

DR. MINER: We will now hear some comments from Dr. Stephen Bai and Dr. Jerry Brunton on the subject at hand. Dr. Bai is Professor of Pharmacology at North Carolina State University and received his Ph.D. degree in 1980 from George Washington University.

COMMENTS ON PHARMACOKINETICS
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Unfortunately, pharmacokinetics is often thought as merely a means to describe the physiological events and rates of a chemical entity. It goes beyond this narrow descriptive definition, and is a tool for achieving a variety of multi-disciplinary research and therapeutic goals.

As indicated by Dr. Koritz, the tool of pharmacokinetics must be superimposed on pharmacodynamic data for its optimal utility. Once the potential for therapeutic efficacy of a drug substance is confirmed, the next goal should be the determination of a safe and effective dosing regimen to yield a desired response with a minimum of toxicity or side effects. Will this be a lucky guess or can one apply the quantitative precision afforded by pharmacokinetics in concert with pharmacodynamic observations to hypothesize and test appropriate dosing regimens? It would obviously be more efficient to start with a pharmacokinetically inspired dosing regimen than to arbitrarily choose one and then drift towards such a dosing regimen by trial and error. Judicious application of pharmacokinetics not only speeds up this process but can also possibly avoid side effects that often occur during clinical trials due to inadvertent overdoing. Success in this area has been shown in human medicine with drugs that have narrow therapeutic indices, such as the aminoglycosides, carditonic agents and anti-arrhythmic drugs. (1). Therefore, a primary question is not: whether pharmacokinetics is of value in designing appropriate dosage regimens, since this has been established, but rather when should pharmacokinetic research for a new drug start?

The inclusion of pharmacokinetic considerations at an early stage of drug development, such as during the efficacy trials, will aid in defining potential problems and suggest the means of overcoming or controlling such problems. It is at this stage that pharmacokinetics achieves its greatest potential. When applying pharmacokinetics retrospectively, one will invariably find it necessary to repeat many costly and time-consuming studies in order to correct these problems, which then are not easily corrected since they may have resulted from a multiplicity of factors.

Clinical pharmacokinetic studies in healthy animals provide baseline data regarding drug disposition per se, but as clearly shown by Dr. Riviere large deviations from baseline values, resulting from disease induced changes in the drug's clearance and/or volume of distribution, can often occur. Such deviations can also occur as a function of the individual's physiological state, such as age, and as a result of drug interactions. Obviously, predictions of a suitable dosing regimen for such animals based on baseline values will be incorrect.

Clinicians are faced, therefore, with the dilemma of how can they take into account multiple physiological, pathological,

and pharmacological variables in predicting dosage regimens? If the clinician is only interested in the treatment of an individual, then based on the patient's pharmacokinetics, the dosage regimen can be easily tailored by appropriate changes in the drug dose and/or dosing interval as pointed out by Dr. Koritz. On the other hand, this approach is not economically practical for food animals. Furthermore, an additional factor unique for food animals - drug withdrawal times must be taken into consideration. As indicated by Dr. Riviere, veterinarians approach therapeutics in food animals on a herd/flock or population basis. Thus, the only practical pharmacokinetic approach to predicting dosage regimens and withdrawal times in food animals would be one based on population kinetics.

Two complementary population pharmacokinetic approaches, as described by Dr. Riviere, should be employed. Based on economic considerations, both approaches could and should be applied simultaneously. The first approach, which is the traditional approach to which most pharmacokineticists are familiar with, involves simple designed experiments of, for example, comparing the pharmacokinetics of the drug in a small group of normal animals with that in animals with some condition such as renal disease. A large number of blood samples are obtained per individual in order to accurately characterize the drug's disposition in each animal. Usually, all other variables such as age, sex and diet are intentionally kept the same for both study groups in order to reduce their influences on the drug's disposition. The individual kinetic parameter estimates in each group are combined, and then correlated with the renal status using relatively simple statistical methods. These data are very important because they serve to define the appropriate kinetic model for the drug as well as give initial indications of how, as in this example, renal disease may influence the drug's disposition. However, since the number of study subjects is usually small, these population pharmacokinetic parameter estimates may substantially deviate from the "true" population; consequently, it is inadvisable to extrapolate these data to the general population. To more accurately predict the "true" population kinetic parameters of the drug as well as to assess how "real life" variables may influence the drug's kinetics, the incorporation of the NONMEN population pharmacokinetic approach, described by Dr. Riviere, appears not only to be the most logical but also, in terms of economics, the most practical approach. This approach pools data across individuals and is therefore less dependent on individual parameter estimates. In contrast to the traditional approach, the NONMEN approach utilizes a large number of subjects from which only 2-3 samples per individual are needed to accurately estimate the population kinetic parameters of the drug. Simulations comparing the traditional and NONMEN approaches as estimators of kinetic parameters of drugs, in which the kinetic model was defined, found both approaches to be accurate and precise when the number of samples per individual was large. The accuracy of the NONMEN approach was maintained as the number of samples per

individual decreased, while that for the traditional approach significantly fell (2-4). As would be expected, the precision of the NONMEN approach increased as the number of individuals increased. When the NONMEN approach was applied to actual clinical data, the results were well within the ranges reported in the literature, validating its potential utility (5). Furthermore, as indicated by Dr. Riviere, a large number of variables that relate to the physiological and pathological status of the animals can be inputted into the NONMEN program, thus allowing for the ability to estimate how each of these variables may influence the drug's disposition. The ability of the NONMEN approach to accurately estimate population kinetic parameters from a limited number of samples per individual is an extremely important economic consideration, since a protocol allowing for its implementation could be easily incorporated into the efficacy trials, as suggested by Dr. Riviere.

As Dr. Teske pointed out in his introductory remarks, the application of pharmacokinetics in the development and application of veterinary drugs and feed additives is a new but rapidly expanding phenomena. We should, however, be smart and learn from the past mistakes experienced in human medicine in when and how to most effectively use the tool of pharmacokinetics. The application of pharmacokinetics should be initiated early in the drug developmental stage, and the approach taken to define the kinetic model should be one which gives the maximum amount of reliable information at a minimum of cost.

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