Target-Controlled Infusion: Not a One-Sized-Fits-All Answer to Drug Administration

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Understanding and applying fundamental pharmacokinetic (PK) and pharmacodynamic (PD) concepts assist anesthesiologists to dose anesthetic agents on a rational basis. However, to dose the individual patient, characterization of variability is required. There are numerous sources of variability. Obesity is 1 source that was mostly disregarded for many years but has been getting more attention recently.

Using target-controlled infusion (TCI) devices, a now relatively old technology (that is unfortunately still unavailable to the American clinician), a plasma or effect-site concentration can be rapidly attained and maintained. The concentration can be adjusted quickly to match the patient's requirement during surgery.

In 2003, Drs Egan and Shafer[1] compared TCI to surfing. Comparing the concentration-effect relationship to a wave, the authors described an optimal dosing strategy that allows the clinician to "surf" the crest of the wave, thereby maintaining a desired therapeutic effect while being able to terminate the effect with small changes in concentration. To stay on the crest of this concentration-response "wave," clinicians rely on 3 fundamental pharmacologic concepts: PK guidance, PD guidance, and a rational selection of a specific drug with the appropriate kinetic and dynamic properties suitable for the case and patient. The fundamental principle of "surfing" this concentration versus effect crest is that a given effect-site concentration will produce a given effect, irrespective of time.

Introducing the reader to big-wave surfing, Warshaw[2] described the sport as "a new and uncharted branch of science—something to be researched, studied, and practiced." The avid big-wave surfer will most certainly attest that the surfing a waist high set on a beach in Southern California is much different than surfing a 40-foot behemoth off the coast of Maui. In keeping with the surfing analogy by Egan and Shafer,[1] it seems unwise then for an anesthesiologist to attempt to stay on the crest of the morbidly obese patient's concentration-response "wave" using TCI systems based on PK/PD models that have excluded obese individuals.

In addition to changes in body composition, obese subjects have significant comorbidities that can alter drug kinetics and dynamics, for example, diabetes mellitus, coronary artery disease, hypertension, and other intercurrent drug therapies.[3] The changes in pharmacokinetics and pharmacodynamics associated with obesity not only narrow the therapeutic indices of our anesthetic agents but also change the shape and steepness of the concentration-effect curve (Figure).

The drawbacks of using PK models derived from nonobese subjects for TCI in obese individuals have been well defined.[4] La Colla et al[5] administered propofol to obese subjects via TCI guided by the Marsh et al[6] model and found unacceptable performance, regardless of weight adjustment, indicating that this model cannot be used in this patient population.[5] La Colla et al[5] recommended that propofol administration to morbidly obese patients be titrated to processed-electroencephalography values to avoid awareness.

Five years later, in their study examining performance of propofol TCI in obese subjects, Cortínez et al[7] showed that using adjusted body weight as opposed to total body weight improved the performance of the propofol PK models described by Marsh et al[6] and Schnider et al.[8] The authors defined the adjusted body weight as the ideal body weight plus 40% of the difference between total and ideal body weight.

In this issue, Cortinez et al[9] have created an elegant PK model of propofol using data from studies specific to obese individuals. They combined this PK model with observed PD data to allow effect-site TCI. This model—derived exclusively from obese subjects—performed nicely in a prospective validation in 14 subjects and compared equally to the model described by Eleveld et al.[10] The major difference between these 2 models is that the model described by Cortinez et al[9] scaled clearance linearly to total body weight, while the model developed by Eleveld and colleagues[10] used an allometric approach. The difference in weight-scaling approaches (linear versus allometric) may be due to the weight ranges of the subjects in each study. Cortinez et al[9] investigated only obese subjects, while Eleveld and his co-investigators[10] (including LI Cortinez) included obese and normal-weight subjects in their study.

Previous PK models of propofol developed for obese subjects found a nonlinear relationship between total body weight and clearance.[10–12] Cortinez et al[9] did explore

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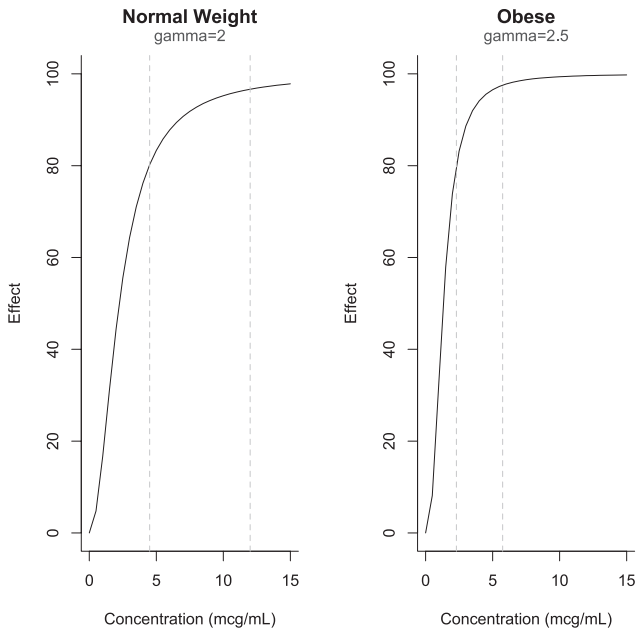

Figure. Concentration-effect sigmoid curves for normal-weight and obese subjects. The concentration-effect curve is steeper for obese subjects ($\gamma = 2.5$) compared to normal-weight subjects ($\gamma = 2$). The gray-dashed lines denote the therapeutic index (concentration of drug required to stay on the crest of the curve). In this example, the therapeutic index is 80%–95% of the maximum effect. The therapeutic index is narrowed in obese subjects compared to normal-weight subjects.

allometric relationships between total body weight and clearance but found equal performance with linear models. While the merits of allometric scaling can be debated,[13] they are beyond the scope of this editorial. Clinicians who cannot use TCI pumps (ie, in the United States) and choose to manually calculate dosing schemes will appreciate the selection of this simpler model by Cortinez et al.[9] Granted, while this model can be celebrated for its simplicity, it must be noted that, because the model was developed using only obese subjects, use of this model beyond this specific patient population (ie, in normal-weight subjects) is not recommended.

Users of TCI systems will appreciate that Cortinez and colleagues[9] combined their PK model with PD data to allow effect-site targeting. The benefits of effect-site targeting over plasma targeting are well documented. Targeting the effect site rapidly achieves a therapeutic peak effect-site concentration with only a transient overshoot in plasma concentration.[14] The time-to-peak effect occurs while the plasma drug concentration is decreasing.[14] Second, the fact that this study integrates PK and PD data obviates the calculations necessary to link PK-only data to PD models.[15]

Cortinez et al[9] caution that the use of this model may result in an underdose in normal-weight subjects. Near–steady-state concentrations during infusions are governed by elimination clearance. Propofol clearance normalized to total body weight ($mL^{-1} \cdot kg^{-1} \cdot minute^{-1}$) increases with decreasing weight (ie, obese versus normal-weight subjects). Therefore, the extrapolation of this obesity-specific model to normal-weight subjects may result in an underestimation of clearance and the aforementioned risk of underdose. While the magnitude of this underdose is difficult to predict, the risk of awareness due to underdosing cannot be ignored. Some may view this lack of model generalizability as a limitation. However, there is no one-size-fits-all approach to drug delivery. More studies such as this one that validate TCI drug delivery to specific patient populations with narrowed therapeutic indices are necessary and long overdue.

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REFERENCES

1. Egan TD, Shafer SL. Target-controlled infusions for intravenous anesthetics: surfing USA not! *Anesthesiology*. 2003;99:1039–1041.
2. Warshaw M. *Maverick's: The Story of Big-Wave Surfing, Updated Edition*. San Francisco, CA: Chronicle Books; 2003.
3. Ingrande J, Lemmens HJ. Dose adjustment of anaesthetics in the morbidly obese. *Br J Anaesth*. 2010;105(suppl 1):i16–i23.
4. Coetzee JF. Total intravenous anaesthesia to obese patients: largely guesswork? *Eur J Anaesthesiol*. 2009;26:359–361.
5. La Colla L, Albertin A, La Colla G, et al. No adjustment vs adjustment formula as input weight for propofol target-controlled infusion in morbidly obese patients. *Eur J Anaesthesiol*. 2009;26:362–369.
6. Marsh B, White M, Morton N, Kenny GN. Pharmacokinetic model driven infusion of propofol in children. *Br J Anaesth*. 1991;67:41–48.
7. Cortínez LI, De la Fuente N, Eleveld DJ, et al. Performance of propofol target-controlled infusion models in the obese: pharmacokinetic and pharmacodynamic analysis. *Anesth Analg*. 2014;119:302–310.
8. 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;88:1170–1182.
9. Cortinez LI, Sepulveda P, Rolle A, Cottin P, Guerrini A, Anderson BJ. Effect-site target-controlled infusion in the obese: model derivation and performance assessement. *Anesth Analg*. 2018;127:865–872.
10. Eleveld DJ, Proost JH, Cortínez LI, Absalom AR, Struys MM. A general purpose pharmacokinetic model for propofol. *Anesth Analg*. 2014;118:1221–1237.
11. van Kralingen S, Diepstraten J, Peeters MY, et al. Population pharmacokinetics and pharmacodynamics of propofol in morbidly obese patients. *Clin Pharmacokinet*. 2011;50:739–750.
12. Cortínez LI, Anderson BJ, Penna A, et al. Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model. *Br J Anaesth*. 2010;105:448–456.
13. Fisher DM, Shafer SL. Allometry, shallometry! *Anesth Analg*. 2016;122:1234–1238.
14. Shafer SL, Gregg KM. Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer-controlled infusion pump. *J Pharmacokinet Biopharm*. 1992;20:147–169.
15. 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;99:324–333.