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EDITORIAL

An Array of TCI Models. Which One to Choose?

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With the use of pharmacokinetic (PK) and pharmacodynamic (PD) models, Target controlled Infusion (TCI) systems enable physicians to attain and sustain exact drug concentrations in the plasma or effect site (usually the brain), marking a significant advancement in the delivery of anesthesia. These automated systems provide a level of precision that manual infusions cannot match by dynamically adjusting infusion rates based on patient-specific parameters.

The Concept of TCI and Propofol

The lipophilic sedative-hypnotic propofol is perfect for TCI because of its quick onset, brief duration of action, and consistent pharmacokinetics. To forecast how propofol will distribute and exit the body, TCI systems use multi-compartmental PK models, which usually have three compartments: central, rapid peripheral, and slow peripheral. These models include variables like intercompartmental transfer rates, clearance rates, and volume of distribution (Vd), which are frequently modified by covariates like sex, age, weight, and height. In order to match drug delivery with clinical effects like unconsciousness, some models additionally incorporate a PD component, such as the effect-site equilibration rate constant (ke0), which targets brain concentrations rather than plasma levels.

Key TCI Models for Propofol

Several TCI models for propofol have been developed, each with unique characteristics. The most prominent ones are Marsh, Schnider, Kataria, Paedfusor, and Eleveld, along with some lesser-known variants.

1. Marsh Model

Introduced in 1991 by Brian Marsh and colleagues, the Marsh model is one of the first and most widely accepted TCI models for propofol. This study is based on a small cohort of healthy adults who received a propofol infusion and uses a three-part pharmacokinetic model. The model scales the volume and clearance in relation to the total body weight (TBW) and is easy to apply. The initial ke0 (0.26 min^{-}) was slow, but the modified version (sometimes called the modified Marsh) uses a ke0 (1.2 min^{-}) that is faster to improve the targeting of the effect sites.[(1)]

It became the gold standard due to its ease of use and incorporation into the Diprifusor, the first commercial TCI system. It has been validated in multiple studies and works well in adults within typical therapeutic ranges

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(3–6 μg/mL plasma concentration). Extremes in age, weight, or physiology are difficult for the Marsh model to handle. TBW-based scaling may overestimate the need for propofol in obese patients, which could result in overdosing. Because of unadjusted covariates like age or lean body mass (LBM), its predictive accuracy declines in children and the elderly. Higher plasma overshoots are required for rapid induction because the slow original ke0 may postpone effect-site equilibration. In open TCI systems, it is widely used (e.g. G. For healthy adults, Alaris pumps) and is dependable; however, based on experience, clinicians frequently modify the targets.

2. Schnider Model

This model was created in 1998 by Thomas Schnider and associates based on a mixed-effects analysis of 24 healthy volunteers. In contrast to Marsh, it uses the James formula to calculate LBM by taking into account several covariates, including age, height, weight, and sex. Smaller initial boluses are produced because the central compartment volume (V1) is fixed at 4point 27 L, which is significantly less than Marsh's weight-proportional V1 (15–20 L for an adult weighing 70 kg). Effect-site targeting is supported by its ke0 (0.456 min^{-1}), which aims for a quick clinical effect without causing excessive plasma overshoot.

Because of its superior effect-site targeting capabilities, the Schnider model lowers the possibility of oversedation during induction. It is more flexible for a variety of demographics, including the elderly, where lower LBM lowers dosage, thanks to its covariate adjustments. If the fixed V1 is not modified, it may underestimate concentrations in obese patients (e.g. G. using body weight that has been adjusted. Its intricacy necessitates meticulous parameter entry, and some contend that, in contrast to Marsh, it underdoses during maintenance. Studies on predictive performance yield inconsistent findings, with bias occasionally present in the most extreme situations. This is pre-programmed in many open TCI systems alongside Marsh, and it is preferred in settings where effect-site control is a top priority. When switching from Marsh, clinicians must use higher initial targets to prevent underdosing.[2]

3. Kataria Model

Developed in 2003, the Kataria model focuses on pediatric patients (those aged 3 to 16). It employs a three-compartment structure with TBW as the main covariate, based on data from 53 children. It is limited to plasma targeting because it does not have a ke0 like Paedfusor does. It fills a void in pediatric TCI by providing children's plasma concentrations with a respectable level of accuracy. When effect-site targeting isn't crucial, its simplicity works well. Its usefulness for dynamic sedation control is diminished since it cannot forecast brain concentrations in the absence of ke0. Compared to adult models, it has less validation and ignores age-related PK changes in the pediatric range. For plasma-targeted infusions, it is therefore very helpful in pediatric anesthesia; however, for effect-site applications, Paedfusor is superior.

4. Paedfusor Model

The Marsh framework is expanded upon by the Paedfusor, which was created for kids ages 1 to 16 and modifies parameters in response to pediatric PK data. It scales volumes and clearances using TBW and employs a ke0 of 0.26 min^{-1}, which is taken from adults. It's among the few pediatric models that allow effect-site targeting, which enhances depth of sedation control. It is incorporated into certain pediatric TCI pumps. It's possible that the adult-derived ke0 (0.26 min^{-1}) does not appropriately represent pediatric physiology. Research such as Munoz *et al*. Higher ke0 values are suggested by's (2004) (e.g. G. 0.91 min^{-1}) may be more appropriate for kids, suggesting that it might not be accurate. Additionally, it is restricted to a small weight range (up to 61 kg) and age range. Although its accuracy is up for debate, this is primarily used in pediatric anesthesia when TCI is available, and clinicians may rely on clinical endpoints (e.g. G. BIS monitoring) to modify goals.

5. Eleveld Model

A more recent and ambitious attempt at a "general-purpose" PK-PD model for propofol is the Eleveld model (2018). It was created by Douglas Eleveld and associates using information from 1,033 patients in a wide range of demographics, including children, adults, the elderly, and obese people. It uses allometric scaling (e.g. G. TBW, age, and sex are included as covariates, along with weight^0.75 for clearance. With a refined ke0 specific to its PK structure, it provides both effect-site and plasma targeting. Its extensive

dataset makes it more applicable to a variety of demographics, including children and obese people. Research (e.g. G. When using TBW, they demonstrate better predictive performance than Marsh and Schnider in obese adults. It seeks to increase accuracy and lessen bias in a range of clinical situations. It is not yet extensively incorporated into commercial TCI systems, and its complexity necessitates strong computational support. There is ongoing validation, and some people wonder if its generalizability comes at the expense of accuracy in particular subgroups. promising for TCI systems in the future, particularly in populations that are mixed or difficult to work with, but because of its novelty, adoption lags behind Marsh and Schnider.(3)

Other Notable Models

a. **Dyck Model:** was derived from low-dose propofol studies, it adjusts for age and weight but shows greater bias and inaccuracy at anesthetic concentrations (e.g., 43% mean prediction error vs. Marsh's -1%). It's rarely used clinically.
b. **The Tackley Model:** like Marsh, it works well in adults but isn't widely used because of its overlap in usefulness.
c. The PGIMER Model was created in India using local data, and it matches Marsh's performance in Indian patients, indicating that accuracy may be improved by population-specific models.

Comparative Analysis

The clinical utility and predictive accuracy (precision and bias) of each model determine how well it performs. Commercial TCI systems are dominated by Marsh and Schnider because of their simplicity and historical validation. Schnider's effect-site focus works well for rapid induction but may underpredict in cases of obesity; Marsh is excellent at plasma targeting for healthy adults but struggles in extremes. While pediatric models like Kataria and Paedfusor fill a need but aren't very well-developed, Eleveld's all-encompassing strategy suggests a future benchmark.

Clinical Implications and Challenges

TCI's promise—precise, patient-tailored anesthesia—faces real-world hurdles. Models assume homogeneity within populations, yet inter-individual variability (e.g., cardiac output, liver function) introduces error. Extreme conditions (e.g., hypothermia, massive blood loss) further skew predictions, as algorithms extrapolate from healthy volunteer data. The lack of real-time propofol concentration monitoring (unlike end-tidal volatile agents) means clinicians rely on model predictions and clinical feedback (e.g., BIS), blending art and science. The U.S. lags in TCI adoption due to FDA hesitancy, limiting its use to research, while over 90 countries embrace it. Future advancements—like integrating physiologic feedback (EEG, neuromuscular monitoring) or refining models with AI—could close this gap.

CONCLUSION

The development of propofol TCI models is indicative of an effort to achieve accuracy in a field that is inherently unpredictable. While Kataria and Paedfusor provide imperfect pediatric care, Marsh and Schnider continue to be workhorses, striking a balance between utility and simplicity. The wide range of applications of Eleveld indicates a move toward inclusive, flexible models. TCI is a dynamic field that is ready for innovation; as some suggest, a consensus model might help to standardize best practices. Clinicians must currently select models carefully, using patient profiles and critical thinking, understanding that while no model is perfect, each one improves our field.

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