

SECTION II

PHARMACOLOGICAL BASIS OF DOSE DETERMINATION  
OF ANTIMICROBIAL DRUGS

DISCUSSION PERIOD

DR. CARNEVALE: I'd like to commend all the speakers this afternoon for their excellent presentations. We'll now proceed with the questions.

DR. KRATZER: Dr. Powers, you separate statistical reasoning from scientific reasoning in deciding upon dose. Are there some areas of this science which are not based on data?

DR. T. POWERS: Let me back up and see if I can make clear what I'm really saying. My wife pointed out this morning that you can run through data and make "n" large enough to find significant differences which may have no biological meaning. We measured several parameters in horses repeatedly for many days and if we saw some differences, I'd hand it to the clinician and ask what the differences were between one animal and another; most of the time he'd say there was no difference. The statistician says there is a significant difference and yet clinically, the values are within the normal range for horses. This is the type of thing we have to think about. I don't want to throw away your statistical data; however, I'm saying that we (as clinical pharmacologists) must draw from all the facts available, both statistical results and professional expertise. Now, when the data are in opposition to clinical judgment, it bothers me. What I'm saying, Dal, is use your pharmacological, physiological, and pathological data bank to interpret the data along with the statistician; I can't get rid of her and I don't want to since I'm married to her!

DR. KEEBLER: Is it necessary to derive the magnitude of correlation between pharmacokinetics and clinical efficacy for each new drug before using pharmacokinetics to determine dose?

DR. TESKE: First of all, let me say that at this point in time, the Bureau does not have requirements for pharmacokinetic

data so what I'm going to say is not in the context of the law, regulations, or policy. However, as a pharmacologist, I would repeat what has already been said, that pharmacokinetics is not a precise science by any means. Therefore, the better the correlation between particular kinetic parameters and the variable factors that you are trying to characterize -- that is, the tighter the correlation -- the better the information is in terms of making extrapolations and drawing inferences from it. In some cases the correlation may be fairly tight while in other cases it may not be tight at all, and it will be important to be able to differentiate between the two when making inferences. Perhaps someone else on the panel -- Drs. Koritz or Riviere -- would like to comment on that as well.

DR. RIVIERE: Well I'll stick my neck out and I'll say if there's a poor correlation of the response with the kinetics, I think you're also going to have a very difficult time getting to that dosage empirically. I really think that pharmacokinetics is not an answer to all problems, it's just an attempt, as Dr. Powers indicated, to explain some of the variability; to explain some of it across drugs and across species. Specific disease processes with unique pharmacodynamic effects and different bacteria may modulate that end result, but at least pharmacokinetics gives you a starting point that can utilize pre-existing data and thus eliminate a lot of work in that light.

DR. CHATFIELD: For the sake of brevity and accuracy, I'll read my question. I understood you, Dr. Powers, to say that antimicrobial drugs may be considered efficacious even when posttreatment cultures are still positive. I would therefore like to ask a two-part question. What role do pre- and post-treatment culture results play, or more pointedly, how much emphasis do they deserve in dose determination or clinical trials? How much emphasis should we place on pre- and post-treatment in vitro sensitivity test results, particularly when dramatic clinical improvement occurs despite the presence of the suggested pretreatment resistant pathogen?

DR. T. POWERS: Ron, I think you may have extrapolated what I said a little farther than what I intended but that's alright, I'll still approach your question. Any and all of the things we're looking at have to be tempered and taken in context with everything else we know. If you have an ear infection in the dog and you treat it and the dog no longer scratches and digs, and it appears clinically normal but you still get a couple of bugs out of the ear, you're probably not going to be too concerned. On the other hand, if the condition relapses, you have another problem. I don't think any single item should be

taken by itself -- you have to look at the entire situation by doing careful clinical evaluations. We realize we can't look at everything, but we should look at as many things as possible; the clinical results (and you were a clinician a long time before you got a Ph.D. in our Department) are still the final judgment of what's going on with that animal.

DR. HARVEY: Before I ask the questions, I'm just going to remark that Dr. Koritz was a classmate of mine -- 1968 was a wonderful year! Would you please comment on the applications, if any, of utilizing the pharmacokinetic data from say, blood and urine, to predict tissue residue depletion, particularly during the elimination phases? To put it another way, can such data be used reliably to determine safe tissue residue levels assuming you know what the tolerance is, without actually sacrificing the animals?

DR. KORITZ: No. I'd say you at least have to do a biopsy and then you're only going to be looking at specific tissues and not the whole spectrum of tissues in that animal. The problem with blood and urine data is that these are concentration data which can be related back to the amount of drug in the body and the amount of drug in a compartment but cannot tell us the concentration of drug in a tissue. On the other hand, if you finally recover 100% of the dose in the urine, then it's all out of the body and at that point there's none in the tissues so if you had that ideal situation, you would not have to sample tissues.

DR. RIVIERE: One other point on that is, urine and blood concentrations of drug are reflecting -- especially urine concentrations -- pre-excreted drug and a lot of tissue residues are probably covalently bound drug or very tightly bound drug, so you easily can deplete serum and urine concentrations and still have drug present in tissue; this creates a real problem.

DR. T. POWERS: This question also hits Dal Kratzer's question because you mentioned if you recover 100% then you have it all. When you do the experiment, it's not uncommon to recover as much as 125%, is it?

DR. KORITZ: No, but if the mean recovery was 100% with a range of 75-125%, I'd feel the results were reasonable.

DR. T. POWERS: Does that have a biological meaning or a statistical meaning?

DR. KORITZ: That's statistical.

DR. SWENSON: I'd like to ask Dr. Baldwin, why concern yourself with too much drug when we have the safety issues handled and addressed by the types of studies that Dr. Livingston just discussed? Why try to blend efficacy and safety all into the same issue? I think that's where we're deluding ourselves by arriving at inappropriate and probably too low doses based upon studies that have been instigated to try to satisfy the dose response issues.

DR. BALDWIN: I think where this came from historically is that no drug is absolutely safe and you should never use more than you need to because you may end up with residues or molecules or so forth that really have no benefit; why use more than what's necessary because you're sort of kinking the benefit-risk ratio when you do this.

DR. SWENSON: I have trouble with that response based upon the types of drug residue studies that Dr. Livingston says that the drug sponsor must perform to demonstrate safety in food animals as far as humans are concerned.

DR. BALDWIN: Again, can you answer why you should use more drug than necessary to accomplish the intended effect? Why should anyone have to use 10 mg when 5 mg would do it?

DR. SWENSON: I think the problem lies in our inability to detect whether 5 mg or 10 mg is the adequate dose. I think Dr. Jean Powers gave an example this morning that we don't test enough doses in enough animals to find out where that breakpoint is.

DR. BALDWIN: Okay, then we're down to methodology and we're not arguing about the philosophy.

DR. SWENSON: Well, I think we're still missing the point somewhere. If the concern for too much drug is human safety, then why do we emphasize the human safety issue to the extent that we do?

DR. BALDWIN: I'm not sure that it's all human safety; I think it has to do with whether or not you're just using drug unnecessarily in animals. Why do you want to use more drug than is necessary; I keep asking you the question. Now, if we have inadequate test methods and we need to have that kind of a range, I think we accommodate for that. I think if we have a very precise method for determining efficacy, then we're more precise. But if we don't, then we do allow ranges.

DR. SWENSON: Are you thinking about the economic concern of using too much drug?

DR. BALDWIN: Economics has to be part of our concern, along with safety and efficacy of a product.

DR. SWENSON: I take issue with that.

DR. BALDWIN: Well, you can take a stand on it, but we have Commissioners that take stands on it in terms of human drugs and they go after companies on economic fraud. It's a very low order of priority, granted, a very low order of priority. But it's still priority, the obligation of the Act; at least that's what has been interpreted by the commissioners.

DR. SWENSON: I fail to understand that reasoning; we could argue all day so I don't want to push it.

DR. BALDWIN: Well, maybe you need to talk to people like Dr. Hays and Dr. Novitch because they have task forces on this subject.

DR. SWENSON: Thank you.

DR. T. POWERS: Gene, I'd like to comment. Bob has the law that he must work with. There's been a lot of clinical failures because we can't find that minimum effective dose. Thus there's a safety factor that we've got to figure out some way so that the law can permit us to use a dose that will give us blood or tissue levels that are 2, 3, 4 or 5 times what it takes to kill that particular bug we are treating. It may well be there's another bug in there we're trying to get that has an even higher MIC. All of you are familiar with how the drugs are produced and how the package insert dose is determined. However, pick up a textbook, or pick up some of the notes of the pharmacologists in this audience, and you'll find that the dose used clinically is often different from the insert. What they're doing is just what you're saying -- trying to accommodate for what really occurs in the clinical situation.

DR. SWENSON: My main concern is with the antibiotics rather than the types of drugs that have direct response on the target species rather than the parasite. Thank you.

DR. LAUDERDALE: Along the lines of the current questioning, Dr. Livingston, we've heard some compelling evidence and presentations that the clinician has the responsibility to tailor a drug dose to an animal. We know that the USDA is concerned about testing for residues. How do we resolve the potential conflict between use of a labeled dose for a product

and identified residues relative to the human safety being based upon the label dose in view of Dr. Powers' contention that the clinician should be able to use 4 or 5 times greater doses than the package insert dose? How do we resolve this potential conflict?

DR. LIVINGSTON: When you initially regulate the drug, withdrawal periods are based on the label dose. If you use 4 or 5 times the amount that's on that label, residues may remain and you're going to have a violation. At that point it's too late to resolve this problem; that is an error in regulating that drug. I think if you have to go higher, it's your responsibility to come back into the Agency, get a new approval at that higher level, and get revised labeling.

DR. T. POWERS: Did you notice, though, in the discussion, that when we use the package insert label there were all kinds of things that were going to affect the drug withdrawal time? All these things that we talked about today -- you could be using the right package insert label and that drug withdrawal time may well be different; it may be different for that animal because he doesn't metabolize it as rapidly, he may not eliminate it as rapidly, it may get tied up in some infected tissue or some involved tissue and stay longer. I would propose that one of the ways to do it is to start out by doing your withdrawal studies so if you're working with factors of 1000, why not start out working with factors of 5 on dose?

DR. LIVINGSTON: I would just quickly say that if you recommended to the company that somebody use 4 or 5 times the label dose, then you've got a problem. If a veterinarian uses 4 or 5 times the label dose on his own, he's got a problem if anything happens. Well I think you'd have more of a problem if you recommended it.

DR. T. POWERS: I feel that we've almost made that package insert "carved in stone" and I just can't believe that that is true. If that is what has happened, we've got to do something about it.

DR. LIVINGSTON: The Food and Drug Act states that the use of a drug, its labeling and the content of the drug, if not in accordance with the way the drug was approved, is illegal.

DR. BALDWIN: I've got a question; this is for the future and anybody can take a shot at it. How do you propose that we keep package inserts and dosage current on 5, 10, 15, or 25-year old products? I think this is a real question and you know a lot of this discussion today centers around it. Maybe

someone can come up with some ideas about it.

DR. T. POWERS: I think we should retreat to the 1967's when the NASNARC Committee did it for you, and do the similar thing again. It involves a lot of work but it involves scientists digging in the literature and coming up with information that's available and using scientific reasoning and logic to come up with some answers for you.

DR. HARVEY: I have a question for Dr. Riviere. You talked a little about extrapolation of residues and I realize that you have problems with trying to do that, trying to use pharmacokinetic data to set a withdrawal period. What about the situation of two products that are similar to one another? Can you have pretty good assurance that the blood level profiles, if they are similar between the two drugs, would result in similar withdrawal periods also?

DR. RIVIERE: I think if you have evidence that the blood level profiles are similar and the fraction excreted or eliminated by specific organs are similar, in all probability then the tissue residue profiles would be similar, with the basic idea that those blood level profiles would be reflecting a similar pharmacokinetic disposition. That's just a way of guessing. You have to realize that the blood level profiles depend upon the sensitivity of the method. They may not actually be reflecting tissue residues but we're trying to get to the point that, if, at the level of concentrations monitored therapeutically, if those profiles are almost identical then that's an indication that disposition is almost identical.

DR. HARVEY: Breaking down that curve, if the uptake portion of the blood level curves are similar between those two products but the depletion phases differ somewhat, what's more important? I guess that's what I'm asking -- does the whole curve need to be comparable within a certain factor or does a pharmacokineticist put more emphasis on the uptake?

DR. RIVIERE: No, I think it's the depletion curve. The uptake portion is going to be a factor in determining a certain concentration on which elimination and distribution processes are acting, so that you can utilize similar depletion kinds of kinetic phases and then factor in the different absorption profiles. In some cases, though, the absorption phases may become the rate limiting step. It's the relative rates which are important.

DR. TESKE: I just want to say that I'm not sure that the

science of pharmacokinetics is at a point now that we can rely entirely on it but certainly if you show that the pharmacokinetic profiles are very similar, that enables you to target much more precisely on those time frames within which you'll want to demonstrate your withdrawal time. And, as a matter of fact, even if the profiles are different, it will still give you information about what time frames to target for those studies where you actually go into the animal, dose the animal, and slaughter to determine when the residues are, in fact, depleted. The bottom line is that under those conditions, it will take less animals, less assay time, and less data points to define than it would if you had no pharmacokinetic profile to work with at all.

DR. T. POWERS: We've made the assumption that increasing the dose increases the length of withdrawal time and this may not necessarily be correct. Recent work with aminoglycosides in the dog (and of course we talked earlier about the uptake in the proximal convoluted tubule and its entering into the lysosome) demonstrated that the peak and trough levels were very important. If you take the dose that you would give, say, in 2 or 3 divided doses during the day and give it as one dose, then repeat it 24 hours later, then it may be less nephrotoxic. The opinion in this case is that the absorption into the proximal tubules is the rate limiting factor. So if you use a high dose, only so much will go into the tubule and the rest will go out in the urine. So, we can't be accused that just because we're increasing the dose that we're increasing residue levels and increasing withdrawal times in all cases. Do you disagree, Jim?

DR. RIVIERE: No, I agree completely. Another factor is, we've been developing pharmacokinetic models primarily in the therapeutic range of drug concentration. There's very little work done at the concentrations which you're setting as tolerance limits for food safety. I think everyone here will agree that a number of processes in that line which are governing that, are entirely different than what are occurring at higher levels. So kinetics is a possible solution to this but we don't have that data yet. I think we can collect that data in the context of pharmacokinetic models but right now we really have to be cautious in extrapolating from mcg levels to nanogram levels.

DR. MUSER: I admire the wonderful scientific comments we have heard. There's quite an argument going on now. We have heard the suggestion that there may be fraud involved if too high doses are used; we are now trying to figure out if using higher doses is really resulting in longer withdrawal times; let's get back to reality. Let me remind you what we said this

morning. What we are really here for is to try to come up with a better approach for putting useful drugs with appropriate instructions into the hands of the practitioner. I don't think we have many practitioners here; we are getting into an academic discussion. Let's try to come up with some practical solutions and let me propose just a few things for your consideration; we can continue arguing after that.

When we talk about giving 3 or 5 times the recommended dose to an animal, what animals are we talking about? We're not talking about a herd of cattle that will then have terrible residues, we are talking probably about one valuable animal -- maybe not even a food-producing animal, so let's keep the issues straight. Then, even when we talk about giving it to a food-producing animal, we are probably not talking about a large group of animals because if it was a large group of animals, a likely alternative would be to not do anything at all because it would be too expensive for the owner. So the chances for very high doses to be used are probably not as great as we may think after this discussion. But if they are used and if it has to be done in a food-producing animal, we have experienced ourselves that FDA may allow us to keep such animals for 180 days, for 6 months; it's a tremendous amount of time but for a valuable animal, it may be an approach a practitioner could take. If he uses a higher dose level, he just may have to make sure that animal is around for an extended period of time and afterwards it is returned to the herd. This is what I consider a practical solution; I don't think we help a veterinarian a lot if we tell him he has to go to his textbooks and try to find out how a drug is excreted and how it does this and that. I would suggest that we try to return to a practical level in our discussion.

DR. DAVIS: I'd like to try to respond to Dr. Baldwin's earlier comment about the drug that has been approved and on the market for 25 years, particularly in the area of infectious disease. I've been in the profession now for 25 years and I don't believe that things have been static during that period relative to the efficacy of drugs that we have on hand now that might have been approved 25 years ago. I suggested in a letter to Les Crawford, about a year or two ago, that what we need are data to see where we stand in 1983 as compared to 1959. My clinical experience and intuition tell me that we are dealing with an entirely different set of disease processes today than we were 25 years ago. What I proposed could be done very economically with some federal support. Most of all, the veterinary colleges are already collecting data regarding the pathogens we're dealing with as part of our routine clinical workups. We are isolating

and characterizing the bacteria and in several of the schools we are routinely deriving MIC information. We need a national system, similar to your adverse drug reaction program, which is a very economical program, for tabulating and reporting bacterial sensitivity data on a geographical basis. Over time, this would provide us with a running epidemiological account of the microbial pathogens that we are having to deal with. Then, if we find that a major segment of the susceptible organisms will respond to 15 mg/lb of tetracycline rather than 5, then we have a basis for that to be a recommendation in practice. I would hope then that we could do the studies appropriate to that dosage adjustment without involving a million dollar investment by the people manufacturing the tetracycline. Apparently the suggestion had no impact as I have heard nothing more about it.

DR. CARNEVALE: Yes, that is a good suggestion; perhaps this Symposium wants to bring it back out again in the task force report. Similar surveillance does go on in the human area -- there are contracts out to different universities and hospitals and in the human area they do rely on this kind of data to change dosages or make recommendations and so forth, so that is a very good suggestion.

The other thing to go along with that is some work to be done to correlate blood levels with clinical efficacy. I think there's a dearth of that information around. I know some people in our Bureau are attempting to do some of that work at Beltsville now -- I see that Dr. O'Connor who is involved in that is in the audience today. That would be very useful if we could correlate effective blood levels, or blood levels I should say, with clinical efficacy.

DR. ALLEN: Talking about raising the dosing level brought to mind some discussions I had with practitioners in Minnesota a few years ago. They were treating bacterial diseases in calves and when the recommended dose did not work, these practitioners did not usually double or triple the dose, they went to another drug that did work. These drugs of choice may or may not be approved for use in that particular species, so I think the problem that I see here is, as Dr. Mercer said, that the usual practitioner has 15-20 drugs that he uses and I think we ought to be talking about increasing the number to 25-35 by applying all that we have heard here today in this august group to get some of these drugs, that we know are being used in an extra-label sense, approved so the practitioner can use them without fear of being prosecuted for illegal drug residues.

DR. WASHINGTON: There are not many practitioners here today, but those of us who are here have heard from the ivory tower -- the regulatory people, the industry -- so I would like to give you a few words from the practitioner's viewpoint. As Dr. Mercer said, the independent and hard-to-regulate practitioner! I want to be able to continue to use my education and my continued education to do the best job for my clients that I can do, to have a safe product in the end, and I think our clients want to have a safe product. They follow our recommendations, but we have to use a lot of drugs. As a food animal practitioner, a dairy practitioner, we have almost nothing we can use in the lactating dairy cow. So we have to use off-label drugs and I hope that I do not have to go back to the time of whisky and TLC as Dr. Powers said, because we probably won't be able to go back to that because whiskey will be an off-label use.

DR. T. POWERS: I certainly do appreciate a practitioner coming forth and commenting, especially a bovine practitioner. I know you're right in the middle of everything, especially the off-label usage problem and in food animal medicine. BUT...there is no way that drugs can be properly used as they are labeled today -- industry can't afford to put every clinical usage claim on the label. The drug is marketed with one or two claims in one or two species of animals, and I don't care if it's dogs or cats or whatever, that drug is then used in 1,000 different situations (different diseases, different species, different sexes, different ages, etc.). So what I'm saying is the package insert needs to be changed to give us the flexibility to practice therapeutics scientifically. Many of the claims for antibiotics will have to be based on in vitro studies, pharmacokinetic studies, and studies from other species.