

DR. ARONSON: Our second speaker this morning is Dr. Harlan Bigbee. Dr. Bigbee is a graduate of Iowa State University, having received his D.V.M. degree in 1964. He is currently the Director of Clinical Research and Technical Service with the Schering Corporation in Kenilworth, New Jersey. I am pleased to introduce Dr. Bigbee.

DR. BIGBEE: Thank you, and thank you for this opportunity to be here. I think it's been a great discussion and Tom, you make a hard act to follow.

Harlan G. Bigbee, D.V.M.

For sake of this discussion, topical applications of antimicrobials will be considered as medication for the eye, ear, or broken or unbroken skin. Because of the complexities of these conditions in a clinical setting, and the variety of "natural and unnatural" etiological agents, I would first like to lay the groundwork by describing the clinical picture in each of these organs while confining the discussion to bacterial agents.

The Eye

Although there are many reports of a wide variety of organisms isolated from clinical affected eyes, little has been done to differentiate those organisms that are contaminants vs those which are primary pathogens. Moraxella bovis infection in the bovine eye is one notable exception. Staphylococcus aureus and Pseudomonas are considered by many as primary eye pathogens in the dog and horse. In fact, a pseudomonas canine eye model was recently developed and published by researchers at Ohio State University.

In addition to the myriad of infectious bacterial agents there are many other factors leading to clinical conjunctivitis and/or keratitis. Wounds, foreign bodies, chemical irritants, and abnormalities of the eyelid (entropion or ectropion) are some of the more common ones. Even other disease conditions such as canine distemper, Streptococcus equi infections in horses, chronic debilitation and decreased lacrimal gland activity will lead to a clinical picture of conjunctivitis and/or keratitis. Many, if not most, clinical cases presented are of multiple involvement.

The Ear

As in the eye, true primary bacterial pathogens of the ear lack appropriate identification. Pseudomonas infections again may be the exception. However, cultures revealing a mixture of unknown significance are isolated from acutely or chronically inflamed ears that are successfully treated with topical antimicrobials. Foreign bodies, ear mites, ticks, and traumatic lesions also create an environment suitable for the growth of microorganisms. Even excess hair growth in the ear canal, as is seen in some Poodles, will lead to an impaired flow of ear wax which creates an additional environment suitable for the growth of infectious agents, thus leading to a

diagnosis of otitis externa requiring multiple therapeutic agents, including antimicrobials.

The Skin

Staphylococcus aureus is widely accepted as a primary infectious agent of the skin. Beyond that the waters become very murky. In the dog and horse, many skin bacterial infections are secondary to other etiologic agents such as parasites, allergies, metabolic diseases, debilitation, trauma (including self-trauma), and even surgical wounds. In many instances multiple therapies must be utilized to affect clinical relief of the patient. An example is an ectoparasiticide, an anti-infective for secondary bacterial infection and antipruritic to prevent further self-trauma.

With this brief background it becomes obvious that the picture as presented to the clinician is very complex with multiple etiologies and a potential for a variety of treatment methods required. From a statistical point of view, the background information of pre-treatment data base requires similarity between cases in order to fully evaluate the response. Similarities of bacterial agent, disease severity, underlying complications and uniformity of population are suggested or required in statistical analyses. Use of multiple therapies which may be required for effective therapy in many clinical conditions greatly impede analysis of any data generated.

Determining objective parameters to evaluate response to topical antimicrobials is often difficult. Microbiological "cure" is not the only concern on the clinician. A clinical cure or restoration to normal is the ultimate goal. Many of the parameters most commonly associated with these disease conditions are subjective in nature. Dealing with the amount and character of discharge, degree of inflammation and/or discomfort across multiple evaluators becomes even more confusing from a statistical point of view. Ofttimes, it is necessary to use multiple evaluators because cases that fit a relatively "pure" protocol appear only sporadically. In order to generate data in a relatively short time period multiple evaluators will be required. Blinding is also difficult under a clinical practice setting since in many instances manpower availability is not always assured. It is by far best to have one individual administering a drug while another makes observations. This leads to a requirement for a multiple man practice or the use of a receptionist or pharmacist to dispense medication and maintain blinding.

An additional point of concern is the use of non-effective levels or placebos in treating clinical cases - particularly

eye diseases and diseases of the ear. Many animals need an effective treatment initiated rapidly to avoid potential severe adverse effects of non-therapy. What owner would sign a release for use of a placebo in acute conjunctivitis/keratitis or in a heavily infected wound or laceration? The charge to the practitioner by his profession and by his clientele is to relieve suffering at an expeditious rate.

Now that I have outlined all the negatives and/or difficulties conducting dose determination in clinical trials, I'd like to propose some solutions. First would be the use of models. As mentioned earlier, a pseudomonas model in the canine eye has been developed. This is done by trephining the cornea and application of a pseudomonas organism which maintains an infected ulcerated keratitis. In the canine ear, thermal cautery has been used to establish an inflammatory process followed by application of an infectious pseudomonas isolated from the canine ear to develop an acute otitis externa. For infected skin conditions in both the horse and dog, thermal cautery followed by infection with either staphylococcus in the canine, or streptococci in the equine, will develop an infected lesion responsive to certain antimicrobial therapies.

In models the following objective criteria have been used in dose titration: a) serial or daily cultures to determine minimum time for elimination of infecting organisms, b) bacterial counts to show decreasing organism load, c) wound size or area, d) depth of lesion (corneal ulcer), e) distance edema extends from wound edge, f) inflammatory response, e.g. leg circumference and stride length in horse, head tilt in canine ears, or counting vessels to show neovascularization of the eye. Subjectively, pain response to specified handling procedures can be employed. Attempts at quantifying or qualifying discharge or erythema have not been successful. Photography is a valuable tool to demonstrate the model and response to therapy. Studies should be arranged in replicates with a minimum of 6 per group. By conducting the study in replicates and constant statistical input the study can be expanded to show significance.

A second alternative is the use of positive controls in clinical cases. Under these circumstances the unnecessary or unwarranted suffering to the animal will be eliminated because use of ineffective or placebo levels will not be used. A positive control would be compared to a potentially effective level and if desired even safe overdoses could be used to demonstrate that the proposed level was effective and that additional levels were not more effective. A third alternative is eliminating the need for dose titrations for a

topical antimicrobial designed for the same therapy and indications between species. Once an effective topical dose is shown in one species, then safety and efficacy by positive control should provide for additional species. How many times does one need to re-invent the wheel for an ophthalmic product destined for use in the dog, the cat, cattle and the horse? Four consecutive trials to demonstrate a single dose level in this example is a waste of resources and creates unnecessary suffering of animals - a point of which we all should be aware.

It is wise for us all to remember that in these conditions we are speaking of low volume product usage. This is not a condition where residues are of primary importance nor do we consider volume use sufficient to cause environmental contamination or detriment to the food chain.

In summary, I would like to again emphasize that the clinical condition is very complex. Pure individual cases are difficult to locate and many of the parameters are of a subjective nature and that alternate methods by use of models are available or in the case of clinical conditions, non-effective levels should not be allowed. Relief of the patient and unwarranted suffering should be the primary point of concern. Leave the clinical cases to confirmation of efficacy after an appropriate dose is determined.