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EDITORIAL

Stability of BIS with Schnider or modified Marsh effect-site targeted infusions: As you like it, or much ado about nothing?

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Although commercial target-controlled infusion (TCI) systems have been available since the late 1990s[1] and have facilitated safe and accurate administration of propofol in more than 90 countries,[2] there remain areas of uncertainty and controversy.[3]

TCI systems are programmed with one or more pharmacokinetic (PK) model, most of which are mammillary models, comprising three compartments: a central compartment (A1), which is the initial volume into which the drug is administered (which includes, but is not necessarily limited to the blood volume – it is an *apparent* volume) and two other compartments (A2 and A3) which represent the volumes into which rapid and slow re-distribution occur. A set of rate constants estimate the proportion of drug moving between the compartments in each unit of time (k_{12}, k_{21}, k_{13} and k_{31}), while elimination or metabolism is represented by k_{10} (the proportion of drug removed from A1 in each unit of time). These rate constants are directional and have subtext to denote the origin and destination of drug movement (Figure 1).

These volumes and rate constants are mathematical constructs that estimate the rates of drug disposition following drug administration and can therefore be used to estimate the plasma- and effect-site concentrations following any given drug administration regimen. TCI systems use these same parameters in the inverse process to calculate the infusion rates required to achieve a user-defined plasma concentration when in so-called plasma concentration targeting mode.

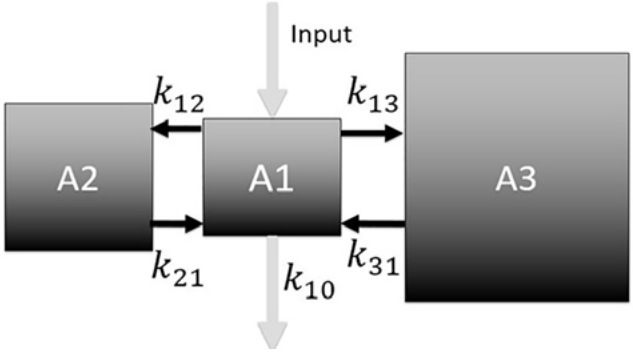

Figure 1: The mammillary pharmacokinetic model

The site of action of most anaesthetic drugs is the central nervous system, and not the plasma. Targeting the plasma-site would therefore seem inappropriate for the dynamic nature of the perioperative milieu. To account for the temporal delay in equilibration between the drug concentration in the plasma- and the site of drug effect (the "effect-site"), an additional micro constant (k_{e0}) can be incorporated to produce a combined pharmacokinetic-pharmacodynamic (PK-PD) model. Most such models use a sigmoidal E_{max} function to describe the relationship between plasma concentration (C_p) and clinical effect, described as the effect-site concentration (C_e). A PK-PD model can also be used to calculate the infusion rates required to achieve a user-defined C_e, when in effect-site targeting mode. In this mode, the TCI device will administer "excess" drug to the plasma compartment to temporarily increase the C_p above the target C_e, to achieve the shortest time to reach the desired C_e, without C_e overshoot. The degree of overshoot in the C_p is strongly influenced by the k_{e0} (a system with a slower, i.e. lower k_{e0} will effect a much higher overshoot than a system with a faster, i.e. higher k_{e0}). An erroneous k_{e0} could therefore introduce unwanted over- or underdosing following a change in C_e target.

When the first-generation TCI pumps were launched in 1997, they were programmed with the Marsh adult PK model for propofol.[4] Soon afterwards a somewhat empirically derived k_{e0} value of 0.26 min^{-1} was added.[5] If this slow value were to be used for effect-site targeting, it would generate large initial plasma concentration overshoots, resulting in unsafe induction doses, especially when used in the elderly population. This k_{e0} was thus only used to enable graphic depiction of the estimated effect-site concentration. A later study showed that the time course of changes in the bispectral index (BIS) with the Marsh model was better explained by a k_{e0} of 1.21 min^{-1}.[6] When the Marsh model is used with this k_{e0}, it is commonly referred to as the 'modified Marsh model'.

When the second-generation pumps were launched a few years later,[1] they were also programmed with the Schnider adult propofol model.[7,8] Clinicians using these pumps were faced with a choice of two models for propofol. The models were developed in different ways and have some striking differences that are

described elsewhere.[9] In brief, the volumes of the Marsh model are all linearly related to the weight of the patient. No age-adjusted parameters are used. The Schnider model uses fixed values for A1 and A3, with A2 varying with age. The rate constant k_{10} is adjusted by using the total body weight, lean body weight, gender and height of the subject.

Clinicians have thus been left with uncertainty when choosing the correct PK model. As much as we pride ourselves in being practitioners of evidence-based medicine, the factors which have driven us to use a specific model have often been rather arbitrary. In this edition of SAJAA, Coetzee et al. report the results of an excellent study that attempted to provide some evidence to inform appropriate PK-PD model selection.[10]

Coetzee et al. used methodology similar to that in a study by Coppens.[11] Healthy, non-obese, young adult subjects received a simple propofol infusion until loss of consciousness (LOC). In one group, the Schnider model was used to estimate C_p and C_e, and after LOC, an effect-site targeted infusion was commenced with the target concentration, the C_e at LOC. In the other group, the modified Marsh model was used to estimate C_p and C_e and to implement an effect-site targeted infusion with the target being the C_e at LOC. In both groups the BIS was used as a measure of clinical effect.

As expected, the C_e at LOC estimated by the two models, were somewhat different. After LOC, both models estimated that the C_e was stable. *If* the PK-PD models were perfect, then one would expect that the BIS would remain stable after the start of the effect-site targeted infusion. In their study, Coetzee et al. found that the BIS value actually continued to decrease over the first observed 20 minutes, with the BIS values remarkably similar between the two study populations.[10] With regards to the models, one might conclude that they performed equally well (or badly), and that the arguments among academics during the preceding 20 years about which model was superior, were 'much ado about nothing'.

In their interesting article Coetzee et al. discusses this finding extensively and mention the possible roles of neuronal inertia and errors due to front-end kinetics. Another possibility is that both models are simply inaccurate and are administering too much propofol in the period after induction. This led us to ask the question whether the recently developed Eleveld general purpose PK-PD model was any better.[12] During model development, propofol concentration and BIS data from more than a thousand individuals enrolled in 30 studies were used (an order of magnitude more than Schnider's 24 healthy volunteers).[12] The patients and volunteers in these studies had a wide range of characteristics, ranging from 27 week-old premature neonates to 88 year-old octogenarians, with weights ranging from 0.68 to 160 kg.[12] The resulting model incorporates allometric scaling of clearances with size, makes some allowance for the pharmacokinetic interactions known to occur when

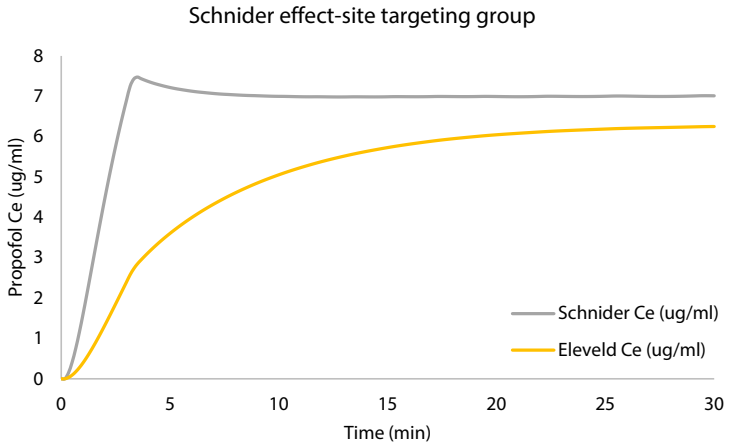

Figure 2: Effect-site estimations of infusion data according to Schnider effect-site targeting group

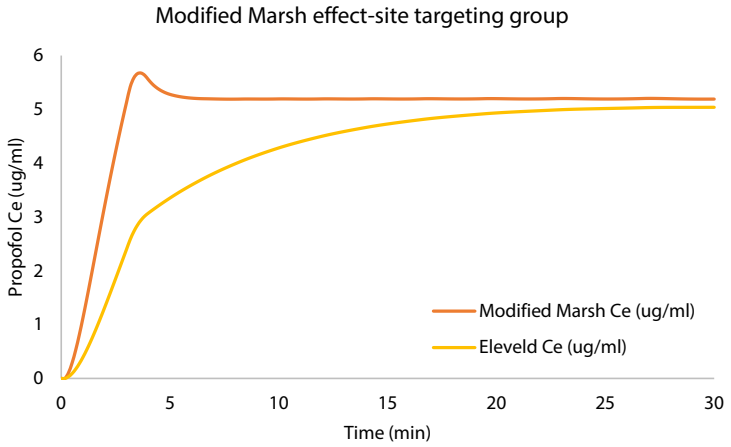

Figure 3: Effect-site estimations of infusion data according to modified Marsh effect-site targeting group

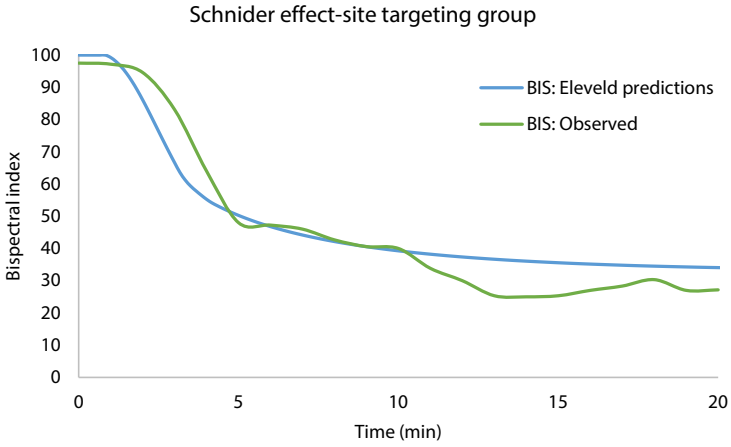

Figure 4: Comparison of predicted BIS from Eleveld and observed BIS from the Schnider effect-site targeting group

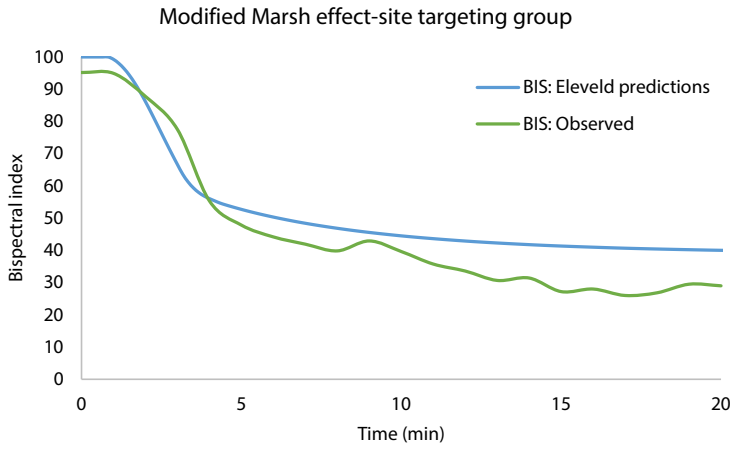

Figure 5: Comparison of predicted BIS from Eleveld and observed BIS from the Modified Marsh effect-site targeting group

opioids are used, and uses a sigmoid function to adjust the model for differences in drug clearance in early age.

A unique feature of the Eleveld model, is that it can be used to predict BIS values based on the C_e and patient age. As Coetzee and colleagues were kind enough to provide us with their study data, we calculated the C_p, C_e and BIS values predicted by the Eleveld model based on the demographics of the study subjects and the propofol infusion rates that they actually received over time. Two very interesting results emerged. Firstly, the Eleveld estimations of C_p and C_e both increased during the first 20 minutes (Figure 2 and Figure 3).

We then used the Eleveld model to predict the BIS values associated with the C_e of propofol. When we compared the Eleveld predictions to the BIS values actually recorded, they were remarkably similar for both arms of the Coetzee et al. study (Figure 4 and Figure 5).

Coetzee et al. have shown that in healthy, young, non-obese volunteers, when the target concentration during maintenance of anaesthesia is chosen or calibrated according to the concentration estimated at LOC, the Schnider model and the modified Marsh model (both in effect-site targeting mode) produce remarkably similar clinical effects (judged by the BIS).[10] After LOC however, the BIS values drift downwards. This is entirely consistent with the practice of experienced anaesthetists around the world, who tend to slowly reduce the target concentrations after LOC and airway management. Interestingly, our own simulations showed that the new Eleveld model was remarkably accurate at predicting the BIS values observed in the Coetzee et al. study. The reasons for this may or may not be related to better specification of the front-end kinetics or of early re-distribution. In any event, this finding is consistent with the findings of a recent prospective validation study of the Eleveld model, which confirmed its accuracy at predicting BIS values.[13] A recent case report in SAJAA has also highlighted the accuracy of the new Eleveld model during TIVA in an infant requiring spinal cord neuromonitoring.[14] Anaesthetists faced with a choice between either the Schnider or Marsh model could reasonably flip a coin to help them decide. Once the Eleveld model is incorporated into commercially available TCI pumps, it might be a reasonable alternative.

Conflict of interest

EC: none.

ARA: his research group/department received (over the past three years) research grants and consultancy fees from The Medicines Company (Parsippany, NJ, USA), Becton Dickinson (Eysins, Switzerland), Dräger (Lubeck, Germany), Paion (Aachen, Germany), Orion (Espoo, Finland), Rigel (San Francisco, CA, USA), Philips (Eindhoven, Netherlands), Arcomed (Kloten, Switzerland) and Janssen Pharmaceutica (Beerse, Belgium). He is an editorial board member and editor for the British Journal of Anaesthesia.

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References

1. Struys MMRF, De Smet T, Glen JB, et al. The history of target-controlled infusion. Anesth Analg. 2016;122(1):56-69. https://doi.org/10.1213/ANE.0000000000001008.
2. Absalom AR, Glen JB, Zwart GJC, Schnider TW, Struys MMRF. Target-controlled infusion. Anesth Analg. 2016 Jan;122(1):70-8. https://doi.org/10.1213/ANE.0000000000001009.
3. Enlund M. TCI : Target controlled infusion, or totally confused infusion? Call for an optimised population based pharmacokinetic model for propofol. Ups J Med Sci. 2008 Jan 12;113(2):161-70. https://doi.org/10.3109/2000-1967-222.
4. Marsh B, White M, Morton N, Kenny GN. Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth. 1991;67:41-8. https://doi.org/10.1093/bja/67.1.41.
5. White M, Engbers F, Schenkels M, Burm A, Bovill J. The pharmacodynamics of propofol determined by auditory evoked potentials. Sydney Abstr World Congr Anaesthesiol. 1996;610.
6. 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 Feb;92(2):399-406. https://doi.org/10.1097/00000542-200002000-00021.
7. 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 May;88(5):1170-82. https://doi.org/10.1097/00000542-199805000-00006.
8. Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. Anesthesiology. 1999;90(6):1502-16. https://doi.org/10.1097/00000542-199906000-00003.
9. Absalom AR, Mani V, De Smet T, Struys MMRF. Pharmacokinetic models for propofol--defining and illuminating the devil in the detail. Br J Anaesth. 2009 Jul 1;103(1):26-37. https://doi.org/10.1093/bja/aep143.
10. Coetzee JF, Links A, Levin AI. Assessment of the clinical validity of an adjusted Marsh pharmacokinetic model using an effect-site rate constant (ke0) of 1.21 min-1. Southern African Journal of Anaesthesia and Analgesia. 2021;27(2):83-91. https://doi.org/10.36303/SAJAA.2021.27.2.2583.
11. Coppens M, Van Limmen JGM, Schnider T, et al. Study of the time course of the clinical effect of propofol compared with the time course of the predicted effect-site concentration: performance of three pharmacokinetic–dynamic models. Br J Anaesth. 2010 Apr;104(4):452-8. https://doi.org/10.1093/bja/aeq028.
12. Eleveld DJ, Colin P, Absalom AR, Struys MMRF. Pharmacokinetic–pharmacodynamic model for propofol for broad application in anaesthesia and sedation. Br J Anaesth. 2018 May;120(5):942-59. https://doi.org/10.1016/j.bja.2018.01.018.
13. Vellinga R, Hannivoort LN, Introna M, et al. Prospective clinical validation of the Eleveld propofol pharmacokinetic-pharmacodynamic model in general anaesthesia. Br J Anaesth. 2021 Feb;126(2):386-94. https://doi.org/10.1016/j.bja.2020.10.027.
14. Coetzee E, Gray R, Hollman C, Enslin JMN, Coetzee JF. Anaesthetic management of a three-month-old baby for cervical limited dorsal myeloschisis repair using propofol and alfentanil infusions guided by pharmacokinetic simulation software: A case report. South African J Anaesth Analg. 2019;25(6):32-5. https://doi.org/10.36303/SAJAA.2019.25.6.A5.