other user may repeat this experiment by using the same system and the same target. On the contrary, if one measures the plasma concentration and reports that a measured concentration c results in an effect E, this information has much scientific impact (it defines a concentration-effect relationship), but for the reader who is interested in clinical information, this is of limited value because he does not know how to achieve this concentration. Moreover, Bruhn et al.[3] showed, in a study on propofol pharmacodynamics, that the prediction probability with regard to sedation as measured by the Observer's Assessment of Alertness/Sedation (OAA/S) rating scale was similar for target concentration and measured concentration.

The circumstance that target-controlled infusion is not used in the United States must be considered, and therefore we agree that the infusion rate and not only the target concentration should be reported. However, ANESTHESIOLOGY is an (maybe "the") international journal for anesthesiologists worldwide and has a great and long tradition of scientific papers dealing with target-controlled infusion; we would like to cite an editorial by Egan and Shafer[4] some years ago in this journal: "How ironic, therefore, that America, the country that brought the world surfing, continues to deny physicians access to the fundamental tools to surf the concentration response curves of intravenous anesthetic agents."

Oliver Bandschapp, M.D., Harald Ihmsen, Ph.D., Wolfgang Koppert, M.D., Wilhelm Ruppen, M.D.* *University Hospital Basel, Basel, Switzerland. wruppen@gmail.com

References

1. Bandschapp O, Filitz J, Ihmsen H, Berset A, Urwyler A, Koppert W, Ruppen W: Analgesic and antihyperalgesic properties of propofol in a human pain model. ANESTHESIOLOGY 2010; 113:421–8
2. Sigtermans M, Dahan A, Mooren R, Bauer M, Kest B, Sarton E, Olofsen E: S(+)-ketamine effect on experimental pain and cardiac output: A population pharmacokinetic-pharmacodynamic modeling study in healthy volunteers. ANESTHESIOLOGY 2009; 111:892–903
3. Bruhn J, Bouillon TW, Radulescu L, Hoeft A, Bertaccini E, Shafer SL: Correlation of approximate entropy, bispectral index, and spectral edge frequency 95 (SEF95) with clinical signs of "anesthetic depth" during coadministration of propofol and remifentanil. ANESTHESIOLOGY 2003; 98:621–7
4. Egan TD, Shafer SL: Target-controlled infusions for intravenous anesthetics: Surfing USA not! ANESTHESIOLOGY 2003; 99:1039–41

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In Reply:

We would like to thank Dr. Kempen for his particular interest regarding our article investigating pharmacokinetic-pharmacodynamic modeling of propofol in children.[1] In response to his comments, we would like to precise that, as real data, the average total dose of propofol administered for induction was specified in our article in table 3. However, unfortunately rates of propofol infusion were not detailed *in extenso* in our article, despite that these data were continuously recorded during the study. Indeed, the aim of our study was to investigate pharmacokinetic-pharmacodynamic modeling of propofol and not to validate an extrapolated propofol infusion regimen. This kind of schema using real data, such as milligram per kilogram per minute and derived from a classic pediatric pharmacokinetic model, has been demonstrated to be associated with prolonged delay of recovery.[2] In addition, taking into account that the pediatric population is characterized by a wide physiologic interindividual variability, a single pharmacokinetic approach may lead to inaccurate dosing, exposing patients to the risk of over- or underdosing and their deleterious clinical consequences, such as perioperative hypotension or awareness. In agreement with the comments of Dr. Kempen, real data such as measured propofol concentrations were used in our study to test pharmacokinetic models. We demonstrated that measured propofol concentrations were poorly predicted whatever the pharmacokinetic model tested, even for those that showed the best prediction of the hypnotic effect, as assessed by the bispectral index. The bispectral index is an electroencephalography-based device that assesses the cerebral cortical inhibition attributable to, for instance, GABAergic hypnotic agents. In anesthetized children, bispectral index values were highly correlated with measured and estimated propofol concentrations, despite the discrepancies between both concentrations.[3] The pharmacokinetic and pharmacodynamic approaches seem inseparable whatever the mode of propofol administration. Pharmacokinetic-pharmacodynamic modeling allows automatic adjustment of drug-dosing profiles to achieve a constant pharmacodynamic target, on that may require a nonconstant time course of drug concentration or rate infusion.

Indeed, during continuous propofol administration, the degree of cortical inhibition might be considered the real electroencephalography endpoint or pharmacodynamic target for the clinical scientist, especially in children in whom this clinical feedback may blunt the interindividual variability of requirements and thus improve anesthetic management.

Agnes Rigouzzo, M.D., Frederique Servin, M.D., Ph.D., Isabelle Constant, M.D., Ph.D.* *Hopital d'Enfants Armand Trousseau, Assistance Publique-Hôpitaux de Paris, Université Pierre et Marie Curie, Paris, France. isabelle.constant@trs.aphp.fr

References

1. Rigouzzo A, Servin F, Constant I: Pharmacokinetic-pharmacodynamic modeling of propofol in children. ANESTHESIOLOGY 2010; 113:343–52
2. McFarlan CS, Anderson BJ, Short TG: The use of propofol infusions in paediatric anaesthesia: A practical guide. Paediatr Anaesth 1999; 9:209–16
3. Rigouzzo A, Girault L, Louvet N, Servin F, De-Smet T, Piat V, Seeman R, Murat I, Constant I: The relationship between bispectral index and propofol during target-controlled infu-

sion anesthesia: A comparative study between children and young adults. Anesth Analg 2008; 106:1109–16

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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 misspecification as pharmacodynamic variability.

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

References

1. Bandschapp O, Filitz J, Ihmsen H, Berset A, Urwyler A, Koppert W, Ruppen W: Analgesic and antihyperalgesic properties of propofol in a human pain model. ANESTHESIOLOGY 2010; 113:421–8
2. Rigouzzo A, Servin F, Constant I: Pharmacokinetic-pharmacodynamic modeling of propofol in children. ANESTHESIOLOGY 2010; 113:343–52
3. Gupta DK, Eger EI 2nd: Inhaled anesthesia: The original closed-loop drug administration paradigm. Clin Pharmacol Ther 2008; 84:15–8
4. Masui K, Upton RN, Doufas AG, Coetzee JF, Kazama T, Mortier EP, Struys MM: The performance of compartmental and physiologically based recirculatory pharmacokinetic models for propofol: A comparison using bolus, continuous, and target-controlled infusion data. Anesth Analg 2010; 111:368–79
5. Minto CF, Schnider TW: Contributions of PK/PD modeling to intravenous anesthesia. Clin Pharmacol Ther 2008; 84:27–38
6. Henthorn TK, Krejcie TC, Avram MJ: Early drug distribution: A generally neglected aspect of pharmacokinetics of particular relevance to intravenously administered anesthetic agents. Clin Pharmacol Ther 2008; 84:18–22
7. Fisher DM: Take it to the limit (one more time). ANESTHESIOLOGY 2007; 107:367–8
8. Struys MM, Coppens MJ, De Neve N, Mortier EP, Doufas AG, Van Bocxlaer JF, Shafer SL: Influence of administration rate on propofol plasma-effect site equilibration. ANESTHESIOLOGY 2007; 107:386–96
9. Avram MJ, Krejcie TC: Using front-end kinetics to optimize target-controlled drug infusions. ANESTHESIOLOGY 2003; 99:1078–86
10. Kuipers JA, Boer F, Olofsen E, Bovill JG, Burm AG: Recirculatory pharmacokinetics and pharmacodynamics of rocuronium in patients: The influence of cardiac output. ANESTHESIOLOGY 2001; 94:47–55

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