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The Relevance of Pharmacokinetics to Optimal Intravenous Anesthesia

THE DEVELOPMENT OF new intravenous anesthetics with rapid elimination from the body facilitated greater control of anesthesia than was heretofore possible. In order to optimize the use of these new agents, anesthetists became concerned about the relationship between dosing regimens and duration of effect. A well-established way of understanding this relationship is to divide it into two parts: the dose–concentration relationship (pharmacokinetics) and the concentration–effect relationship (pharmacodynamics). While anesthetists quite clearly understand the concentration–effect relationship,[1,2] strategies are required that afford optimal plasma concentration profiles. In this editorial, we shall explain how the work of Maitre *et al.*,[3] published in this issue of ANESTHESIOLOGY, can be used to reach this goal.

In principle it is easy to achieve the desired plasma concentration–time profile of an anesthetic in any particular patient. Knowledge about the underlying pharmacokinetic (PK) model and the individual's PK parameters (volume of distribution, clearance, *etc.*) is required. But how is this knowledge obtained? The model is assumed to be identical for all patients, but the PK parameters are certainly not. Two strategies are available to deal with this. Either one tries to estimate the individual PK parameters or one forgets about them. The former strategy involves the measurement of plasma concentrations in the individual patient and is therefore generally impractical for anesthetic drugs that are only used once per patient over a period that ranges from fractions of an hour to several hours. The latter strategy ignores an individual's PK parameters and tries to dose most of the patients optimally by taking only average PK parameters into account.

These average values are obtained from any group of subjects given the drug who also had plasma levels measured at known time points. Obviously, the larger the group of subjects (and the more patients among them), the more representative the average PK parameters. At this point the advantages of a so-called "population" PK analysis compared with a "conventional" PK analysis become apparent. Conventional PK analysis deals with complete PK profiles (10–20 concentrations) in a small number of subjects (<20), mostly healthy volunteers. Population PK analysis[4] deals with fewer concentrations per subject and considerably more subjects, generally patients. It can cope with fewer concentrations because it analyzes all the data of all subjects at once and, consequently, produces no individual PK parameters (like conventional analysis) but only the average population PK parameters.

But population PK analysis achieves much more than this. It also gives a realistic estimate of the intersubject variability in the PK parameters and of the residual variability that is caused by model misspecifications, assay error, and intrasubject variability. The program that is generally available for this type of analysis is called NONMEM.[5] This program also allows the inclusion of multiple nonlinear regressions to investigate the influence of patient factors (sex, age, weight, cardiac failure, renal impairment, *etc.*) on variability in the PK parameters. This feature of NONMEM, however, may raise more expectations than it can meet. The analysis by Maitre *et al.*[3] is a typical example. Despite the identification of age, weight, and sex as causes of variability, there still remained 48% intersubject variability for clearance, 33% for volume of distribution, and a residual variability of 25%.

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What, then, is the value of this population PK analysis in terms of intravenous anesthesia? We should point out here that average PK parameters obtained from a small group of patients by conventional PK analysis are not useless. In fact, a recent report[6] shows that alfentanil infusion schemes based on such PK parameters led to concentrations that were unbiased compared with the model predictions. However, only a population PK analysis gives a realistic picture of the variability with which anesthetists are faced when using standardized infusion schemes. Knowledge about this variability can be incorporated into the design of an infusion scheme, as is shown in figure 4 of the article by Maitre *et al.*[3] As a result, the anesthetist can be reasonably confident that at least most of the patients receive adequate infusion rates to obtain the desired concentration–time profile.

And what happens to the patients who are not included in the 68% confidence interval? Their infusion rates obviously need adjustment to obtain the desired clinical responses. For such adjustments and, in general, for the application of complicated infusion schemes, computer-driven infusion pumps have proved useful.[6,7] The computer calculates the required sequence of infusion rates for any concentration–time profile according to the PK model and parameters, and transmits the impulses to the infusion pump. If deeper anesthesia is required, one just has to increase the desired target concentration.

But progress in the optimal use of intravenous anesthetics does not end with the development of computer-driven pumps. These pumps are already part of new prototypes of control systems.[8] The aim of this development is to dose intravenously according to the individual patient's needs. The infusion rate is continuously adjusted according to clinical observations (feedback) that are monitored by the system. It is said that "the control system receives automatic feedback and the model parameters are adapted in order to optimize the output." In such a system the dose–effect relationship is directly described by mathematical functions and the split into PK and pharmacodynamics is not necessary. However, there remain difficulties, mainly in sampling meaningful clinical responses. Therefore, at least for the time being, an appreciation of PK and its variability will be required from the specialty of anesthesiology.

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