Experimental Designs for Clinical Studies With Anti-Inflammatory Drugs

by S. W. Dawley, D.V.M.*

When Dr. Paul asked me to address this subject, he suggested that I discuss problems associated with designing clinical studies with anti-inflammatory drugs. Fortunately, he did not ask for solutions! Before embarking on discussions concerning specific problems in this area, there are a few points which, although basic to most of us, need to be kept in mind when developing any clinical study program. They are not restricted to studies with anti-inflammatory drugs.

Clinical studies are the final test of a product which has survived extensive preclinical work - formulation research, pharmacokinetic and residue studies, toxicity studies in non-target and target animals and "in-house" safety and efficacy work. All preclinical work has a bearing on the experimental design of clinical studies

But then, we must keep in mind that most preclinical work has been carried out in an ideal environment with sophisticated equipment which is not usually available in the field and with automated machinery not usually found where clinical studies should be done. Clinical studies should be carried out in the same type of environment in which the drug will eventually be used e.g. the feedlot or the busy small animal hospital.

Clinical studies place the new drug in the position to be used in the natural disease state for which it is to be indicated and tests the drug's performance in a herd or flock environment, under uncontrolled temperature and "black and white" husbandry conditions, in animals of a wide range of ages, breeds and classes or in animals which may be "near and dear" to the heart of a very fussy client. The clinical study also places the new drug in unfamiliar hands - hands which belong to people of wide diversified technical ability and powers of observation. We recognize that 80% of all swine products used in this country are administered by producers while 80% of companion animal drugs are used

*Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

or directed for use by veterinarians. The terms "protocol flexibility" were used in this slide because I believe that the factors which I have mentioned have a marked impact on whether data generated from clinical studies will signify whether under a great diversity of conditions, we can expect the product to perform as safely and effectively as anticipated from preclinical work. Preparation of an acceptable flexible protocol is, in itself, an art!

In consideration of experimental designs for anti-inflammatory drugs, there is one further point which should be addressed. Inflammation occurs in wide degrees, at any anatomical site and from many causes. Is there justification to modify the dosage of an anti-inflammatory drug in clinical use as related to the degree of the inflammation, its chronicity, anatomical location or etiology? I fully realize that dose ranges (which have been discussed many times) present regulatory problems but lack of an acceptable dose range provides a problem for the veterinarian in the field. As we are all aware, most veterinarians cope with the problem by creating their own dose range! They readily recognize that there are a large variety of inflammatory conditions -- some of which do not respond to therapy!!

This then leads me to my mandate at this meeting - idiosyncracies and related problems in developing protocols specifically for anti-inflammatory drugs. In discussing these peculiarities, due to time limitations, my remarks will be general rather than attempt to address experimental designs for different classes of anti-inflammatory drugs or for specific inflammatory conditions. I will also assume that each experimental protocol for clinical studies, regardless of the drug class, will provide required information regarding objectives of the study, the product to be tested, the patient's history, the treatment regimen, blinding procedures, response to treatment and report of any observed side effects. I would prefer to spend the allotted time discussing some special concerns related more specifically to clinical testing of anti-inflammatory drugs:

1) Use of subjective parameters
2) Variability in cardinal signs of inflammation
3) Concomitant therapy
4) Use of controls
5) Role of the clinical investigator

Response to treatment with anti-inflammatory drugs is frequently assessed subjectively. When this is required, we attempt to provide a numerical grading system based on reduction of severity of signs over

time, recognizing that seldom do two investigators place equal values on their observations. Occasionally, objective parameters may be used especially if a vital body system is involved. As a partial solution to this problem, it is proposed that, when subjective parameters must be used, increasing the numbers of investigators and reducing the numbers of patients per investigator would provide more meaningful data without significantly increasing development cost of the product. Numerical assignment of the investigators ratings of the product's performance should then be applied to acceptability of efficacy. Also, use of investigators studying 20 animals each would provide more meaningful data and a greater insight into the product's future performance in the field than would 3 investigators studying 100 animals each. As stated, objective parameters should be reported if possible and if investigators can be convinced to take the time to measure them. In these pulmonary emphysema victims, body temperature, respirations per minute, body weights, incidence of coughing and time to return to eating can be accurately reported as criteria for assessment of efficacy of a drug but how does one evaluate this objectively?

The next concern to be considered is the strength of the test to be placed on each of the cardinal signs of inflammation. We recognize that the dog with an acute cervical disc is in acute pain but with no evidence of swelling externally or heat on palpation. This condition will often respond well to anti-inflammatory drug therapy but the response will be elicited only by relief of pain. In designing the experimental protocol for this indication, relief of pain is the only criterion which can apply. On the other hand, this trotter with an acutely bowed tendon will show all the classical signs of inflammation and all signs should therefore enter into the evaluation. To develop an adequate protocol, it is essential that associated signs with specific inflammatory conditions be known and reflected in the protocol and case report form.

Third, and not necessarily in order of priority, is the very common requirement of concomitant therapy with anti-inflammatory drugs. It is no secret that, clinically, anti-inflammatory drugs are not used alone - in fact, in many instances, one might be considered suspect if antibiotic coverage is not provided when an anti-inflammatory drug is indicated. And there is no question that concomitant or adjunctive therapy or surgical procedures influence and confuse assessment of the test product's efficacy. But, since anti-inflammatory drugs will be used pre- and post-surgically, in traumatized patients in varying stages of shock, in association with antibiotics, before and after anesthesia - even as "shotgun" therapy before a positive diagnosis is

made, would not proper documentation of use of concomitant therapy provide added information needed to support safety and efficacy of the drug in clinical use? The experimental design should provide this avenue of information but should encourage use of similar concomitant therapy by all investigators for a specific inflammatory disorder. An anti-inflammatory drug alone would be unlikely to correct this pony's condition but in combination with proper concomitant therapy, could make the difference between survival and non-survival!

The next point which I would like to address is use of controls in clinical studies. When a "positive" approved control drug is available, there can be no objective to incorporating it into the experimental design but when no positive control drug exists, I cannot concur that, even for a limited period of time, there is professional justification for use of a negative placebo especially in patients of investigators' clients. In fact, every effort is made to reduce unnecessary animal use and suffering in the laboratory climate. Clinical investigators agree with this position to the point where many of them refuse to cooperate in clinical studies if negative controls are requested.

And, finally, the role of the investigator in clinical trials. The clinical investigator plays the leading role in clinical studies no matter how carefully one prepares the experimental design. If a doctor accepts this role, he or she should be aware that the claims for the products' safety and efficacy will be based on his or her testimony. Experienced investigators can make a significant contribution during the experimental design planning stage and, in addition to input of their expertise, this practice allows them to become an integral part of the drug's development program. Also, during clinical studies, observant and well-informed investigators may make suggestions for beneficial additions or deletions to the study design which, by addenda, can legally be made and communicated to the regulatory body concerned for approval.

Presented here is a case report form for an anti-inflammatory drug clinical trial. This form contains space for the information to which I previously referred, is concise for practical purposes but allows space for flexibility at the discretion of the investigator. As anyone who has reviewed clinical case report forms can attest, two of the major sins committed by clinical investigators is failure to fill in all identified areas and their inability to write legibly.

To summarize, variability of severity and etiology of inflammation, presence or absence of cardinal signs in specific disorders, frequent presence of concomitant disorders and need for adjunctive therapy and lack of objective parameters for evaluation complicate experimental designs for clinical studies with anti-inflammatory drugs. Regulations do not define either "proof of safety" or "efficacy" for drugs of this class, and, indeed it may be undesirable to design such regulations. The demonstration of efficacy cannot be based meaningfully upon some pre-determined numbers of animals or investigators. Flexibility in protocol design, trial execution and interpretation of results is essential to adapt to the variabilities in patients, drugs and diseases. Additionally, our understanding of what is required to demonstrate efficacy must change with our increasing knowledge and experience.