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Presenting Data *versus* Predictions as Basic Scientific Information: Target-controlled Infusions *versus* Microgram per Kilogram per Minutes

To the Editor:

In the August issue of ANESTHESIOLOGY, I found two articles of particular interest regarding propofol administration.[1,2] I was simply confounded by the fact that target-controlled infusion (TCI) "predicted" concentrations have become the basic jargon for scientific papers. In both articles, I never found any TRUE raw data disclosing the actual dose of drug administered to these patients. In addition, the index of anesthesia in the article by Rigouzzo *et al.*[2] was the bispectral index value (another proprietary, *i.e.*, undisclosed program). In particular, the article by Rigouzzo *et al.*[2] demonstrated that true differences exist between the multiple studied TCI models (and probably all others as well). I was confounded for several reasons: (1) TCI is not currently used in the United States and probably will remain withheld from clinical use by the Food and Drug Administration; (2) there apparently are multiple TCI devices with unknown (to any U.S. clinician) validity and deviations in ability/accuracy; and (3) TCI values are *predictions* and not measured values in any individual study; (4) multiple variables influence *actual* plasma concentrations in any given patient or patient group; and (5) finally, the actual TCI infusion rates change over time. Our journal (ANESTHESIOLOGY) is a publication of the American Society of Anesthesiologists, where practice remains relevant in terms of microgram per kilogram per minute during propofol infusion. It would seem appropriate to require, at a bare minimum, presentation of this pertinent information to the readership (at least alongside TCI values) for several reasons: (1) microgram per kilogram per minute is the American "frame of reference"; (2) microgram per kilogram per minute is REAL and not proposed/extrapolated scientific information; and (3) TCI devices should/must disclose the instantaneous infusion rate during the relevant study periods.

Although I understand the practicability of "indexing anesthetic depth" to some form of electroencephalogram monitor for studies for total intravenous anesthesia anesthetics, I would hope the *Journal* would also require end-tidal gas concentration disclosure for any inhaled agent mentioned in a manuscript. As a clinical scientist, it is essential to *know* what is *actually* being administered to correlate to truly dependent variables such as bispectral index or TCI, especially because no single electroencephalogram monitor or TCI program has been accepted as the standard for scientific studies or even clinical use in the United States. I concluded that I simply came away from both articles without meaningful clinical information—clinical information being why I read this journal. I personally suspect Bandschapp *et al.*[1] found "analgesic properties of propofol" simply because pain is the *conscious* perception of noxious stimulation, and impairment of consciousness resulted in these findings (with probably 60 microgram per kilogram per minute of propofol infusing). Perhaps ANESTHESIOLOGY might lead the world's journals to take on such a basic standard of presenting facts (infusion rates) instead of predictions (TCI/bispectral index) as basic science and in the interests of our readership.

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In Reply:

We have read with great interest and also some concern the letter of Dr. Kempen regarding our manuscript.[1] To begin with the last point, the problem of discriminating analgesia from other effect-like sedation is discussed in our article. This is a typical problem when studying pain and has been discussed in a recent article on ketamine, where the euphoric effect of the drug interacted with its analgesic effect.[2]

With regard to Dr. Kempen's main criticism, he is completely right that dose is basic information that should be given in the article. Therefore, we are glad to have the opportunity to supply this information *ex post*: the total dosage was 4.4 mg/kg in 45 min with a maintenance infusion rate of approximately 90 $\mu g \cdot kg^{-1} \cdot min^{-1}$. However, we do not agree with Dr. Kempen that the predicted/targeted concentrations are not "real." Of course, these concentrations are predicted values that will differ from measured concentrations. However, if one looks at these concentrations as "targets," the view changes a bit: for the user, the target concentration set at the target-controlled infusion system is as "real" as the infusion rate set at a normal infusion pump. If one uses a defined system, that means a commercially available target-controlled infusion system with a defined pharmacokinetic parameter set, the information that a defined concentration was targeted is as definite as the information that a defined infusion rate was chosen. This means that any

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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."

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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 administrated 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.

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