REPORTS OF SCIENTIFIC MEETINGS

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Association of University Anesthesiologists Satellite Symposium: Pharmacokinetics and Pharmacodynamics. Lake Bluff, Illinois, May 3–5, 1994.

The Association of University Anesthesiologists (AUA) Satellite Symposium on Pharmacokinetics and Pharmacodynamics was held in Lake Bluff, Illinois, on May 3–5, 1994. This scientific session preceded the annual meeting of the AUA. Participants from 36 institutions had the opportunity to hear presentations covering three broad topics: (1) modeling issues, (2) pharmacokinetic/pharmacodynamic models, and (3) physiologic/pharmacokinetic models. In addition, many scientific posters were on display throughout the meeting and discussed during poster sessions.

Arthur J. Atkinson, Jr., M.D. (Northwestern University), began the meeting with an overview of pharmacokinetics and pharmacodynamics with emphasis on the physiologic interpretation of pharmacokinetic and combined pharmacokinetic/pharmacodynamic models. He summarized the historic development of the anatomic/physiologic interpretation of compartmental pharmacokinetic models, with heterogeneity of the interstitial fluid space due to transcapillary exchange being the rate-limiting step in drug distribution from the intravascular space into the interstitial and the intracellular fluid spaces. With this approach, the central compartment represents the intravascular space and the interstitial fluid of very rapidly equilibrating tissue. The rapidly equilibrating compartment represents predominately the splanchnic tissue with sinusoids and fenestrated capillaries offering low resistance to transcapillary exchange, and the slowly equilibrating compartment represents tissue with continuous capillaries. Using the approach developed independently by Segre and by Sheiner of linking the pharmacodynamic profile of a drug to its concentration profile *via* an effect compartment, or biophase, a combined pharmacokinetic/pharmacodynamic model was created that characterized this relationship and quantified any hysteresis between the plasma drug concentration and the drug effect. This physiologic interpretation of pharmacokinetic models leads to the creation of pharmacokinetic/pharmacodynamic models that correlate well with clinical physiologic measures.

Modeling Issues. The first session, moderated by Davide Verotta, Ph.D. (University of California, San Francisco), presented statistics and methods important to the development of pharmacokinetic and pharmacokinetic/pharmacodynamic models. Dennis M. Fisher, M.D. (University of California, San Francisco), provided a summary of population pharmacokinetics and the nonlinear mixed-effects model (NONMEM) program, which many use to analyze population pharmacokinetic data.

There are three general categories of population pharmacokinetics: two-stage, naive pooled data (NPD), and mixed-effects models. The two-stage approach essentially is an average of the pharmacokinetic model parameters of the different subjects. Although this method yields a population average and a standard deviation, there is no way to predict how clinical variables (*e.g.,* weight and body surface area) might explain interindividual variations in pharmacokinetics. The NPD method fits a model through all the data of all subjects without taking into account which data came from which subject. This so-called "one giant rat" model is a good predictor of the observed data but provides no estimate of the interindividual variability.

The mixed-effects approach (NONMEM) also fits a single pharmacokinetic model to all the data but at the same time tracks each subject's data. In addition to estimating the mean population pharmacokinetic model, it characterizes interindividual variance and assesses covariance among the pharmacokinetic model parameters and, for example, a patient's specific clinical characteristics. The most notable additional advantage of mixed-effects modeling is that it is possible to use sparse data sets obtained with different sampling schedules for each subject. Thus, NONMEM can help answer questions such as whether weight affects the pharmacokinetics of rocuronium in a pediatric population, from which it is only possible to obtain a few blood samples per subject.

Steven L. Shafer, M.D. (Stanford University), discussed the differences between the NPD model and NONMEM based on the application of the derived pharmacokinetic model and the amount of data available. The NPD approach is optimal when the goal is to have the pharmacokinetic model that best characterizes the data from a population sample, such as for use with a programmable infusion pump. The NPD model always describes the observed data and is computationally relatively simple. However, because the NPD method describes observed data, it is only as good as the data set: Nonrandomly censored data, very sparse data, and errors in the drug assay result in less accurate predictions. The inability of the NPD method to describe inter- and intra-individual variances also limits its application in stochastic control applications and in describing the correlation between pharmacokinetic parameters and physiologic covariates.

The NONMEM approach is optimal when the goal is to describe a correlation between physiologic parameters and pharmacokinetic parameters. The NONMEM model describes the "truth" and designates the deviation of an individual from the "truth" as being due to inter- or intra-individual variance. Although computationally more complex than the NPD method, NONMEM can deal with sparse data sets and nonrandomly censored data. Shafer demonstrated that, because NONMEM is concerned with determining both a pharmacokinetic model and a variance model, in certain situations, it may sacrifice accuracy in describing well the concentration *versus* time data for a more accurate model of inter- and intra-individual variance. Thus, pharmacokinetic models from analyses using NONMEM may not be ideal for the design of dosing regimens.

One important area of analysis in modeling is the identifiability problem, whether a defined mathematical model can be characterized by errorless data obtained by the observations made during an experiment. John A. Jacquez, M.D. (University of Michigan, Ann Arbor), outlined the identifiability problem. One of the remarkable things about the identifiability problem is that it is possible to determine whether a given experiment and a given model can be used to calculate the system parameters of interest before the experiment is performed. One can determine whether an experiment merits the use of valuable resources or is worth further refinement. It also helps in distinguishing between competing mathematical models of the same system. Thus, the mathematics relating to the identifiability problem can be used to distinguish between competing models and design optimal sampling schedules.

Pharmacokinetic/Pharmacodynamic Models. The second session, moderated by Steven L. Shafer, M.D. (Stanford University), and Thomas K. Henthorn, M.D. (Northwestern University), featured the development and application of combined pharmacokinetic/pharmacodynamic models. Meindert Danhof, Ph.D. (University of Leiden), described various methods of modeling pharmacokinetic/pharmacodynamic data.

One purpose of pharmacokinetic/pharmacodynamic models is to predict the time course of drug action during both health and disease. Various mathematical models have been derived to describe the relationship between drug concentration at the site of action and observed effect, the most popular of which is the Sigmoid Emax model (the Hill Equation), a nonlinear model that plateaus at maximum drug effect. When studied at steady-state, however, these models cannot describe the difference in phase between plasma concentration and observed effect. This phase difference (hysteresis) may be due to a delay in onset of drug action at a mechanistic level, a delay in equilibration between the plasma and the site of drug action and the plasma, or a combination of the above. In either case, this hysteresis can be treated as being due to a delay in drug equilibration using the method derived independently by Segre and by Sheiner that links the effect-site drug concentration with the plasma concentration.

There generally are two approaches to this linked pharmacokinetic/pharmacodynamic model—a parametric method and a semiparametric method. The parametric approach assumes a mathematical form for both the pharmacokinetic model (*e.g.*, a sum of exponentials) and the pharmacodynamic model (*e.g.*, Sigmoid Emax) and uses the first-order rate constant linking the effect site to the central compartment to account for the observed hysteresis and the delay in onset of drug activity. The semiparametric approach does not assume a mathematical form for either the pharmacokinetic model or the pharmacodynamic model but does assume a first-order link between the plasma and the effect site. Thus, the semiparametric method makes the least number assumptions about the system and may give some insight that might be lost by assuming a standard model *a priori.*

In some instances, the plasma concentration-effect hysteresis may not be due to a delay in plasma drug concentrations at the effect site: if there are interactions with other drugs, if tolerance develops to a drug's action, if the system is nonstationary, or if the marker of drug effect is indirectly affected by the drug. In these cases, an indirect model of drug effect is used to create a pharmacokinetic/pharmacodynamic model. An indirect model characterizes the drug effect by assuming that the measured drug effect is proportional to the concentration of an endogenous substance whose synthesis, degradation, and/or distribution is affected by the drug and other homeostatic mechanisms. Most drugs in anesthesia are modeled using direct markers of drug effect and, in the experimental situation, are assumed not to display tolerance and nonstationarity. The majority of the pharmacokinetic/pharmacodynamic models in the literature are of the direct type.

One obvious application of pharmacokinetic/pharmacodynamic models is the development of new drugs and their approval by the Food and Drug Administration (FDA). Curtis Wright, M.D. (FDA), described pharmacokinetic/pharmacodynamic modeling as a tool that, "like a lantern on a dark night, is valuable for the illumination it provides." Pharmacokinetic/pharmacodynamic modeling has four main applications in the Investigational New Drug approval process: (1) It can evaluate and quantify the data from doses producing an adverse response. (2) When actual pharmacokinetic/pharmacodynamic data is lacking, simulation of pharmacokinetic/pharmacodynamic models may predict the doses producing an adverse response and suggest pathophysiology. (3) Plasma concentrations from the time of an adverse effect can help determine whether an adverse effect was due to the drug. (4) Models can be used to combine data from different trials to explore the effects of age, gender, race, and other characteristics that may emerge only from large numbers of data. Giving several examples of how pharmacokinetic/pharmacodynamic models helped or might have helped the FDA approval process, Wright stressed that, whereas the most complicated model, with all its "bells and whistles," may make sense to an expert in the field, drug approval committees are manned by "consumers" of pharmacokinetic/pharmacodynamic models whose interest is geared toward the bottom line. He emphasized that the FDA audience is diverse, and that, if proposals were pitched at many levels, it would save all concerned a lot of time and frustration.

James Jacobs, Ph.D. (Duke University), proposed ten ways in which pharmacokinetic/pharmacodynamic models might be applied: (1) teaching, (2) plasma concentration monitoring, (3) regimen design, (4) predictions of drug response, (5) risk assessment, (6) drug design, (7) hidden quantitative relationships, (8) experimental design analysis, (9) physiologic function, and (10) "what-if" experiments. Although pharmacokinetic/pharmacodynamic models are used to drive infusion pumps, make predictions of the time course of drug response, explain toxicologic phenomena, and quantitate the known effects of drugs, they are not used frequently enough to teach pharmacology to undergraduates, design new drugs according to desired pharmacokinetic/pharmacodynamic profiles, analyze proposed experimental designs, and explore how drugs that alter physiology in turn affect other drug responses.

Many of the pharmacokinetic/pharmacodynamic models used to understand drugs are developed in animals with a surrogate marker as a measure of effect (*e.g.*, electroencephalogram). Two logical questions are whether models derived in animals can be scaled up to be used in humans and whether the electroencephalographic marker of effect actually correlates directly with clinical effect. Jaap Mandema, Ph.D. (Stanford University), discussed studies that attempted to answer these questions along with a third question, whether there is a correlation between the molecular mechanism of action of a drug and its electroencephalographic effect. The answer to all three questions can be conditionally stated as yes. It is possible to scale up animal models to help understand the pharmacokinetic/pharmacodynamic relationship of a drug in humans. Furthermore, many drugs (benzodiazepines and opioids, to name two classes) maintain a clinically correlating order of potency when ranked by maximum electroencephalographic effect and by maximum drug receptor binding affinity. Mandema presented exciting new work in which electroencephalographic patterns generated by rat brain slices correlated directly with receptor and molecular events. These correlations open a wide avenue of clinical possibilities: Animal pharmacokinetic/pharmacodynamic models using easily quantifiable surrogate markers can be used to investigate the possible effects of physiologic perturbations that cannot be ethically or easily carried out in human subjects. Furthermore, the molecular/cellular relationship between a drug and its actions during various physiologic states can be investigated using pharmacokinetic/pharmacodynamic models.

To address the problem of whether the pharmacodynamics of a drug are described better by a direct or an indirect model of drug

action, Davide Verotta, Ph.D. (University of California, San Francisco), described the mathematical development of a generalized conceptual model for pharmacokinetic/pharmacodynamic data. This generic model incorporates both the direct and indirect effect models of action and allows effect data to be described as a combination of both mechanisms. For drugs best described by one method or the other, the model reduces to a pure direct or a pure indirect effect model. Hybrid effect models may be best suited for describing the effects of prolonged administration of drugs that have a direct initial effect and a secondary/delayed indirect effect, including tolerance. Thus, this model may give more accurate insight into the true physiologic action of drugs.

Physiologic/Pharmacokinetic Models. The third session, moderated by Arthur J. Atkinson, Jr., M.D. (Northwestern University), was dedicated to the physiologic interpretation of pharmacokinetic models and the development of physiologic models that describe the concentration profiles of drugs. Sven Björkman, Ph.D. (Malmö and Stanford University), presented a physiologic model that described the arterial and tissue disposition of fentanyl and alfentanil.

Physiologic interpretation of pharmacokinetic models is facilitated if the structure of the model is identified anatomically *via* tissue blood flow and tissue drug concentration measurements. Because it is difficult to independently manipulate one type of tissue within a whole animal, it is necessary to construct a hybrid model of each tissue and relate it to the arterial drug concentration. A hybrid physiologic model with a parallel architecture similar to the anatomy of the cardiovascular system can be constructed by sampling various tissues and the corresponding local arterial inflow. Each tissue can be represented as a superficial tissue compartment with a local blood compartment in contact with systemic arterial blood. Occasionally, the addition of a deep parenchymal compartment is required to explain the observed tissue concentration profiles. In the hybrid model for fentanyl and alfentanil described by Björkman *et al.*, the calculated extraction ratio was similar to the extraction ratio in the literature for all organ beds except the heart and brain. In the heart, which has a high extraction ratio, it is possible that the nonstationarity due to active control of coronary blood flow affects the extraction ratio of injectable anesthetics. The brain was found to have an extraction ratio for injectable anesthetics that varied with time. The development of hybrid physiologic models has clinical applications in determining the impact of physiologic parameters on arterial and brain tissue concentrations. These models may help predict changes in effect that result from physiologic perturbations.

The lung is in a unique position as a tissue compartment in that it is exposed to 100% of the cardiac output. Besides being responsible for gas exchange, the lung is a metabolically active tissue. The system controlling the distribution of blood flow throughout the lung and the exchange of fluid and micro- and macromolecules between the lung's vascular and interstitial compartments is complex. Thomas R. Harris, M.D., Ph.D. (Vanderbilt University), explained the mathematical models of the exchange of molecules in both the normal and abnormal pulmonary capillary beds. Basic chemical engineering theory of mass and momentum balance combined with the use of tracers of known size and characterized physical properties has helped elucidate pulmonary microvasculature transport processes. Experiments in animal models, *in vitro* preparations, and clinical subjects revealed that urea may be useful as a marker in characterizing the lung microcirculation during various physiologic and pathologic perturbations. Future studies with urea not only may give greater insight into the physiology of mass exchange in the pulmonary capillary beds but also may lead to development of potential modes of therapy that may help to prevent lung sequestration of water (pulmonary edema) and endogenous and exogenous substances.

The closing presentation by Michael J. Avram, Ph.D. (Northwestern University), was an overview of circulatory-based pharmacokinetic models. Based on the early work of investigators including Price, Jacquez, Dedrick and Bischoff, and Atkinson, Avram and colleagues developed compartmental models to describe the intravascular mixing of drugs and markers from the moment of injection, thus characterizing the pharmacokinetics during the timeframe of drug action of many of the intravenous drugs used in anesthesia. First developed using Indocyanine Green (ICG), an inert marker of intravascular space, their model is a parallel circuit compartmental model of lumped blood circuits based on the concentration profile obtained from rapidly sampling a single arterial site. The intravascular space model is physiologically interpretable in that it accounts for the recirculation of ICG and describes the distribution of cardiac output between a low-capacitance circuit and a large-capacitance circuit. Models for markers of extracellular fluid space (inulin) and total body water (antipyrine) have been developed by assuming that the intravascular mixing of these markers, administered concomitantly with ICG, are described by the ICG model. By superposition, any differences between the drug profile and the ICG profile are modeled as distribution of drug out of the intravascular space. These compartmental recirculatory pharmacokinetic models can be used to describe alterations in the pharmacokinetics of these markers and various intravenous anesthetics during physiologic perturbations, define the pharmacokinetic basis of interindividual differences in drug response, and reveal the interrelationship between physiology and drug disposition.

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At the opening session, Mark C. Norris, M.D., the 1994 Society for Obstetric Anesthesia and Perinatology (SOAP) meeting host, along with the incoming president, Barbara L. Leighton, M.D., and their Philadelphia cohorts, greeted the attendees with warm words of welcome. After a moving eulogy by Mark A. Rosen, M.D., and Samuel C. Hughes, M.D., in memory of the late Sol Shnider, the scientific program commenced.

The first scientific session was the Gertie Marx Resident Research Competition. Five well prepared and diverse oral presentations set the tone for a meeting of excellence in obstetric anesthesia research.