

DR. SIMMONS: Next on the program with his comments on animal models is Dr. William Jenkins. Dr. Jenkins graduated from the University of Pretoria in South Africa in 1958; he received an advanced degree in veterinary pharmacology from the same university in 1966. In 1970, he received his Ph.D. degree in pharmacology from the University of Missouri. He then practiced for four years after which he taught at the Veterinary School of the University of Pretoria for 16 years. He then joined Texas A & M University in 1978 where he is known as the "Terror of the Soccer Field." His teaching efforts include basic and clinical pharmacology; his research efforts include the pathogenesis and therapeutic management of bovine respiratory disease and other areas of clinical pharmacology. Bill...

DR. JENKINS: Thank you. As the last of a series of commentators, I find myself at some disadvantage so I thought what I would do instead would be to look at our own model very very briefly and then spend some time in rebuttal of my own model, as it turns out -- or certainly pointing out some of its shortcomings.

Comments on Use of Animal Models

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The frequent use of antibiotics and other antimicrobial agents to treat cattle suffering from bacterial pneumonia and related respiratory diseases, or to prevent their occurrence, is widespread today. The dosage rates and frequencies, and general therapeutic guidelines that are most often followed are usually based on findings in normal animals and may, in fact, be quite inadequate or inappropriate for cattle suffering from acute, subacute, or even chronic respiratory tract or lung infections. Although some information is available about the pharmacokinetics of antimicrobial agents in cattle, very few studies, indeed, have been conducted in diseased animals, notwithstanding a growing body of evidence gathered from several other species that suggests significant effects of disease states such as fever, shock, cardiac failure, hepatic and renal insufficiency, and enteritis, on established pharmacokinetic patterns, particularly of antimicrobial agents.

The Federal Drug and Cosmetic Act poses these questions with regard to the safety and effectiveness of new animal drugs: "1. What blood levels of an antibiotic should be used to avoid possible toxic or untoward effects?, and 2. What level of drug is needed at the site of the pathogenic activity to be effective in treating a well-characterized disease process?" It is clearly of concern that acute bacterial bronchopneumonia which occurs as part of the bovine respiratory disease complex may markedly alter the disposition and elimination kinetics of those antimicrobial agents that are commonly used to treat these infections and, as a result, the dosage regimens which are currently recommended may not necessarily produce adequate concentrations at the site of infection to assure therapeutic success. The difficulties and unpredictability associated with the treatment of pneumonic calves are well known. Recent findings have even suggested that, in some instances, antibacterial therapy as currently carried out may only delay death in shipping fever cases and that ultimate mortality rates may not be significantly different between treated and untreated animals. This would seem to imply that the pharmaceutical preparations commonly employed in the field are not being utilized to their maximal benefit.

It is imperative to establish, as quickly as possible, the scientific criteria necessary to make rational use of those antimicrobial agents administered to calves suffering from respiratory disease because:

1. For the foreseeable future, antibacterial drugs will continue to play an important role in food animal production and,
2. The economic impact of the correct and beneficial use of these agents is self-evident to all concerned.

In order to respond to this obvious need, an experimental model has been developed that allows comparative pharmacokinetic studies to be conducted on antibacterial agents in healthy and then in bronchopneumonic calves. The system facilitates the determination of concurrent plasma and pulmonary tissue disposition kinetics. Standard procedures are followed for the evaluation of the pharmacokinetic parameters that describe the disposition of a selected antibacterial agent in calves following the intravenous injection of a single dose. The calves then have a cellulose dialysis membrane sachet (volume 4 ml, m.w. exclusion 3500 daltons) and a set of Spectra/Por hollow fiber bundles (i.d. 215 μ , volume 250 l, m.w. exclusion 5000 daltons) surgically introduced into the apical lobe of the right lung. Following a recovery period, the plasma kinetic study is repeated but, in this case, the rate of diffusion of the agent into the fluid (dextran 75 in saline) filled sachet or perfused fiber bundles is also measured. Finally, following the administration of betamethasone parenterally and 4% acetic acid intratracheally, a culture of pathogenic Pasteurella haemolytica (Biotype A Serotype I, 10-15 ml of 10^7 - 10^9 c.f.u./ml) is delivered into the trachea via a nasal tube. An acute bronchopneumonia usually develops within 36-48 hours. The kinetic study is then repeated in the sick calves. The plasma disposition kinetics and intrapulmonary diffusion kinetics between normal and bronchopneumonic calves, when using a variety of antibacterial agents, can then be compared and dosage regimens adjusted to alter the antimicrobial concentrations at the actual site of infection.

These investigations are still at a very preliminary stage and several short-comings of the experimental approach already have been identified, but several features are worthy of note. These relate directly to the use of animal models or simulated disease syndromes for dose determination of antimicrobial drugs.

1. Though the half-lives, clearance values and other plasma-derived pharmacokinetic parameters may show notable differences between healthy and pneumonic calves, the antibacterial concentrations attained at the actual site of infection within the lung are still not readily predictable because of multiple compounding factors.

2. The minimal inhibitory concentrations for the many strains of bacterial pathogens involved may differ several hundred fold between strains so that successful therapy will depend very much on recognizing the presence of more resistant organisms and adjusting dosage regimens accordingly. Field experience coupled with bacterial isolation and subsequent sensitivity testing of the isolates is a very significant facet of managing respiratory disease in cattle.
3. The environment at the site of infection may play a vital role in determining the effectiveness of an antibacterial agent. The features of special note include tissue necrosis with hypoxia or anoxia being present. This leads to a low pH in the affected tissues which is, in turn, very detrimental for the action of several classes of antibiotic (aminocyclitols, macrolides, lincomycins and others). A low oxygen tension favors the emergence of pathogenic anaerobic bacteria in chronic infections. Binding of antimicrobial agents to tissue proteins, quiescent organisms, fibroplasia and consequent encapsulation of infected areas, altered blood supply and a highly unfavorable milieu for the action of phagocytic cells are additional pharmacotherapeutic considerations in infected tissue.
4. The concentrations reached by antimicrobial drugs within the fluids surrounding the bacteria seem to be dependent on the same physicochemical factors and the same physiological considerations that generally govern the intracorporeal distribution of drugs. Thus, concentration gradients, pH/pKa relationships, lipid solubility, molecular size, degree of plasma protein binding, blood flow and integrity of cellular membranes may all play a role. It also seems as if the degree of fibroplasia may well determine the rate at which at least some antibiotics (especially the macrolides) diffuse into infected tissue.
5. The immunocompetence of pneumonic calves and their ability to sustain and subsequently overcome acute broncho-alveolar infections with Pasteurella haemolytica and other potential pathogens is an issue of great importance. The success of antimicrobial therapy bears a direct relationship to intact host defense mechanisms and this fact should always be borne in mind whenever one is evaluating the success or failure of a particular therapeutic regimen, whether it be in naturally occurring infections or in disease models. Key considerations here include the immunosuppressive effects of stress, anorexia, nutrient deficiencies and hypogammaglobulinemia due to a variety of causes. The

concurrent administration of corticosteroids clearly would complicate the issue.

6. The final point that deserves mention is the recognition of paradoxical effects that may be observed with certain antibiotics at low or at excessively high levels. Concentrations of antibacterial agents that are greater than or equal to the minimum inhibitory concentration or the minimum bactericidal concentration produce dramatic changes in bacteria. At lower concentrations, these effects might be expected to be proportionately milder but, in fact, are usually qualitatively different. Certain morphologic changes in Gram-negative bacilli and Gram-positive cocci have been observed only with concentrations of antibiotic lower than the minimal inhibitory concentration. Penicillins, cephalosporins, tetracycline, gentamicin and rifampin, amongst other agents, have been shown to possess such subinhibitory effects on bacteria. At high concentrations, certain antibacterial drugs may interfere with leukocyte chemotaxis and phagocytosis and this, in turn, clearly impairs host defense responses. Leukocyte phagocytosis may be inhibited by tetracyclines, aminoglycosides and chloramphenicol whereas the tetracyclines interfere with both functions. These observations, once again, illustrate the difficulty of establishing absolute dosage regimens for antimicrobial drugs in clinical cases.

In closing, I would like to re-emphasize that there are a number of confounding factors that make the direct extrapolation of dosage rates for antimicrobial drugs from healthy calves to bronchopneumonic calves extremely tenuous. A great deal of additional information is still required in this area and the use of experimental models will serve an important role in this regard.