1.6 min in the later models is the time to *initial* effect rather than the time to *true peak* effect?

Potential benefits with the Marsh II- and Schnider models are reduced hemodynamic- and respiratory effects, especially in the elderly and fragile patients (5). Age is included as a pharmacokinetic co-factor in the Schnider model, which may have a value, although the impact of age on pharmacodynamics is much stronger (5). This unavoidable fact will be best handled by drug titration, starting with a low target and by increasing the infusion time, irrespective of the model used. If we accept to use the Marsh II- and Schnider models, we have to learn about and agree to higher initial targets, especially to young and fit patients. The potential hemodynamic benefit may then be lost or decreased.

It should be noted that the TivaTrainer is in some details programmed with values that differ from those presented in Table 1. The TivaTrainer uses a fixed-k_{eo} method to calculate a patient-individualised TTPE for each patient for the Schnider model. In contrast, a modern infusor such as Alaris Asena PK uses a fixed-TTPE method to calculate a patient-individualised k_{eo} for each patient for the same model (personal communication, Dr Anthony Absalom, Camebridge, UK). In the present simulations, we used the $t_{½}k_{eo}$ values presented in table without bracket, and the fixed TTPE values (from the simulation program) are shown within parentheses. Thus, $t_{½}k_{eo}$ was the "leading" parameter. The reason for using the lower TTPE, suggested in the simulation program, was that the probable "true" TTPE would be lower than 4.5 min. As

suggested, the TTPE should be used when kinetic and dynamic models have been calculated from different study populations (11,12). Therefore, we also did the other way around (not in Table) and used the listed TTPE of 4.5 min in the Marsh I model, accepting another value of $t_{½}k_{eo}$ suggested by the simulation program. Then, the time to reach peak effect-site concentration in Marsh I was prolonged in the plasma- and the effect-site target simulations with 13 and 25%, respectively. Otherwise, only minor deviations in results were found (1.7–9.5%).

After the introduction of open TCI, different models and their different attached numbers for targets may confuse enthusiasts of total intravenous anaesthesia, not to mention new users. This is more than an academic question; it also includes aspects of patient safety. Therefore, we call for an optimised population based pharmacokinetic model for propofol – a consensus model!

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References

1. Russell D, Wilkes MP, Hunter SC, Glen JB, Hutton P, Kenny GN (1995). Manual compared with target-controlled infusion of propofol. Br J Anaesth; 75: 562–6.
2. Gepts E, Camu F, Cockshott ID, Douglas EJ (1987). Disposition of propofol administered as constant rate intravenous infusions in humans. Anest Analg; 66: 1256–63.
3. Marsh B, White M, Morton N, Kenny GN (1991). Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth; 67: 41–8.
4. Struys MM, De Smet T, Depoorter B, Versichelen LF, Mortier EP, Dumortier FJ, Shafer SL, Rolly G (2000). Comparison of plasma compartment versus two methods for effect compartment–controlled target-controlled infusion for propofol. Anesthesiology; 92: 399–406.
5. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ (1999). The influence of age on propofol pharmacodynamics. Anesthesiology; 90: 1502–16.
6. Barakat AR, Sutcliffe N, Schwab M (2007). Effect site concentration during propofol TCI sedation: a comparison of sedation score with two pharmacokinetic models. Anaesthesia; 62: 661–6.
7. Rehberg B, Bouillon T, Zinserling J, Hoeft A (1999). Comparative pharmacodynamic modeling of the electroencephalography-slowing effect of isoflurane, sevoflurane, and desflurane. Anesthesiology; 91: 397–405.
8. Kennedy RR (2005). The effect of using different values for the effect-site equilibrium half-time on the prediction of effect-site sevoflurane concentration: a simulation study. Anesth Analg; 101: 1023–8.
9. Kuizenga K, Wierda JM, Kalkman CJ (2001). Biphasic EEG changes in relation to loss of consciousness during induction with thiopental, propofol, etomidate, midazolam or sevoflurane. Br J Anaesth; 86: 354–60.
10. Harris RS, Lazar O, Johansen JW, Sebel PD (2006). Interaction of propofol and sevoflurane on loss of consciousness and movement to skin incision during general anesthesia. Anesthesiology; 104: 1170–5.
11. Minto CF, Schnider TW, Gregg KM, Henthorn TK, Shafer SL (2003). Using the time to maximum effect site concentration to combine pharmacokinetics and pharmacodynamics. Anesthesiology: 99: 324–33.

12. Absalom AR, Struys MMRF (2002). An overview of TCI & TIVA. Gent: Academia Press, 2005.
13. Enlund M, Hassan HG. Intraoperative awareness: detected by the structured Brice interview? Acta Anaesthesiol Scand; 46: 343–4.
14. Albertin A, Casati A, Federica L, Roberto V, Travaglini V, Bergonzi P, Torri G (2005). The effect-site concentration of remifentanil blunting cardiovascular responses to tracheal intubation and skin incision during bispectral index-guided propofol anesthesia. Anesth Analg; 101: 125–30.

Appendix

When using the Diprifusor, we have learned that most patients need a predicted effect-site concentration of 3-4 μg/mL of propofol in combination with an adequate dose of opioid to tolerate tracheal intubation without the use of a neuro-muscular blocking agent. As follows, the patients are then properly anaesthetised without having the risk of poor anaesthesia masked by muscle relaxation (13). This clinical experience tallies with the findings by Albertin and co-workers (14). They found that a patient population aged 20–65, whom were given a predicted remifentanil effect-site concentration of 4.7–5.4 ng/mL (95% c.i.) for eliminating responses to intubation, needed propofol to a predicted effect-site concentration of 3.1–3.7 μg/mL (95% c.i.) to keep Bispectral index at the recommended interval of 40–50.

We also know that the equilibration time between plasma and effect site seems to be longer than our patience - considerably longer for some of us. Thus, we cannot choose 3–4 μg/mL as the *initial* plasma target. Instead, we aim higher in order to reach the desired level in effect-site within a reasonable time frame, i.e. we deliberately create a plasma over-shoot (the same idea as is used in the effect-site target models). On the other hand, after securing the airway there will be a period with sparse stimulation (cleaning and draping). Hence, a marked over-shoot at that time must be prohibited for avoiding haemodynamic side-effects. In order to tailor the anaesthetic, we first program the Diprifusor to give drug enough to reach a predicted plasma concentration of e.g. 6 μg/mL. Later, when the predicted effect-site concentration reaches 3 μg/mL, as indicated by the infusor display, we reduce the plasma target to e.g. 3 μg/mL. The pump then stops the infusion, while the high concentration gradient between plasma and effect-site will continue to drive the drug into the effect-site. If tracheal intubation is luckily performed (at the effect-site peak concentration), we can then further reduce the target ahead of cleaning and draping, at least if this procedure is assumed to take a considerable time before skin incision can be performed.

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