

SECTION III

CLINICAL STUDIES: MANAGEMENT AND EVALUATION OF PERFORMANCE

Chairman

Dr. Dwight Mercer
Mississippi State University

Dr. Mercer: Welcome to the last and final session of our program. Today we have a speaker that has been charged with the responsibility of kind of summarizing and consolidating all of the suggestions and ideas. Our speaker is Dr. Art Aronson. Dr. Aronson spent most of his early years in the coal country of Minnesota. He got his degree there and later spent the majority of his career at Cornell University. More recently, in the last seven or eight years, Dr. Aronson has been at North Carolina State University and is involved in a new program down there--and I can sympathize with him in that regard. I think everybody ought to be involved in at least one building of a new program but I would not advise more than one. That is usually enough. So Dr. Aronson is going to talk to us about the role of therapeutic drug monitoring in the design and execution of clinical trials. Dr. Aronson.

ROLE OF THERAPEUTIC DRUG MONITORING IN THE DESIGN AND EXECUTION OF CLINICAL TRIALS

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Therapeutic drug monitoring (TDM) in clinical patients is relatively new in veterinary medicine. In this presentation we shall concentrate on how TDM may be useful in clinical studies rather than discuss specific details of methodologies. Methodologies involved in TDM of human patients are discussed in several recent texts (1, 2, 3, 4). We shall cover three main points in this presentation:

1. First we shall consider a working definition and description of TDM.
2. We suggest a concept for a Cooperative Agreement between CVM/FDA, Industry, and an Academic Consortium for developing protocols and utilizing TDM in clinical trials. This could provide a mechanism for securing adequate numbers of patients for an in-depth clinical study in a reasonable period of time.
3. We suggest adopting a policy for selective condemnation of individual organs and tissues of food animals, rather than the entire carcass, where drug residues are limited to certain individual organs and tissues. If a Cooperative Agreement were in place and established, the collection of appropriate data by TDM for applying a policy of selective condemnation could be readily accomplished. However, on the basis of current information, we still can consider the feasibility of a policy of selective condemnation.

Working Definition and Description of Therapeutic Drug Monitoring

Therapeutic drug monitoring involves measuring drug concentrations and computing kinetic parameters during the course of drug therapy in a clinical patient. Thus we are considering animals that are patients in a Veterinary Hospital (client-owned) and not animals recruited solely for the purposes of the study (owned by the research project).

The goal of TDM is to optimize individual dosage regimens of drugs for individual patients. This is why it is so important to consider dosage ranges for certain classes of drugs, for example, antimicrobial, cardiac and CNS-acting drugs. Pharmacologic (clinical, biological) responses are correlated with serum concentrations (especially concentrations in serum water) rather than body weight for the simple reason that the correlations are much closer. One takes into account, in addition to drug assays, the physiologic and pathophysiologic condition of the patient as established by clinical examination and results obtained, where appropriate, from Clinical

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Chemistry, Immunology, Microbiology, Virology and Parasitology Laboratories. Thus the Clinical Pharmacology Laboratory operates as other clinical laboratories. This approach provides an ideal environment to carry out in-depth clinical, as well as pre-clinical drug evaluations and screening in a highly controlled clinical setting. In this sense we can view a Veterinary Teaching Hospital as a laboratory for studying naturally-occurring disease - providing the best interests of the patient are served. For example, a Clinical Pharmacology Laboratory, together with a Clinical Microbiology Laboratory, cooperatively can provide an integrated infectious disease consultation service. The pathogen is identified, a MIC determined and a specific dosage regimen calculated and verified by serum and/or other body fluid or tissue analysis at specific times. This would provide the opportunity to correlate actual and kinetically predicted drug concentrations and to define those disease conditions in animals where the correlation fails. Additionally, disease conditions can be defined which are characterized by an inadequate response to therapy when the MIC indicates otherwise.

This approach has been applied to a project involving the treatment of clinical cases of septic arthritis in horses at NCSU. We are convinced, on the basis of results obtained so far, that this approach is valid. However, only eight cases suitable for study (i.e., fit the protocol) were presented to us in a one-year period. The problem is self-evident. It is difficult for many clinical trials to get sufficient numbers of patients in a reasonable time period for an in-depth study at a given Veterinary Hospital. How to approach this problem? How can a clinical investigator secure a sufficient number of suitable clinical cases to study so that a project does not drag on for, perhaps years? We certainly do not want to stifle or inhibit an investigator in academia from pursuing individual initiatives. Still, there are some advantages for an organized approach to this problem. This is what we wish to pursue.

Suggestion for a Cooperative Agreement Between CVM/FDA, Industry and an Academic Consortium for Developing Protocols and Utilizing TDM in Clinical Trials

A problem common to many aspects of Veterinary Medicine is a lack of critical mass. Our profession is small in numbers relative to the other medical professions. We certainly could serve ourselves better were we to have a larger critical mass of faculty in our Schools and Colleges of Veterinary Medicine for our academic disciplines; certainly this is true for pharmacology. We also would find larger Teaching Hospitals more conducive to carrying out clinical trials because of larger numbers of patients to study in a given period of time. However, there is not much hope of appreciably increasing our number of faculty or the size of our Veterinary Hospitals in the immediate future. But we do see a solution to this problem if a consortium of institutions with individual faculty dedicated to working together would be formed with input and support from the drug industry and CVM/FDA. Fig. 1 represents a broad sketch of how such an arrangement might function.

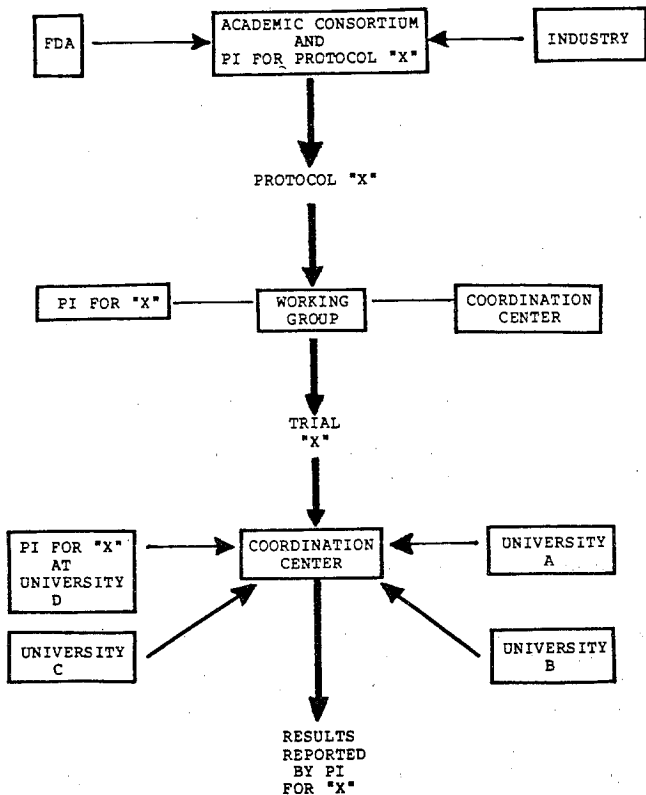


Fig. 1. Suggestion for a Cooperative Agreement Between CVM FDA, Industry and an Academic Consortium for Developing Protocols and Utilizing Therapeutic Drug Monitoring (TDM) in Clinical Trials

The American Academy of Veterinary Pharmacology and Therapeutics long has advocated a spirit of cooperation between academia, industry and the FDA; this proposal is consistent with that spirit.

Academic Consortium refers to a group of Clinical Pharmacology Units involved with TDM at academic institutions (designated A, B, C, D in Fig. 1). It is implicit that each of the institutions comprising the Academic Consortium would have a core of clinicians keenly interested in the application of clinical pharmacology to clinical trials and would have a Clinical Pharmacology Laboratory equipped for TDM that worked closely with the other clinical laboratories.

Note that a PI from a member of the Academic Consortium works together with Industry and CVM/FDA in developing the protocol for a clinical study. This is important for several reasons. A clinical investigator, being intimately involved in carrying out a clinical trial, can make a critical contribution to the practicality of a protocol. From the academic point of view it is imperative that a PI have a positive and meaningful input into the design of his or her scholarly activity. At the same time we in academia must be sensitive to societal needs (in this case represented by FDA and industry), especially when we request support for our efforts. We need scientific input from industry and FDA in conducting clinical trials. Thus, once a protocol has been agreed upon, the PI for Clinical Trial X becomes the leader of the working group within the Academic Consortium for that particular Clinical Trial X. A collaborative effort, between industry and FDA with a PI from academia, in developing protocols provides an additional benefit. It would provide an excellent training opportunity for residents and graduate students interested in clinical pharmacology. The student would gain first-hand experience in appreciating the objectives and responsibilities of industry and the FDA.

A Coordination Center Staff, probably located at one of the participating academic units, would serve to receive and process the data from individual investigators of the Working Group in accordance with the objectives of the protocol. More on the Coordination Center later.

Clinical Trial X thus is conducted at several institutions (represented by A, B, C, D) according to a pre-agreed upon protocol. We point out that Clinical Trials Y, Z, etc., could and should be going on concurrently with PI's from other institutions within the Academic Consortium. Thus a PI on one clinical trial would likely be a CoI with a PI at another institution on a different clinical trial. This is the kind of arrangement which could provide sufficient numbers of patients for completing valid clinical trials within a reasonable period of time.

Function of the Coordination Center. It seems logical for the Coordination Center to be located at one of the institutions comprising the Academic Consortium. The Coordination Center should be equipped with a computer capable of data processing and communicating, for example, via electronic mail with other members of the Academic Consortium, CVM/FDA and Industry. Staffing should include a Data Entry Operator, a Programmer, and a

Statistician. It would function, as already stated, to receive and process the data from individual investigators of the Working Group in accordance with the objectives and design of the protocol. Treatments would be assigned according to the predetermined experimental design by various randomization and stratification techniques. As Clinical Trial X is in progress at A, B, C, D, data are sent to the Coordination Center via electronic mail and are immediately available to members of the working group. A central databank of all cases processed by the Academic Consortium would be maintained which could subsequently be used in the design of future clinical trials.

We emphatically emphasize that the role of the Coordination Center should be a facilitory role and NOT a dictatorial management role. Dictatorial management does not work in an academic setting. Individuals comprising the membership of the Academic Consortium would function as Principal, Co-Principal or Coinvestigators on cooperative projects involving clinical trials. Individual egos would have to be modified where necessary to achieve a cooperative attitude of mutual respect for other individuals in the group. Note that results and publication would be the privilege and the responsibility of the PI of a specific clinical trial.

We certainly are not suggesting that an arrangement of this kind be done in addition to requirements already necessary for drug approval; we would hope that a Cooperative Agreement between CVM/FDA, Industry and an Academic Consortium would be a cost-effective alternative because of the soundness of the science produced.

Suggestion for Adopting a Policy for Selective Condemnation of Individual Organs and Tissues Rather than the Entire Carcass where Drug Residues are Limited to Certain Individual Organs and Tissues.

TDM can play a role in making feasible a concept of selective condemnation of individual organs, rather than the entire carcass, where drug residues are limited to certain individual organs. We are introducing this concept of selective condemnation, relative to drug residues, because of a deep concern regarding the lack of approved drugs in food-producing animals that are effective against life-threatening infections caused by gram-negative organisms (for example, pseudomonas, proteus, klebsiella, and *E. coli*.) The aminoglycoside group of drugs are potentially useful in life-threatening infections due to gram-negative organisms, but their long and persistent residues in the kidney precludes their approval for systemic use in food-producing animals.

As background for this consideration, we feel it appropriate to consider the Veterinarian's Oath (Fig. 2). It is good to remind ourselves periodically of this oath to which all veterinarians have subscribed. We also feel it important that our non-veterinarian colleagues working with us on animal health problems are aware of the Veterinarian's Oath. We invite you to subscribe to the spirit and substance of this Oath.

Veterinarian's Oath

BEING ADMITTED TO THE PROFESSION OF VETERINARY MEDICINE, I SOLEMNLY SWEAR TO USE MY SCIENTIFIC KNOWLEDGE AND SKILLS FOR THE BENEFIT OF SOCIETY THROUGH THE PROTECTION OF ANIMAL HEALTH. THE RELIEF OF ANIMAL SUFFERING, THE CONSERVATION OF LIVESTOCK RESOURCES, THE PROMOTION OF PUBLIC HEALTH, AND THE ADVANCEMENT OF MEDICAL KNOWLEDGE. I WILL PRACTICE MY PROFESSION CONSCIENTIOUSLY, WITH DIGNITY, AND IN KEEPING WITH THE PRINCIPLES OF VETERINARY MEDICAL ETHICS. I ACCEPT AS A LIFELONG OBLIGATION THE CONTINUAL IMPROVEMENT OF MY PROFESSIONAL KNOWLEDGE AND COMPETENCE.

Adopted by the American Veterinary Medical Association House of Delegates, July 1969



Note that we have vowed to use our knowledge and skills to protect animal health and to relieve animal suffering. We interpret this to mean that a responsibility exists to use our skills in healing for the animal patient as well as as to the animal owner. Saving animal life and productivity are consistent with our oath to conserve animal resources. But note that we also have pledged to promote public health. We interpret this to mean that in the process of alleviating suffering and preserving the productivity and life of food-producing animals we must not create a public health problem; in the context of drug use we have a responsibility to ensure that violative drug residues do not occur in edible tissues.

Let us consider the situation of a food-producing animal affected with a life-threatening infection due to a gram-negative organism. Suppose an approved drug, for example, penicillin G, ampicillin, tylosin, oxytetracycline, or a sulfonamide is not effective against this organism. Chloramphenicol cannot be used today. There is a good, at least a reasonable, possibility that an aminoglycoside such as gentamicin or amikacin, may be effective in treating the animal. If so, the veterinarian is presented with a serious dilemma. The use of an aminoglycoside may indeed save the productivity and lives of the patients, but we know that residues will persist in the kidney for a long period of time. To knowingly send an animal to market with drug residues would be a violation of the oath taken to promote public health.

Adoption of a policy of selective condemnation may offer a solution to this dilemma in the case of the aminoglycoside drugs and perhaps other groups of drugs as well. The primary organ involvement in violative tissue residues of the aminoglycosides is the kidney. If a system could be established whereby kidneys alone were condemned, a significantly shorter withdrawal time for other tissues would result.

Selective condemnation of tissues and organs is not a new concept. It is part of the daily responsibility of meat inspectors in packing plants. A research investigator can apply for salvage of parts of the carcass (especially muscle) shown to be free of residue or to contain an acceptable level of drug residue. The only new idea is the application of selective condemnation to the use of drugs in the clinical practice of veterinary medicine.

It would seem that a policy of selective condemnation could be considered at this time now that a valid veterinarian-client-patient relationship has been defined and agreed upon by the AVMA and CVM/FDA. We believe, on the basis of the oath to which we subscribe, that veterinarians will be willing to maintain the records and identify the animals that would be required for such a policy to be adopted.

Summary:

Recent and continuing advances in computer and analytical technology are making it possible to consider innovative ideas involving clinical trials with clinical patients. Computers are making it possible to

accumulate vast stores of data and transmitting this data in an organized way to appropriate individuals. Analytical techniques are being developed (for example, enzyme-linked immunoassay (EIA)) that are reported to be sensitive, cost-effective and simple to perform. We need to adjust our thinking and develop policies that will permit us to take advantage of these technological advances to meet our common objectives.

References

1. Benet, L.Z., N. Massoud and J.G. Gambertoglio. Pharmacokinetic Basis for Drug Treatment. Raven Press, New York, 1984.
2. Gerson, B. Essentials of Therapeutic Drug Monitoring. Igaku-Shoin, New York, 1983.
3. Pribor, H.C., G. Morell and G.H. Scherr. Drug Monitoring and Pharmacokinetic Data. Pathotox Pub. Co., Park Forest South, IL, 1980.
4. Rowland, M. and T.N. Tozer. Clinical Pharmacokinetics: Concepts and Applications. Lea & Febiger, Philadelphia, 1980.