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Propofol in Pediatrics

Lessons in Pharmacokinetic Modeling

Propofol recently was approved for use in children 3 yr of age and older. One study sponsored by its manufacturer, Zeneca, and performed by Kataria *et al.*[1] reports the pharmacokinetics of propofol in children aged 3–11 yr. There are several important findings in this study, some related to general issues of pharmacokinetic modeling, others specific to the administration of propofol to children. As in other pharmacokinetic studies, the goal of Kataria *et al.* is to determine the "typical" values for the pharmacokinetic parameters, *i.e.,* those values that best describe the overall population. However, a reader who expects a traditional pharmacokinetic study will be surprised, and possibly frustrated, by the manuscript presented by Kataria *et al.:* The study bears little resemblance to many of the pharmacokinetic studies published previously in ANESTHESIOLOGY.

A major focus of Kataria *et al.* is to compare three approaches to determining typical values for the pharmacokinetics of propofol in children, a traditional approach in which data from individuals are analyzed separately, and two "population" approaches, in which data from all individuals are analyzed simultaneously. In the traditional approach, pharmacokinetic parameters are determined in each of several individuals and then averaged (Kataria *et al.,* recognizing that their values were not distributed normally, appropriately averaged the logarithms of their parameters). Although this "two-stage" approach has been popular in studies of the pharmacokinetics of many anesthetic drugs, its utility may be limited. For example, the averaged results may be influenced by "wild" values (Kataria *et al.*'s description of outliers), particularly when a small number of samples are obtained from some subjects. Kataria *et al.* obtained as few as five (and as many as 18) samples in their subjects, a reflection of ethical limitations on the amount of blood that may be obtained from children. When few samples are obtained from an individual—a technique known as "sparse sampling"—pharmacokinetic parameters estimated for that individual using compartmental or noncompartmental techniques may be inaccurate. For example, if few samples are obtained, an estimate of each half-life depends on the accuracy of the even fewer plasma samples obtained during that phase. Recognizing that all measurements contain error (usually defined by the coefficient of variation of the assay), having more samples during each phase allows for better definition of the half-life associated with that phase. In contrast, newer population approaches described below provide reasonable estimates of pharmacokinetic parameters, even when only small numbers of samples are obtained from each individual.[2] As a result, subjects previously excluded from pharmacokinetic analyses for practical or ethical reasons reasonably might be studied using sparse-sampling regimens when pharmacokinetic parameters are determined using population approaches.

Recognition that the two-stage approach was limited led to the development of several techniques by which the pharmacokinetics of drugs could best be described in a population.[3] Two approaches emerged. With the "naive pooled-data" approach (referred to by Kataria *et al.* and hereafter as the "pooled-data" approach), all the data are analyzed simultaneously, not accounting for random variation between individuals but allowing for differences in "fixed effects" such as dosing regimen, age, or creatinine clearance. The second technique, known as "mixed-effects" modeling, allows not only for these fixed effects but also for random variation between individuals. The latter approach can be implemented using various software, the most popular of which is NONMEM* (nonlinear mixed effects model).

Kataria *et al.* compare the pooled-data and mixed-effects approaches and conclude that the pooled-data approach is best because of its mathematical and computational simplicity and its adequacy, at least for certain data sets. Does their "success" with the pooled-data approach imply that this method is preferred to the mixed-effects modeling approach? Probably not. Kataria *et al.* obtain parameter estimates for each of the pooled-data and the mixed-effects approaches by

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* Beal SL, Sheiner LB: NONMEM Users Guides. San Francisco, NONMEM Project Group, UCSF, 1989.

minimizing an "objective function," a complicated mathematical function of the differences (known as residual differences or residuals) between their measured propofol concentrations and the propofol plasma concentrations predicted by the "typical" pharmacokinetic parameters. Then they evaluate the "goodness of fit" of these parameter estimates by comparing the values for a different mathematical function, which I term their "predictive function." This approach seems illogical. As an analogy, if automotive engineers "optimized" the performance of an automobile for either speed or maneuverability (analogous to the objective functions minimized by the two approaches), would it be appropriate to judge the vehicle based on its appearance (analogous to the predictive function)? If Kataria *et al.*'s goal is to minimize the value of their predictive function, they should have minimized their predictive function rather than the two objective functions. Perhaps their predictive function is more similar to the objective function of the pooled-data approach than to that of the mixed-effects approach, thereby assuring that the pooled-data approach performs better (or returning to the analogy, perhaps in their case appearance of the vehicle relates more to its maneuverability than to its speed). It also is unknown whether Kataria *et al.*'s predictive function is "reasonable": The objective function used with mixed-effects modeling is designed to properly weight data from different individuals, accounting for interindividual differences in covariates and random unexplained interindividual differences (in contrast with random intraindividual differences), factors deemed important in describing and analyzing pharmacokinetic data from populations. In contrast, the predictive function used by Kataria *et al.* has not been demonstrated to account for these factors adequately. Finally, parameter estimates typically are validated using a new set of plasma concentration data rather than the same data used to obtain the estimates; Kataria *et al.* could have partitioned their data set, using one portion to obtain the parameter estimates and the remainder to test these estimates. Despite these potential problems in Kataria *et al.*'s approach, values for the predictive functions from the pooled-data and the mixed-effects approaches differ little. Therefore, it is questionable whether either approach performs better with their particular data and using their predictive function.

The contrast between the pooled-data and the mixed-effects approaches is more evident regarding the analysis of "unbalanced" data sets. For example, a sampling regimen might be influenced by the pharmacokinetics of the drug itself: An investigator might collect two samples to determine the pharmacokinetics of an opioid, the first 1–5 min after drug administration, the second at the time at which each subject begins spontaneous ventilation. Allowing for the improbable circumstance that patients differed in their pharmacokinetics but all began to breathe at the same plasma concentration, a pooled-data analysis for this study (fig. 1) might suggest a two-compartment model with an infinite terminal half-life, whereas a different sampling regimen might yield markedly different conclusions. A second example of an unbalanced design might occur if an investigator administered a one-compartment drug and obtained early samples in one group of subjects and late samples in another. In certain instances, a pooled-data approach would suggest a two-compart-

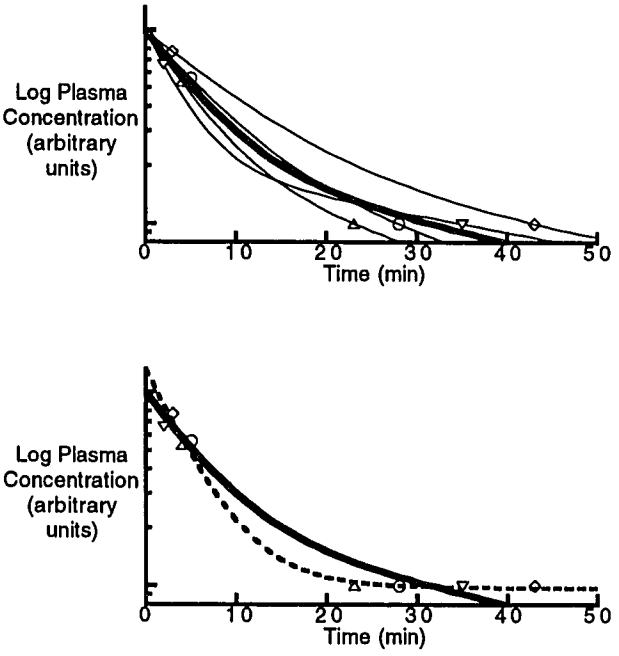

Fig. 1. Data are shown from a hypothetical pharmacokinetic experiment in which two plasma samples are obtained from each subject, the first 1–5 min after drug administration, the second at the time at which each subject begins to breathe. Allow for the improbable circumstance that all subjects begin to breathe at the same plasma concentration. (*Top*) The four thin lines represent the "actual" plasma concentration *versus* time curves for individual subjects, and the symbols overlying these lines represent values sampled from these subjects. The thick solid line represents a possible "fit" obtained using mixed-effects modeling; note that it "typifies" the population. (*Bottom*) The thick dashed line represents a possible "fit" to the data using the pooled-data approach; note that it does not "typify" the population.

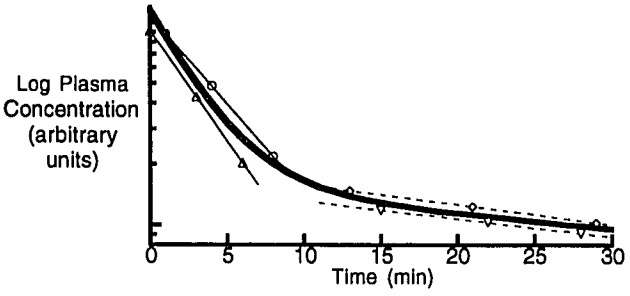

Fig. 2. Data are shown from a hypothetical pharmacokinetic experiment for a drug that displays a monoexponential decay (*i.e.*, a one-compartment model fits the data well). Men differ from women by having a longer halflife and a larger volume of distribution. Lacking that information and assuming that men do not differ from women, the investigator samples early from women and later from men. The four thin lines represent the "actual" plasma concentration *versus* time curves for individual subjects, and the symbols overlying these lines represent values sampled from these subjects; solid lines represent women, and dashed lines, men. The thick line represents a possible "fit" to the data using the pooled-data approach, incorrectly suggesting a two-compartment model. Both mixed-effects modeling and the two-stage approach would suggest a one-compartment model and would recognize differences between men and women.

ment model (fig. 2), *i.e.*, with a faulty study design, the pooled-data approach might suggest an incorrect structural pharmacokinetic model. Kataria *et al.* warn the reader that such problems might occur, acknowledging that the pooled-data approach is only appropriate if the data being analyzed represent a random sample from the underlying plasma concentration *versus* time curves. Yet, investigators rarely know this when the data are collected or analyzed, particularly if sampling regimens differ between individuals (as in the Kataria *et al.* study). In contrast, mixed-effects modeling should deal appropriately with these problems of unbalanced data sets.

Another limitation of the pooled-data approach is that, although it estimates the "typical" pharmacokinetic parameters, it does not describe the variation of these pharmacokinetic parameters within the population. Kataria *et al.*'s results suggest that random interindividual variability is an important factor in their data: Using the mixed-effects approach, their value for the objective function (214) is markedly less (*i.e.*, better) than that obtained with the pooled-data method (380; see their table 3). If knowledge of this variability is important, mixed-effects modeling is preferable and the pooled-data approach has limited utility.

The final issue of interest regards the applicability of the pharmacokinetic parameters reported by Kataria *et al.* Should their terminal half-life of 398 min (the value determined from the pooled-data approach) be considered different from the various values reported in adults (ranging from 184 to 1,411 min in representative studies[4,5])? Should their clearance of 34 $ml \cdot kg^{-1} \cdot min^{-1}$ be considered different from values reported in adults (ranging from 1.3 to 2.2 l/min, or approximately 19–31 $ml \cdot kg^{-1} \cdot min^{-1}$ for a 70-kg adult, in representative studies[4])? In turn, can the clinician interpret these pharmacokinetic parameters to suggest that children require higher or lower infusion rates than adults do to maintain comparable plasma propofol concentrations during anesthesia? Probably not. Shafer and Varvel[6] demonstrated that pharmacokinetic parameters cannot be interpreted in isolation as suggesting differences in infusion rates or differences in rates of recovery. For example, after an infusion of 8 h or shorter, sufentanil (for which the terminal half-life is >9 h) is associated with a more rapid twofold decline in effect site concentrations than is either alfentanil (terminal half-life is <2 h) or fentanyl (with a terminal half-life of 8 h). This apparent discrepancy occurs because all three drugs have sufficiently large distribution volumes that, even during prolonged infusion, tissues do not equilibrate with plasma; as a result, the decline in plasma concentration after an infusion is governed largely by distributional rather than metabolic clearance. Hughes *et al.*[7] introduced the term "context-sensitive half-time" to describe the time it takes plasma concentrations to decline twofold after infusions of different duration. In a similar manner, Kataria *et al.* model both the decline of propofol's plasma concentration after termination of an infusion and the infusion rates necessary to maintain constant plasma propofol concentrations. Only by comparing the results of these simulations (rather than the pharmacokinetic parameters themselves) can one ascertain whether children differ from adults.

A reader might be frustrated attempting to interpret pharmacokinetic parameters reported by Kataria *et al.*, which may limit the utility of the manuscripts by Kataria *et al.* and others. Yet, such analyses are important in guiding our administration of intravenous anesthetic drugs, particularly by infusion. In addition, computer-controlled infusion devices programmed with "typical" pharmacokinetic data presently have limited availability. However, as technology improves and software becomes more user-friendly, anesthesiologists someday may administer all intravenous anesthetic drugs and adjuvants using these devices. Data such as

that reported by Kataria *et al.* are essential to the development of such drug regimens.

The manuscript by Kataria *et al.* raises several stimulating issues regarding pharmacokinetic analysis, and I encourage the reader to contemplate these issues.

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