Where's the Beef?

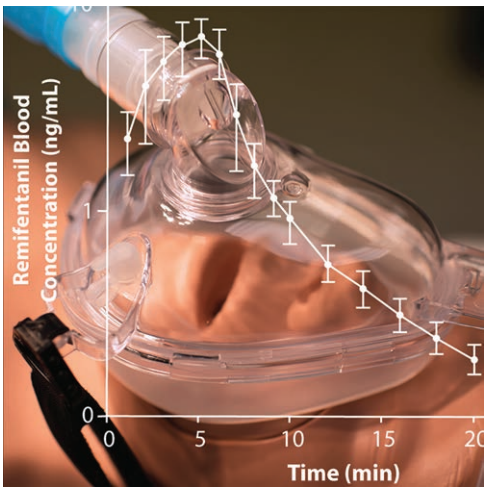
How Much Can We Skimp on Pharmacokinetic–Pharmacodynamic Data?

Thomas K. Henthorn, M.D., Erik Olofsen, Ph.D.

Pharmacokinetic–pharmacodynamic models have been used extensively in clinical pharmacology to move beyond the dose–response relationship to more directly relate drug concentrations to drug effects.[1,2] Pharmacokinetic–pharmacodynamic studies require plasma (or other relevant fluid) drug concentration measurements to characterize the pharmacokinetics as well as drug effect measurements, usually including onset and offset of the effect, to characterize the pharmacodynamics.

Use of pharmacokinetic–pharmacodynamic studies rather than dose–response studies is especially prominent in anesthesiology research, because anesthesia providers require the additional information about the time delay between attainment of plasma drug concentrations and their corresponding drug effects, and this information is not obtainable with a mere dose–response study.[3] To fully capture this time delay (or hysteresis), pharmacokinetic–pharmacodynamic studies of anesthetic drugs require frequent plasma drug concentration measurements and drug effect measurements during both the onset and offset limbs of drug effect. This usually translates to obtaining both drug concentration and drug effect measurements during a drug infusion and for some time after discontinuing drug administration.

To conduct such a pharmacokinetic–pharmacodynamic study is resource-intensive given that it requires the timely collection of multiple blood samples for plasma drug concentration measurements, both of which are time consuming and expensive. In modern operating rooms, time is indeed money, and this maxim makes the conduct of clinical studies in anesthesiology increasingly difficult even though the pharmacologic issues confronting contemporary anesthesia providers have become increasingly daunting.



"We should be very cautious drawing conclusions in the language of pharmacokinetic–pharmacodynamics when there are no drug concentration (pharmacokinetic) data."

A representative example of economized pharmacokinetic-pharmacodynamic studies appears in this issue of Anesthesiology in which the authors report on a clinical pharmacokinetic–pharmacodynamic study from the operating room environment addressing the clinically important question of whether patients with obstructive sleep apnea are more sensitive to the respiratory depressant effects of opioids, in this case remifentanil.[4] If patients with obstructive sleep apnea are more sensitive to the effects of remifentanil, we would expect them to have a leftward shift in their remifentanil concentration *versus* minute ventilation relationship (or curve) compared with controls. This leftward shift would show up as a statistically significant decrease in the concentration at the midpoint of the concentration-effect curve or the concentration producing 50% of the maximum effect (EC_{50}).

The authors infused remifentanil at a constant rate for 10 min and measured minute ventilation *via* the anesthesia monitor at baseline and continuously during the 10 min of the remifentanil infusion, reporting the value at 5-s intervals. They economized on several key aspects of the usual pharmacokinetic–pharmacodynamic study paradigm. First, there were no plasma remifentanil concentration measurements. Instead, a published remifentanil pharmacokinetic model was used in place of an individual's remifentanil pharmacokinetics. Second, the clinical monitor reported a rolling 1-min average of minute ventilation rather than

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snapshots in time or discrete time averages. Third, only the onset of the drug effect was measured because of the time constraints imposed by the operating room; the time course of the offset of effect was not evaluated. Fourth, although end tidal pCO_2 measurements were obtained, hypothetical pCO_2 values and their effect on minute ventilation were simulated, based on an indirect model of pCO_2 and its effect on minute ventilation.[5]

Close examination of the raw data presented by Doufas *et al.*[4] indicates that their primary conclusion—that there was no significant difference between patients with and without obstructive sleep apnea in their respective sensitivity to the onset of ventilatory depressant effects of a 10-min remifentanil infusion—is correct. However, it is worth examining in detail the effects of some of the pharmacokinetic–pharmacodynamic study design restrictions[6,7] because the pressures to compromise on ideal study design are not likely to dissipate as further, increasingly difficult therapeutic dilemmas arise.

A pharmacokinetic–pharmacodynamic study has time and dose as independent variables and drug concentration and effect as dependent variables. If a study provides no drug concentration measurements, then drug concentrations are no longer a dependent variable and, instead, become an intervening variable, which is a hypothetical, unmeasured variable used to explain causal links between other variables, in this case between dose, time, and effect.[8] Thus, changes in the magnitude and time course (kinetics) of the pharmacodynamic measurements from baseline will infer only the time course of changing drug input or drug concentrations because the latter are unmeasured. Verotta and Sheiner[9] carefully examined this situation, pointing out the difficulties in identifying pharmacokinetic–pharmacodynamic model parameters in such circumstances. They proposed an inverse relationship between model or parameter identification and "the extent of knowledge of the input into the effect site." They proposed a hierarchy in which expense and information share a similar rank order: (1) experiments at steady-state conditions; (2) experiments in which concentrations are measured; and (3) experiments in which only the total input into the system are known. As Doufas *et al.*[4] point out in their discussion, they have performed a type 3 experiment or a dose–response study.

Jacqmin *et al.*[10] considered type 3 pharmacokinetic–pharmacodynamic studies in which plasma drug concentration data are not available, and the principles they described have been used in the anesthesiology literature.[11,12] Jacqmin *et al.* termed this approach kinetic–pharmacodynamic as the "pharma," or drug concentrations, are absent. They relate drug infusion rate (rather than concentration) to a parameter they call EDK_{50}. This is an effective dose or infusion (ED) that produces a half maximal response. The rate constant, K, indicates that there is kinetic variability in addition to the pharmacodynamic variability in the kinetics of drug effect. Thus, EDK_{50} is the product of the EC_{50} and elimination clearance.

$$EC_{50} \cdot Cle = ED_{50} \cdot K = EDK_{50}$$

Although such an approach does not yield familiar terms such as EC_{50}, it does retain the interindividual variability of both the pharmacokinetics and pharmacodynamics, even though their variability cannot be separated because of the inability to identify specific pharmacokinetic-pharmacodynamic model parameters in a type 3 dose–response study.[9]

Second, an issue with performing complex pharmacokinetic–pharmacodynamic experiments in a simple clinical setting is that the effect measurements afforded by clinical monitors may bias the estimates of model parameters. If a clinical monitor of minute ventilation reports a rolling 1-min average, then the values may have serially correlated residual error which, in turn, may affect estimates of interindividual variability.[13,14] Does this affect the conclusion of this study? No; but the extremely low estimate of interindividual variability in EC_{50} reported by Doufas *et al.* (7.9%) appears to be biased to a lower value by this mechanism and, therefore, should not be extrapolated beyond this study.

Third, a key aspect of meaningfully estimating the link between measures of drug input (*e.g.*, drug concentrations) and drug effect (*e.g.*, minute ventilation) in a type 2 experiment is closing the hysteresis loop of the drug concentration *versus* effect relationship. The differing concentration–effect relationships during onset and offset can be modeled, or mathematically reconciled, by k_{e0} in a direct pharmacokinetic-pharmacodynamic model[2] or the combination of k_{in} and k_{out} in an indirect pharmacokinetic–pharmacodynamic model.[15] Having concentration–effect data for both the onset and offset limbs of the hysteresis loop improves the confidence in the estimates of k_{e0}, k_{out}, EC_{50}, and E_{max}. Remember that EC_{50} is the parameter estimate central to hypotheses that test drug sensitivity differences between groups in a type 2 experiment.[4]

There are two modeling approaches to linking pharmacokinetics to pharmacodynamics. The method used most frequently in the anesthesiology literature is the direct approach in which a k_{e0} is a rate constant into and out of a hypothetical effect site, which closes the concentration–effect hysteresis loop, thus creating a hypothetical effect site concentration *versus* time curve.[1,2] The second approach is indirect pharmacokinetic–pharmacodynamic modeling, in which the observation of an effect (*e.g.*, pCO_2) is determined by the rate constants k_{in} for effect production (*e.g.*, CO_2) and k_{out} for effect elimination, respectively.[15] Both or either k_{in} and k_{out} can be affected by plasma drug concentrations. With an indirect model adjustment of k_{in} or k_{out} is sufficient to close the hysteresis loop, making a k_{e0} and a theoretical effect site concentration redundant. To invoke remifentanil plasma and

effect-site concentrations Doufas *et al.*[4] used the direct pharmacokinetic–pharmacodynamic model of Minto *et al.*,[16] and to model the effect of pCO_2 on minute ventilation they used the indirect pharmacokinetic–pharmacodynamic model of Bouillon *et al.*[5] It is not clear what the effect on parameter estimation might be by combining direct and indirect modeling approaches.

It is possible to assess various modeling techniques by fitting simulated data to various models. To examine the issues introduced by scaled-down pharmacokinetic–pharmacodynamic study designs discussed earlier, existing population pharmacokinetic–pharmacodynamic models can be used to simulate remifentanil concentrations and remifentanil effects on minute ventilation to answer specific modeling questions.[17,18] We, therefore, generated data for 250 virtual patients, receiving a 10-min infusion of remifentanil, *via* Monte Carlo simulation with NONMEM 7.4.3 (Icon, USA) with random values generated using the pharmacokinetic–pharmacodynamic models of Doufas *et al.*,[4] Minto *et al.*,[16] and Bouillon *et al.*[19] The data for these 250 individuals were then fit to the following pharmacokinetic-pharmacodynamic models with (1) a fixed pharmacokinetic model (*i.e.*, as Doufas *et al.*[4] did), (2) an actual pharmacokinetic model (*i.e.*, using each individual's pharmacokinetic model), or (3) no pharmacokinetic model (*i.e.*, using a kinetic–pharmacodynamic model). As expected model selection criteria, using the −2 log likelihood objective function, showed that using a fixed literature-derived pharmacokinetic model is inferior and that there is a preference for the use of individual pharmacokinetic parameters based on actual, measured remifentanil concentrations. We found that the contribution of the interindividual pharmacokinetic variability to the estimate of the interindividual variability of the estimate of EC_{50} had about the same order of magnitude as Doufas *et al.*[4] reported.

The simulations also showed that there might be a preference for the simpler kinetic–pharmacodynamic model, as it was able to fit the data equally well. In the absence of plasma concentration data, as shown by Romberg *et al.*,[12] a kinetic–pharmacodynamic model may capture the time course of effect measurements, although it cannot separate potential differences in pharmacokinetics from differences in pharmacodynamics. An interesting observation made by Doufas *et al.*[4] was the lack of an inverse relationship between remifentanil effect site concentrations at the end of a 10-min infusion and minute ventilation (*i.e.*, one would expect higher concentrations to be associated with lower minute ventilation; fig. 5a[4]). Our simulations verified the findings of Doufas *et al.* of a loss of correlation between the effect site remifentanil concentration at the end of the 10-min infusion when a fixed pharmacokinetic model is used. However, we found a clear relationship of decreasing minute ventilation with increasing remifentanil concentrations when simulated using each individual's pharmacokinetic parameters, and with the variabilities set to those reported by Doufas *et al.*, but not when set to those of Bouillon *et al.*[5] Nonlinear mixed effects models, using NONMEM or similar software, have difficulty estimating data variability when data are correlated with each other.[13] Steps that account for serially correlated data may be required when devices such as clinical monitors that display rolling averages are used.[14] How rolling average (*i.e.*, correlated) data interplays with non–steady-state clinical studies and with fixed *versus* known pharmacokinetics deserves further study.

Near the dawn of pharmacokinetic–pharmacodynamic modeling, Verotta and Sheiner[9] outlined the difficulties of describing the relationship between drug concentration and effect as investigators deviate from optimal study design. We are now entering an age in which there are libraries of population pharmacokinetic and pharmacokinetic–pharmacodynamic results, coupled with decreasing research funding and increasing clinical production pressures. The desire to marry literature-derived pharmacokinetics as an intervening variable with ordinary clinical data as dependent variables to address therapeutic dilemmas is understandable. But do we know enough about such reduced techniques to analyze these problems in the language of traditional pharmacology, using rate constants, E_{max}s, Hill coefficients, effect site concentrations, and EC_{50}s? Might deep "machine learning" or AI be more robust?[20] Our opinion, based on the above analysis, is that we should be very cautious drawing conclusions in the language of pharmacokinetic–pharmacodynamics when there are no drug concentration (pharmacokinetic) data and when there is non–steady-state effect data and either the onset of effect or offset of effect is missing.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Henthorn: thomas.henthorn@ucdenver.edu

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