

SECTION III

EXPERIMENTAL DESIGN OF DOSE DETERMINATION
STUDIES WITH ANTIMICROBIAL DRUGS

DISCUSSION PERIOD

(PART II)

DR. SIMMONS: Thank you, Dr. Jenkins. If the rest of the speakers from this session will please come forward, we'll open the floor for discussions.

SECTION III - PART II - DISCUSSION PERIOD

DR. POST: I'd like to ask Dr. Gunderson about the significant difference between the two dosage levels of the trimethoprim in the results he presented as far as effectiveness is concerned.

DR. GUNDERSON: They're both effective; this is only one study in two or three million dollars worth of work to get the Tribrissen NADA cleared. When one looks at all other diseases, all other indications, it appeared to us that the best dose was 30 mg per kg rather than 15 mg per kg in order to cover a broader spectrum with a fixed labeled dose.

DR. GINGERICH: Dr. Ling, can you select an organism from your bank with a predetermined sensitivity pattern?

DR. LING: Yes we can, and that's one thing I tried to touch on but perhaps didn't have enough time to elaborate on. The gram negative bacteria that are present in the urinary tract in disease have a great capacity to change their antimicrobial susceptibility as you know. They primarily do this by means of passing back and forth throughout their population, small pieces of extrachromosomal DNA that are called variously, R-plasmids or R-factors, and they encode for mechanisms by which the bacteria can then render themselves "resistant" to a single antimicrobial agent or to groups of antimicrobial agents. The answer to your question quite simply though, is yes, that is possible and in fact very desirable in some cases, especially when you're dealing with combinations of antibiotics to select organisms with predetermined susceptibility.

DR. SIMMONS: If I might comment on that -- we've made extensive use of Dr. Ling's array of organisms and they are quite useful for evaluation of sensitivity patterns.

DR. J. POWERS: My concerns regarding untreated controls are in the context of clinical trials and not in the animal model setting. What are your thoughts, Dr. Colaianne, on ethics vs. statistical completeness in the clinical trial area?

DR. COLAIANNE: I have none; actually that's way out of my field, Jean. Obviously you can't be against motherhood and apple pie, Jean, and I don't think any of us here are. No one wants to do research that's unnecessary, that might in any way risk animal life or even cause the animals harm, but just as in human medicine, they've been forced to face this ethics question over and over again. In the veterinary field the question's kind of been pushed aside. It's the easy answer to say, well, we can't do unmedicated control groups under clinical conditions because it's unethical but that doesn't answer the question, it only puts you at the point of trying to define what is unethical about it. If we're not talking about a life-threatening, life-shortening situation where concomitant therapy could be brought in in a few days if treatment isn't successful, I find it hard to see that there's an ethical problem. I know there's an educational problem. The practitioners are none too happy about this, but neither were the human practitioners when they started to face this problem; that's really all I'm trying to say. I would much prefer to handle that whole issue of the placebo and the unmedicated group in a model and I would like to keep it out of the field, but as we all know that hasn't been the case. If there is no model, FDA is going to continue to want you to give us some kind of data on a placebo (unmedicated) group if it's at all feasible.

DR. JOCHEN: With respect to this matter of positive control, who should decide what positive control to use? And, is there any basis for vetoing some positive controls, especially drugs or materials that may contain a number of drugs and the approved drug available have been approved prior to, say, 1970?

DR. COLAIANNE: Is that addressed to me? Again, that's way outside of my field; I'm not sure I can answer that at all. I'm not even the right one to ask what has been the criteria for an adequate positive control in past control studies. Maybe Dr. Baldwin or someone can answer that.

DR. BALDWIN: Yes, we have a problem with this from time to time depending upon the products we're talking about. With topicals, for instance, especially with combinations, a number of those were approved prior to 1970 and before the NASNARC looked at them, so that they do not meet the combination drug policy. It was established in 1973, reestablished in 1978, and just republished. So to compare a 1970 product or even a 1962 product to a product going out on the market today is just about the same as putting the medicine back that many years. We do have a problem with that, even though the law says we can use an active control. We still have to

look at what that active control is, whether it contains something like contemporary data, and if it doesn't, then we have to look at the science of it and not just the legalities.

DR. DAVIS: I have a question for Dr. Ling. Do you have any information in terms of spontaneous remission following infection in your dogs? That is, if untreated.

DR. LING: We do have some data in that regard. The spontaneous "cure rate" is quite low, probably less than 5% and occurs at that level only after about 3 to 4 weeks.

DR. DAVIS: The reason I asked that is that we just heard a paper in Chicago this week - a cystitis model - in which the dogs would recover spontaneously in 4 days. Many of us were wondering how one could use such a model as this to thoroughly evaluate an antimicrobial product.

DR. SIMMONS: If there are no other questions, I'd like to take this opportunity to thank the preceding speakers for their fine presentations and say that we appreciate their work.

Our final speaker for today and for this Symposium will be Dr. Robert Baldwin who will be talking on the future of dose determination. Dr. Baldwin received his D.V.M. degree from Michigan State University in 1951 and his M.S. degree from Colorado State University in 1964. He interrupted 14 years of practice in Wyoming to receive his M.S. degree. Dr. Baldwin served with the FDA/BVM for 17 years and is currently the Associate Director for Scientific Evaluation. Dr. Baldwin...