Feedlot Session

Dr. M. S. Silberman, Chairman

Antimicrobial Agents: Pharmacology

Thomas E. Powers, *D.V.M., Ph.D.*
Department of Veterinary Physiology and Pharmacology
College of Veterinary Medicine
The Ohio State University
Columbus, Ohio 43210

Introduction

The impact of chemotherapy on the practice of veterinary medicine cannot be overstated. It resulted in a very strong link between the disciplines of biochemistry, microbiology, molecular biology, and pharmacology.

For many years following the discovery of the clinical value of antimicrobial agents, production and usage far surpassed scientific research and development in the field of antimicrobial agents due to their immediate and overwhelming acceptance. It is no wonder that antibiotics and sulfonamides have often been misused by the veterinarian and physician as well as the agriculturalists.

In order to administer the proper treatment, we as veterinarians must understand the characteristics of the disease, physiology of the species, nature of the infectious disease process, and the pharmacological properties of the antimicrobial agent. The latter should include a basic understanding of the chemistry, mode of action, spectrum, dosage, elimination kinetics, and toxicity. This knowledge is constantly being generated for a few species (laboratory animals, dog, and man) but not at a fast enough pace in any case and, especially, not for food-producing animals. This fact necessarily led us to extrapolation of data from kinetic studies from one species to another, and more often than not, these have led to erroneous conclusions.

The use of antimicrobial agents either as in a true therapeutic sense or as food additives for growth promotion and disease prevention and control in food-producing animals is accompanied by the additional risk of residues, that may be harmful to man, in the food derived from these animals. This places an additional constraint on the food animal practitioner as to the number of chemotherapeutic agents available for his usage.

Specific Therapy for Specific Pathogens

The main premise one must assume in the treatment of infectious diseases is that specific infections are caused by specific microorganisms. One then tries to select that drug which will produce an inhibitory, bacteriostatic, or bacteriocidal effect on the etiological agent or agents involved. With this specific therapy one must have the animal on an adequate supportive therapy regimen and maintained in a proper environment. The final cure will come about in most cases as a result of the animal's defense mechanisms being able to eliminate the etiological agent and its products. The antimicrobial agent assists by reducing the number of pathogens that the defense mechanisms have to combat.

Although drugs should be selected that are highly active against the pathogen or pathogens involved, usually we must begin therapy based upon our clinical judgment of possible causative agents present. This therapy may be changed after we receive the laboratory reports on the sensitivity of the isolates.

Concept of Spectrum

It would be optimal to have a drug that would be effective against all pathogens and inactive against the normal flora. Unfortunately, this is not the case. Certain drugs have been classified in the past as gram positive in spectrum, others as gram negative, and others as broad spectrum in action. All of these terms have been misleading and often misused. They are simply very general terms used to describe the range of type of bacteria against which the agent is considered effective. Thus, a drug is said to have a broad spectrum if it is effective against bacteria in a wide range of species types and narrow in spectrum if it effects only a few species. For example, a drug like penicillin is considered narrower in spectrum than tetracycline; however, if one increases the concentra-

tion of penicillin in contact with the microorganisms involved then one increases the effectiveness and spectrum of penicillin. Therefore, it is possible for penicillin to act as a broad spectrum agent if one uses a high enough dosage level.

Combinations of Antimicrobial Drugs

Commercial preparations of combinations of drugs have been detailed to the practicing veterinarian with claims of synergistic actions, additive effects, broadened spectrums, prevention of the emergence of resistant strains, or simply treatment of undiagnosed infections with so-called "shotgun therapy." Usually none of these claims can be fully documented and almost never documented in the animal species and the specific infection to be treated. The demonstration of synergism, additive effect, or antagonism in the test tube does not mean unequivocally that these drugs will do the same in an *in vivo* situation. Also, the production of one of these actions against one microorganism does not necessarily imply a similar effect against another microorganism. The results one obtains using a combination of products depend not only upon the drugs used, but their relative and absolute concentrations, the number and type of bacteria, the growth status of bacteria, the time of contacting the antibiotic, and the time of observing the outcome–to mention only a partial list. It is virtually impossible to predict the effect of antimicrobial drug combinations in a variety of clinical situations.

There are instances when one can possibly justify the use of combinations of drugs. These include acutely and seriously ill patients in which the etiological agent is unknown and one administers two or more antimicrobials simultaneously in the hope of inhibiting the etiological agents. In any case, all measures should be taken to make a rapid and correct diagnosis by using all clinical and laboratory capabilities needed.

In veterinary medicine, we see many local infections and several bacteremias involving two or more pathogens of different sensitivities to antimicrobial agents. It becomes necessary that we then use two or more agents to be effective against each pathogen involved. The agents we use must not only be effective against infecting organisms but must also be compatible for use simultaneously. Because of the variety of mixed infections one can have, it becomes very difficult to prepare ahead of time every proprietary preparation to cover every case. Instead, it becomes necessary that the veterinarian administer two or more compatible drugs simultaneously that are specific for the case being treated.

The drugs trimethoprim and sulfonamides have been shown to exert a synergistic action against many pathogens. Not only does the combination produce a bacteriocidal rather than a bacteriostatic action, but also the minimum inhibitory concentration of the combination is markedly less than that of either trimethroprim or the sulfonamide. The combination can have activity against organisms that are resistant to sulfonamides.

Another justification for the combination of drugs is in possible reduction of toxicity. An example of this is the combination of two or more sulfonamides. Each may be additive to the other in bacteriostatic action, whereas each has its own solubility rate. Thereby one can reduce the amount of each used and overcome the toxicity related to formation of crystals in the urinary tract.

From a practical point of view, one of the major disadvantages of the use of combinations of drugs is inability to properly dose the combination product. The drugs used should produce effective levels for the same duration of time in order for the second, third, etc., dose to be administered at the proper interval. If drug A produces an effective blood level for 12 hours and drug B an effective blood level for 4-6 hours, when does one give the second dose of a combination of drug A and B? Other factors arguing against the use of combinations include reduced effectiveness, possible increased toxicity, and often an increase in cost without increasing effectiveness.

Acquired Resistance to Antimicrobial Agents

Acquired drug resistance can be due to mutations, alteration in the structure of chromosomal DNA, or "infectious drug resistance" (transferrable drug resistance) which is associated with extra-chromosomal DNA. Transferrable drug resistance, according to Watanabe, T. (1971), is the more important cause of drug resistance, clinically, because it can produce epidemic multiple resistance to drugs. The genetic exchange of the extra-chromosomal DNA can be spread from one bacteria to another by means of a bacteriophage infection (transduction) by simply incorporating genes lysed bacteria in its environment (transformation) or by mating with another bacteria (conjugation). By any of the above methods, it is possible for a bacterium to acquire resistance to antibiotics without ever having been directly exposed to same.

Plasmids are the extra-chromosomal DNA molecules (R factor) which are capable of reproducing themselves. These R factors are frequently found in gram negative organisms, especially enteric bacteria, and consist of two types of genes: (1) those carrying the resistance factor for the antibiotics (resistance determinant = RD) and (2) those needed for transfer from one cell to the other during conjugation (resistance transfer factor = RFT).

R factors have been reported mainly from intestinal bacteria which include *Salmonella, Shigella, Proteus, Klebsiella, E. coli, Enterobacter, Pseudomonas,* and *Vibrio.* The list of bacteria involved in R factor resistance increases as scientists study the problem more. Bacteria carrying R factor are an enormous problem because of their capability

of transferring this resistance to not only their own species but to other species as well. For example, an R factor-resistant *E. coli* from the gut of a pig could mate (conjugate) with a *Salmonella,* pathogenic for man, and transfer this resistance to the *Salmonella sp.*

The antibiotics most often involved in R factor resistance are those with a bacteriostatic action such as the tetracyclines, chloramphenical, sulfonamides, and aminoglycosides. The list has grown however to include many others such as the penicillins. No single mechanism is responsible for R factor resistance. They may inactivate antibiotics by conjugating with acetyl, phosphoryl, or adenyl groups. Some prevent activity by altering permeability of bacterial cells to the drug.

Clinically, R factor resistance presents some very major problems. A sensitive strain of bacteria can become resistant within minutes, especially during therapy. The fact it is a multiple resistance often to 4-6 antibiotics emphasizes its potential to rapidly decrease the number of effective agents we have and emphasize the need for a more judicious usage of antibiotics.

The public health impact of this phenomenon has raised severe criticism on the usage of antibiotics in agriculture, especially as feed additives for growth promotion effects. It has been shown that the increased prevalence of infectious drug resistance is directly related to the increased use of antibiotics in all areas of medicine and agriculture. This use of antibiotics exerts a selective pressure for promoting infectious drug resistance in the bacterial population.

An early documented epidemiological study in Great Britain showed the extensive use of antibiotics for preventing salmonella infections in cattle was followed by an outbreak of antibiotic-resistant *Salmonella typhimurum* infection in man (1). Very recently a prospective study showed an increase in resistant intestinal bacteria in farmers in contact with tetracycline-fed chickens (2). This farm personnel did not show resistant bacteria until 3-5 months after the tetracycline feed was introduced on the farm. This same report summarizes numerous other epidemiological studies in this area.

R factor has been shown to exist in communities which have had no previous exposure to commercial antibiotics (3). Thus, commercial antibiotic production and its usage have not created the problem. The voluntary development can best be explained as a result of exposure to other organisms in their environment, producing antibiotics and the selection of R factor bacterial populations as a survival mechanism of the species.

Reasons for Failure With Therapy

If the organism is innately resistant or if it has acquired resistance during therapy then one can expect little or no response. Sometimes by increasing dosage one can overcome a low level of resistance. However, whenever we increase dosage above package insert directions, then we must lengthen the safe withdrawal time accordingly to insure no residue is present in meat at slaughter time.

Failure can result, as mentioned earlier, from using two or more incompatible antibiotics or drugs. In this regard, as a general rule, antibiotics should not be administered by adding to solutions used for fluid therapy since many antibiotics will be inactivated by the pH of these solutions.

Inadequate drug at the site of infection due to too low a dose or improper route of administration can lead to failure in response to the therapy. Other factors such as inadequate debridement, inadequate defense mechanisms, toxicity of the drug, possible multiple infections, and superinfection must all be considered in evaluating the reason for failure with a particular therapy regimen.

Antimicrobial therapy will be most effective when combined with proper supportive therapy which includes adequate nutrition and proper environment.

References

1. Anderson, E. S.: The Ecology of Transferable Drug Resistance in the Enterobacteria. Annual Rev. of Microbiol. 22: 131-180, 1968. - 2. Davis, C. E., Anandan, J.: The Evolution of R Factor. A Study of "Preantibiotic" Community in Borneo. N. Eng. J. Med. 282: 117-122, 1970. - 3. Levy, S. B., Fitzgerald, G. B., Macone, A. B.: Changes in Intestinal Flora of Farm Personnel After Introduction of a Tetracycline-Supplemented Feed on a Farm. N. Eng. J. of Med. 295: 583-588, 1976. - 4. Powers, T. E.: Antimicrobial Therapy in Veterinary Medicine. A Teaching Manual, College of Vet. Med., The Ohio State University, 1976.