In Reply:
The letter by Kempen regarding two published articles\(^1\)\(^-\)\(^2\) raises several important issues. All of these can be reduced to the basic principle that drug administration based on dose is subject to more interindividual variability in response than is drug administration based on targeting plasma concentration or, even more optimally, effect-site concentration. For volatile anesthetics, the latter is easily accomplished because at pseudo-steady-state, the real time measured end-expiratory alveolar concentration reflects both the plasma concentration and the effect-site concentration.\(^3\)

Continuous real-time plasma concentration measurements of intravenously administered hypnotics and opioids would provide the anesthesiologist analogous information to help guide their administration. Unfortunately, such measurements are not practicable. Therefore, investigators have developed numerical solutions to pharmacokinetic models to calculate the infusion schemes required to target a desired plasma or effect-site concentration. In addition, these models can predict the time course of plasma and effect-site drug concentrations during and after drug administration. Although several of the better-known and more commonly used pharmacokinetic models have been shown to be significantly biased and inaccurate in predicting actual measured plasma drug concentrations during and after drug administration by boluses, short infusion, long infusion, or target-controlled infusion,\(^4\) they have clearly proven useful in guiding drug administration given the worldwide administration of more than 13 million target-controlled infusion propofol-based anesthetics.\(^5\)

Therefore, reporting the predicted plasma or effect-site drug concentration and its associated effect, such as a processed electroencephalogram (e.g., bispectral index, entropy, etc.) effect, in clinical studies in which an intravenous anesthetic has been administered is as important and meaningful to many of the readers of ANESTHESIOLOGY as is reporting the end-tidal anesthetic concentration in clinical studies in which a volatile anesthetic has been administered. In fact, simply reporting the infusion rate of an intravenous anesthetic is akin to reporting only the vaporizer dial setting of a volatile anesthetic without reporting the fresh gas flow, the alveolar ventilation, and the many other factors that influence uptake and distribution of volatile anesthetics.

Use of predicted plasma drug concentrations and measured drug effect to create a pharmacokinetic-pharmacodynamic model is another matter. The prediction of plasma drug concentrations is subject not only to the biases and inaccuracies of the commonly used pharmacokinetic models but also the interindividual variability in pharmacokinetics and physiologic changes that may affect the underlying pharmacokinetic model.\(^6\)

Errors in the predicted plasma drug concentrations can lead to substantial errors in the pharmacodynamic model and erroneous conclusions.\(^7\)\(^,\)\(^8\)

Therefore, it is highly desirable that pharmacokinetic-pharmacodynamic studies measure a sufficient number of plasma drug concentrations at times that will allow optimal characterization of pharmacokinetics, including early drug distribution,\(^9\) and subsequent accurate and precise estimation of the pharmacodynamic parameters.\(^10\) Such models could improve the accuracy of effect-site targeted target-controlled infusion\(^8\) more than is possible by reworking flawed existing models.

In conclusion, although reporting the predicted plasma or effect-site concentration at the time of important outcome assessments in clinical studies is better than reporting the dose, studies aimed at investigating the important physiologic covariates or drug-drug interactions that alter pharmacokinetics or pharmacodynamics should include measurements of plasma drug concentrations to prevent erroneously accounting for the variability caused by pharmacokinetic mis specification as pharmacodynamic variability.

Michael J. Avram, Ph.D., Northwestern University, Feinberg School of Medicine, Chicago, Illinois. mja190@northwestern.edu

References

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