SESSION VI:

Demonstrating Drug Efficacy in Veterinary Medicine

Co-Chairs: Joseph Bertone and Scott Brown

Use of Experimental Animal Models to Evaluate Drug Efficacy

Scott A. Brown, DVM, PhD, Dipl ACVCP
Pharmacia & Upjohn Animal Health, Kalamazoo, Michigan, USA

Animal models of disease can have a variety of uses. Perhaps the most widely known use is to study the pathogenesis and pathophysiology of the disease, the parameters or surrogate variables that are affected in association with the disease, and to fulfill Koch's postulates with respect to the causation for the disease syndrome. These are vitally important roles that experimental animal models can serve in medicine. From a pharmaceutical company's perspective, animal models of disease can be useful in the evaluation of potential therapeutic interventions in the disease for a variety of reasons, provided some characteristics of an experimental animal model are known and validated. This discussion will focus on the requirements for establishing efficacy, the characteristics of experimental models of animal disease that are required for successfully using these models in the drug discovery and development process, and what characteristics of a disease model are usually avoided when used for that purpose.

Efficacy

The best indicator of efficacy of a new animal drug is clinical outcome in a well-controlled efficacy study in the naturally occurring disease syndrome. Particularly when the infection is remote from the plasma and not well-modeled by tissue homogenates, the efficacy will not directly "map" from concentrations to efficacy. In these instances, there may be a relationship between the observed concentrations and efficacy, but the relationship may be quite complex. Examples of situations in which the pharmacokinetics and minimum inhibitory concentrations (MICs) did not accurately predict efficacy are with oral and parenteral ceftiofur in colibacillosis in baby pigs, and with spectinomycin sulfate for bovine respiratory disease.

Clinical endpoints of efficacy studies must be reproducible, reflective of a true clinical response, and relevant not only to the herd in which a single location study is done but also predictive of the efficacy of the drug across a wide variety of management conditions and disease strains. In addition, the cost:benefit cannot be included in pivotal efficacy studies, because not only can the cost change, but the "critical" break-even point is different in different operations. Finally, the clinical endpoints must allow discernment of various doses of a therapeutic agent in comparison to a negative (placebo) control group or a positive (known effective) control group.

The difference between a positive control efficacy study and a negative control (placebo) efficacy study is that, with a positive control alone there is no evidence that either drug was effective over a "tincture of time", whereas with a negative control alone you can compare with assuredness that the drug was better than doing nothing alone. In the field, doing nothing is rarely an option when there is a disease outbreak, but for strict experimental comparison to be absolutely sure the drug is better than nothing, a negative control study is required. On the other hand, being "better than nothing" is rarely useful clinically, and the positive control studies provide a comparison of the "new" product with the "tried and true" remedy.

Mechanism of Action

While *in vivo*, clinical studies are the best ways to evaluate efficacy, *in vitro* systems are typically the best method of targeting the mechanism of action of a new animal drug. These *in vitro* studies are valuable, because they allow for complete control over variables that are not to be tested, and allow investigators to focus on specific pathways through which a drug may work. In addition, when the quantity of experimental compound is limited, *in vitro* studies provide a greater return on quantity of drug used than *in vivo* studies (this is also the reason that laboratory animal models are widely used early in the drug discovery/development process, rather than larger target animals).

In vivo Experimental Models

Considerable attention is currently paid to models of respiratory and enteric diseases, and these models are often quite useful for elucidating the pathogenesis of the disease. On the other hand, many of these models are unresponsive to standard treatment regimes, either because the models are so severe that the disease process would overwhelm any course of treatment, because the models may have iatrogenically suppressed the host immune system, or simply because the models do not represent the true disease process accurately. For disease models to be useful in evaluating new treatment modalities, they must first be shown to be responsive to treatment and to be able to reproducibly discern between different courses of treatment. In addition, *in vivo* experimental models provide a higher and more predictable incidence of the disease, allowing research to be conducted in a more efficient and concerted manner. Furthermore, the models must have defined clinical endpoints that can be quantitated with precision (this is one reason mortality is used commonly as an endpoint...it is easily quantifiable). The model must be reproducible from animal to animal within a trial, and must be reproducible from study to study. For this reason, both negative and positive control groups are usually required to ensure the study has the correct severity of disease to provide meaningful results. Last, and perhaps most difficult, the results from the experimental model must be predictive of what will occur in the real world situation. Ideally, this prediction would be quantitative, allowing a dose to be predicted to be effective in the target animal based on what dose was effective in the experimental model. More frequently, the prediction is qualitative, assuring that some dose will be effective in the target animal but not allowing estimation of an effective dose in the target animal. In the latter situation other covariates, such as the pharmacokinetic differences between the experimental animal and the target animal, may provide insights into the quantitative prediction of an effective dose.

Although disease models can have utility if they produce similar pathophysiology as the naturally occurring disease, their relevance to drug development is dependent upon their reproducibility under dynamic conditions and their responsiveness to treatments of known efficacy. As an example, an animal model of endotoxemia is very useful for understanding the sequelae to the release of endotoxin in gram-negative septicemias, but unless the model responds to antibacterials or treatments known to be beneficial in naturally occurring endotoxemia, the model is of little utility in evaluating a potential new treatment. Likewise, disease models in which a large percentage of the animals spontaneously return to normal without therapeutic intervention also provide difficulties in discerning whether the test drug produced a real therapeutic effect or whether the treatment group would have gotten better without the test drug.

Experimental models of animal disease can be used as a screen for determining if a drug has any effect at all, at which point the drug would be dosed at the maximum tolerated dose to look for efficacy. Perhaps a more important role for experimental models of animal disease is to allow the estimation of the dose-response relationship in that disease complex. Once a dose-response relationship is known, then other surrogate markers of efficacy (eg, pharmacokinetic/pharmacodynamic markers) can be established to continue the research.

For this approach to work, there must be an established dose-response (or concentration-response) relationship. In particular, knowledge of whether the response is associated with a threshold concentration or is a function of the concentration is critical. These data may be generated for the class of drug (if it is well-described for that class), or it can be determined in a model situation or in the laboratory. However, if a surrogate response variable is used, it must be justified or correlated to the clinical response. In many instances, such information is not available until sufficient data have been generated for an initial approval; therefore, pharmacokinetic determination of dose may be considerably more applicable to adding additional indications or species to the approved label rather than to the initial approval.

Although traditional efficacy studies directed toward bovine or swine respiratory diseases have been carefully designed and conducted, the industry continues to search for more efficient methods for conducting clinical efficacy studies for infectious diseases, and increasingly for noninfectious diseases. These approaches may include studies in a model of the disease, or alternate methods for evaluating the response to the therapeutic agent. Further, the focus must remain on studies that result in decisions leading to the approval of a dosage regimen for the targeted disease indication. Even exploratory studies must fit into the overall research plan, designed to generate profitable product.

Animal welfare considerations

Although there are those who will passionately argue that the use of experimental models of animal disease are a violation of the sanctity of life, others will point out that use of experimental animal models in the long run decreases pain and suffering in animals by getting new, more effective products out on the market faster. In addition, by controlling the disease in an experimental setting, the investigator has the opportunity to more closely monitor the animals than if they were in the natural setting, thereby allowing more rapid intervention to reduce pain and suffering when animals do become moribund. Regardless, it is required of every investigator to review the practices and procedures involved, and to constantly review the literature, to assure animal care and use committees that the studies are truly providing advantages over either *in vitro* techniques or spontaneously occurring disease studies.

Conclusions

There is, and will continue to be, a critical role for *in vivo* animals studies in the discovery and development of new animal drugs. The industry continues to search for better *in vivo* experimental models of animal disease which have the characteristics needed to more effectively evaluate compounds. The genesis of those models will continue to come from creative scientists and investigators who know the naturally occurring disease and can capture and control it in a reproducible fashion. We look to you, those individuals intensively studying the diseases and management of domesticated animals, for the models of the future.