## CORRESPONDENCE

alerting us to the high oxygen content in our tank. We contacted the Compressed Gas Association to determine whether such a guideline currently exists in the United States. Although current U.S. guidelines do not require that the body of the tank bear the color of the "predominant" gas, the Compressed Gas Association will forward this suggestion to the medical gases committee for their consideration. Compressed Gas Association publication C-9, "Standard Color Marking of Compressed Gas Containers intended for Medical Use" is scheduled for the standard 5-yr review in 1998.

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# Clarification of Kinetic Terminology

*To the Editor:*—The heavy statistical content and rapidly expanding terminology in studies with pharmacokinetic/dynamic modeling can make the significance of the results difficult to interpret. For instance, Kapila *et al.* report that the concept of context-sensitive half time (CSHTs) has been verified clinically because the measured CSHTs for two opioids are similar to their modeled CSHTs.[1] Yet the similarities between the CSHT's shown in table 3 are merely mathematical artifact of their methods. Their measured CSHT is obtained by fitting a single exponential curve to the plasma disposition data, and measuring the time for a 50% decrease in plasma concentration (the half life) after the 3-h infusion (the context). Their modeled CSHT is derived by fitting a multiexponential curve to the same plasma data, and then calculating the CSHT from the kinetic parameters that describe the curve. The number of terms in an equation needed to describe a data set depends on the accuracy desired, so-called "statistical satisfaction".[2] For some data sets, the "goodness of fit," measured objectively by a measure such as log likelihood, is not dramatically improved by adding more terms to the equation. The similarity between the measured and modeled CSHT in table 3 is merely due to the single exponential equation providing a "satisfactory" approximation to the multiexponential equation, but this has no clinical relevance. A more valid comparison for table 3 would be the one made in the discussion, between the CSHT predicted by the model programmed into the infusion pump and the measured CSHT. This comparison is noteworthy because the utility of these studies to the clinician is the ability of these models to predict drug disposition and recovery without sampling drug levels. Making these comparisons in this study suggests, as have other recent studies,[3,4]

that one can use kinetic sets from the literature to drive an infusion pump and have a "reasonable" expectation of drug disposition.

The authors finish by interpreting the pharmacodynamic offset of the drugs, a term they don't define. By inference, it's the time for the effect to decrease by 50%, as calculated from a single exponential curve fit to the data on recovery of minute ventilation. Confusion occurs when they use this term interchangeably with measured pharmacodynamic CSHT in table 3. This seems inappropriate, because the pharmacodynamic CSHT, by definition, is the CSHT of the relation between the effect site concentration and the effect.[2] This is usually a nonlinear, sigmoidal relation that includes measurement of maximum and minimum effects ($E_{max}$, $E_0$) and cannot be defined by measurements made solely over the linear portion of the curve (40–70% decrease in ventilation), as was the study design in this case.

As we define the language of total intravenous anesthesia, we implore these and other authors laying the foundation to define and use their terms and statistical results with clarity and precision.

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*In Reply:*—We appreciate the suggestions of Overdyk and Roy and agree that the essential point of our manuscript was to validate the context-sensitive half-time (CSHT) predicted by the pharmacokinetics previously programmed into our Computer Assisted Continuous Infusion device. This was done, and the modeled CSHT from our measured data was not significantly different from CSHT calculated from historical pharmacokinetic parameters. For alfentanil, the "historical CSHT" was published previously and is reported in the first paragraph of the discussion section as 59.4 min. The measured alfentanil CSHT was reported in table 3 as 51.9 ± 12.3 min (mean ± SD) and represents a validation of the "historical" calculation of CSHT. The same is true for remifentanil. In hindsight, we may have presented confusing nomenclature by using the terms "modeled" and "measured" CSHT (table 3). These terms would probably have been better called "measured CSHT: entire data" and "measured CSHT: terminal data", respectively, to indicate that they both represent measured CSHTs, but that each was based on different parts of the same data set. We used the exponential functions simply because one cannot directly measure the precise time for a 50% decrease in concentration with intermittent (discrete) blood samples. Instead, one has to develop a continuous function, fit to the data, from which the time to a 50% decrease can be interpolated accurately.

As Overdyk and Roy correctly observe, the essential point is that no matter how the measured CSHT was calculated, it should (and does) confirm the previously published *a priori* expectation of CSHT. We appreciate the opportunity to clarify this portion of the article.

As for their concern of the pharmacodynamic CSHT regarding the "usually . . . sigmoidal relationship between effect site concentration and the effect," we simply re-state that we have reasonable assurance that we were measuring ventilation effects over the middle range of the sigmoidal curve, where the change in effect site concentration and effect is nearly linear. Therefore, we do not require a sigmoidal curve to define our change in minute ventilation because we did not seek to measure a 50% change in minute ventilation from maximal effect ($E_{max}$) to no effect ($E_0$), but rather a 50% change in the measured effect over the linear portion of the curve, as exhibited in our study population.

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