

DR. ARONSON: Our next speaker is Dr. Lloyd Davis. Dr. Davis is a graduate of The Ohio State University, receiving his D.V.M. degree in 1959. Lloyd received his Ph.D. degree in pharmacology in 1963 from the University of Missouri College of Medicine. Currently, he is Professor of Pharmacology and Professor of Veterinary Clinical Pharmacology at the University of Illinois, and it is with pleasure that I introduce Dr. Lloyd Davis.

DR. DAVIS: I'll have no further comments on the proposed safety guidelines! What I would like to do this morning is make comments from the standpoint of an academic clinical pharmacologist and I'd like to base these comments on several fundamental premises.

COMMENTS ON CLINICAL TRIALS

Lloyd E. Davis, DVM, PhD

My comments on the role of clinical trials in the estimation of safe and effective doses of drugs for use in domesticated animals are from the perspective of an academic clinical pharmacologist. My subsequent recommendations will be derived from three fundamental premises: 1) most of the individuals participating in this symposium from the pharmaceutical industry, Bureau of Veterinary Medicine of the FDA, and academe are veterinarians; 2) drugs employed in the treatment of animal patients must be relatively safe and effective for their purported use as mandated by the Congress of the United States; and 3) the need to deal with uncertainty is intrinsic to medical decision-making in general and the determination of optimal drug therapy in particular.

As veterinarians, we have the sworn duty to relieve animal suffering, to conserve our livestock resources, to care for the health of our patients, and to serve the best interests of our clients and that of our fellow man (from the Veterinarian's Oath). Our activities in new drug development, regulatory affairs, and education must be consistent with the ethical foundation of our profession. What we profess is different from that of the other learned professions and the application of our ethical concepts ultimately resides within the context of a clinical event in which the veterinary practitioner in conjunction with a client (in most cases) undertakes the treatment of an animal patient or patients with curative intent. Because of the uncertainties imposed by species and individual differences in response to drugs among animals, variations in disease processes, and the effects of a variety of factors, many of which may be unknown, it is absurd to believe that a single dosage regimen can be universally applicable in terms of absolute safety and efficacy. The final determination of adequate dosage of any potent drug must be made by the attending veterinarian who has made a diagnosis and is in a position to monitor the target animal's response to therapy. The veterinary therapist and the public, on the other hand, must have assurance that the drug to be administered has been proven to be relatively safe and effective for its intended purpose. In order to accomplish these aims, it is necessary that both industry and the regulatory agency maintain their credibility in the eyes of the profession and the public at large and that the veterinarian has sufficient information to make informed decisions regarding his/her therapeutic use of the drug.

An important feature of clinical trials of animal drugs by veterinarians is that of ethical constraints when dealing with target animal species for which a new drug is being developed. Many of our problems in this area devolve from the failure to recognize that these subjects of our investigation

are the same animals that we are duty-bound to care for as veterinarians. Our approaches must be modified in such a way that we respect the fact that the drug is being developed for safe and effective use in the target species rather than that the animal is simply being exploited as a test object to fulfill some regulatory requirement. The ethical implications are entirely different from those of preclinical animal studies required for clearance of a drug for human use. Along this line, I take exception to the use of the term "animal models" when applied to the study of animal diseases within the context of drug testing in target species. The calves discussed elsewhere in this symposium were not models of pasteurellosis, they were calves suffering from the (experimentally-induced) disease. The term "animal model" entered our lexicon by way of veterinarians and other scientists who have sought the NIH research dollar by studying experimentally-induced diseases in animals as potential models for naturally-occurring human diseases. It is a particularly inappropriate term when discussing evaluation of drugs for use in target animal species. I repeat--these subjects for investigation are not models, they are sick animals which deserve adequate veterinary medical attention.

How might we reconcile these considerations with the need to establish relative safety and efficacy of a new drug entity before it is approved for marketing? I believe that we can begin by defining the term "clinical trials." For animal drugs, all studies conducted in the target species of intended use should be included within the definition. Thus, the preliminary studies of acute and chronic toxicity, metabolism, pharmacodynamics, etc., performed in laboratory animals, chemical studies, development of analytical methods, etc., would be termed preclinical studies and would provide information essential to the planning of the clinical investigations. The clinical trials themselves would be conducted in four phases as for human drugs. Phase I would be concerned with defining routes of elimination, pharmacokinetic behavior, dosage range, minimal toxic doses, and other such essential information in healthy animals of the target species. Phase II would utilize this information to design trials for evaluation of safety and efficacy in a limited number of animals with the disease for which a claim is sought or in animals with an experimentally induced disease similar to that seen clinically. Phase III trials would be conducted in an appreciable number of patients in a variety of settings to confirm the generality of the information acquired in Phases I and II. Following approval of the NADA, Phase IV would involve the long-term surveillance of the product during widespread clinical usage in the field. This is the ultimate test of safety and efficacy, as adverse drug reactions which have a low incidence may require years of use to become apparent and to be placed within a useful clinical perspective. An example of this is our recent observations of death, due to acute renal failure, of five cows with endotoxemia from E. coli which were treated with approved doses of

oxytetracycline. This drug has been in continuous use for over 30 years and has been relatively safe. These unfortunate events could not have been anticipated from routine clinical testing. This episode currently is being investigated at the University of Illinois.

Phased clinical trials would permit us to acquire information germane to safety and efficacy considerations without wasteful sacrifice of life and the imposition of needless suffering. It would allow veterinarians participating in the drug approval process to utilize their clinical training and expertise in a manner which would be ethically and esthetically acceptable to the profession and others who are concerned with the welfare of animals.

Veterinary medicine has advanced rapidly over the past 10 or 15 years. We have the scientific knowledge, expertise, and instrumentation available to make accurate diagnoses in animals without having to kill the patient. I am confident that veterinarians can clinically evaluate efficacy and safety of new drugs in a scientifically acceptable manner. Clinical pharmacology is a relatively new specialty of veterinary medicine whose objectives include the provision of a basis for rational drug therapy and the training of veterinarians who are expert in the clinical evaluation of drugs. This discipline is expanding rapidly and is in a highly dynamic state of development. Veterinary clinical pharmacologists can play a major role in the conduct of well controlled clinical trials while, at the same time, influencing our practitioners to use drugs in a more rational manner. A number of institutions have made a commitment to clinical pharmacology. These include Animal Medical Center, University of California, University of Guelph, University of Illinois, North Carolina State University, Ohio State University, Oklahoma State University, University of Pennsylvania, Texas A&M University, and the Virginia-Maryland Regional College of Veterinary Medicine. Trained specialists are beginning to emerge from these programs who, in collaboration with other veterinary clinicians, can provide the manpower for conducting phased clinical trials.

Finally, the results of such clinical trials should go beyond the mere satisfaction of regulatory requirements and provide essential information necessary for the safe and effective use of the drug in the animal patient. The labelling of the product should include information which the veterinarian can use as a basis for making informed decisions relative to its clinical use. I would like to see dosage information expressed as a range which defines the therapeutic window described by Drs. Mercer and Koritz earlier in the symposium. The upper end of the range could approximate the minimal toxic (but nonlethal) dose or in the case of food-producing animals could reflect the limit in terms of drug residues. The label or package insert should also include pharmacokinetic data, information concerning routes of elimination, physicochemical properties of the active drug, contraindications and any other

precautions, and bioavailability. Veterinary students currently are being trained to utilize such information to make clinical decisions but often the values needed for ratiocination are not conveniently available, so by default, the tendency is for them to resort to the following of recipes when they enter practice. The availability of such information derived from the clinical trials would have another salutary effect in that it would facilitate further clinical investigations of the drug entity by eliminating the need for academic scientists to continually "reinvent the wheel." I suspect that a great deal of effort is wasted by clinical investigators in conducting studies to determine relevant parameters which were defined during the course of drug development, but then sequestered in the sponsor's files and never published.

During the past year, I had the privilege of reviewing a tentative description of labelling information which was composed by Dr. Gingerich for a cephalosporin. It incorporated a comprehensive listing of clinically relevant data concerning the drug in the target species. I believe that such package information would allow the practicing veterinarian to utilize his/her training to the fullest extent and, hence, would enhance the objectives of drug safety and efficacy rather than detract from this effort.

In closing, I would like to comment that many of our difficulties concerning the determination of drug dosage for animal drugs is due to the lack of a clear separation between OTC and legend drugs. This results in the formulation of policies which are inimical to the attainment of the objectives of relative safety and efficacy. Inadequate dosage of an antimicrobial drug in a patient that is desperately ill from an infection caused by a potentially susceptible organism constitutes unsafe use of the drug because of lack of efficacy!