Pharmacokinetics of Drugs Used Systemically in Mastitis Therapy

Daniel A. Gingerich, *D.V.M., M.S.*
Senior Research Clinician
Pitman-Moore, Inc.
Washington Crossing, N. J. 08560

Introduction

The control of mastitis in cattle has been one of the most complex and challenging disease problems confronting the veterinary profession over the past 50 years. Current mastitis control strategy rightly places major emphasis on the modification of various management factors and the dynamics of udder infections in herds (14), but every bovine practitioner is, nevertheless, called upon from time to time to treat individual clinical cases.

This paper is an attempt to present an approach to rational mastitis therapy by discussing the pharmacokinetics of several representative drugs which might be used. Emphasis is placed on systemic drug therapy in the bovine and the factors which favor distribution of drugs to the mammary gland.

Some Historical Aspects of Mastitis Therapy

Modern mastitis therapy really began with the advent of the use of penicillin in the treatment of streptococcic and staphylococcic mastitis. In 1944, Dr. J. C. Kakavas reported that the intramammary infusion of a raw filtrate obtained from the growth of *Penicillium notatum* in whey broth culture was effective in eliminating gram-positive infections from a majority of infected quarters (19). Interestingly, subsequent trials using crude extracts of penicillin as well as various preparations of purified penicillin salts in intramammary infusions often resulted in severe local irritation within the mammary gland (19,7,10). These local reactions were serious enough to arouse interest in the use of penicillin systemically in cows to control infections in the udder. The early experiments conducted first to determine whether intravenous dosage of penicillin would eliminate udder infections (10) and later to determine whether penicillin could be detected in normal or mastitic milk following parenteral dosage (25,8,28) were uniformly unsuccessful. It was not until 1948 that Welsh and co-workers reported that the lactating bovine mammary gland is indeed permeable to penicillin (29). The key factors in demonstrating penicillin activity in milk were (1) large enough parenteral dosages to produce high and persistent blood concentrations of the drug, and (2) extremely sensitive methods for the detection of penicillin in milk.

The fact that parenterally administered penicillin can diffuse into the bovine mammary gland is of great academic interest, particularly to pharmacologists. The interpretation of importance to the clinician, however, is that penicillin is **very poorly** distributed into the milk. Thus, injectable penicillin would appear to be a very poor choice of treatment for most cases of mastitis.

Considerations in the Choice of Drugs

The aim of drug therapy is to provide a suitable concentration of the active form of the drug, at the site or sites of action, for a suitable period of time. The clinician must have some idea of the characteristics of the drug with regard to these three factors in the species at hand.

Suitable Concentration

The definition of a therapeutic concentration or range of concentrations of drugs is extremely difficult because of the many pharmacological and biological variables which should be accounted for. For most drugs, it is assumed that there is a direct relationship between the plasma concentration and the therapeutic or toxic effects. For some drugs accumulated knowledge of the dosage vs. response has been helpful in elucidating the concentrations required to produce the desired effects. Suitable concentrations of antimicrobial drugs, however, have rarely been adequately defined, particularly in animal systems. Methods which can be used to more adequately define suitable concentration of antimicrobial drugs are discussed below.

Disc Susceptibility Testing: The Kirby-Bauer disc susceptibility test method (15) has traditionally been relied on to define the antimicrobial spectrum of activity of drugs. This method is recommended for routine antibiotic sensitivity testing in practice, but usually does not define suitable concentration in a quantitative sense (20). Results of disc susceptibility tests should, therefore, be regarded only as a first approximation of the susceptibility pattern of a given drug.

Minimum Inhibitory Concentration (MIC) Testing: A quantitative definition of suitable concentration *in vitro* can be obtained by determining the minimum concentration of drug incorporated into

broth media inoculated with the test micro-organism which will inhibit the growth of that organism. This is done in the laboratory by the tube dilution method (6) and provides a more accurate definition of suitable concentration.

At the Site of Action:

Rarely is the plasma concentration *per se* of a drug responsible for its activity. It is in the extravascular space where the drug micro-organism interaction usually takes place. Plasma concentrations are important only inasmuch as the concentrations in plasma are pharmacologically related to concentrations elsewhere. It is clinically obvious that if an antibiotic were given systemically to treat mastitis, a drug that is well distributed to the mammary gland should be selected.

The extent to which drugs are distributed to the extravascular spaces depends, to a large degree, on the ease with which they cross biological membranes (4,2). The properties of drugs which influence their passage across biological membranes are complex but include the following:

Lipid Solubility: Because of the lipoid-pore nature of the biological membrane, those drug molecules that are highly lipid-soluble penetrate the membrane readily and, other factors permitting, are widely distributed in the extravascular space.

Extent of Protein Binding: Most organic compounds used as drugs are bound to some extent by plasma proteins. Extensive protein binding can be an important factor limiting the distribution of some drugs.

Degree of Ionization at Prevailing pH: Many of the drugs used are weak acids or bases, present in solution in both the non-ionized and ionized forms. Only the non-ionized (lipid-soluble) form diffuses readily across the biological membrane. The proportion of the drug which is non-ionized depends on whether it is an acid or base, the dissociation constant (pKa) of the drug, and the pH of the solution in which it is dissolved. An interesting and relevant example of the importance of this concept stems from the fact that normal milk is an extravascular fluid which is acidic in comparison with plasma. Acidic drugs tend to be more ionized (non-diffusible) in plasma than in milk and therefore tend not to diffuse readily into milk. Basic drugs, on the other hand, tend to be less ionized in plasma than in milk and often diffuse readily into milk. At equilibrium, the milk-to-plasma ratio for acidic drugs is theoretically always less than 1:1 and for basic drugs greater than 1:1 (3) (assuming both are lipid soluble and not extensively protein bound).

Although the above brief discussion of the pharmacology of distribution is greatly oversimplified, it is useful to recognize that those drugs which are (1) highly lipid-soluble, (2) only moderately bound by plasma proteins, and (3) largely non-ionized at plasma pH 7.4 (e.g., organic bases) tend to be widely distributed in the body including distribution into the milk.

For A Suitable Period of Time

One of the fundamental principles of pharmacology is that the body regards virtually all drugs as foreign substances which must be eliminated. The specific mechanisms of elimination of drugs or classes of drugs are of clinical as well as academic interest, but of particular importance to the clinician is the **rate** of elimination of drugs. Plasma drug concentration studies and pharmacokinetic analyses, in the target species, are extremely important as a means of calculating proper dosage intervals and predicting the length of time a given dosage will exert its effect at the receptor site.

Drugs Used in Mastitis Therapy

The following is a discussion of representative examples of several classes of drugs which have been suggested for use in bovine mastitis treatment. An attempt is made to correlate what is known about suitable concentration of each drug with what is known about its pharmacokinetics in the bovine as a means of ascertaining its suitability as a systemically administered drug in mastitis therapy.

Aspirin

The recent finding that the anti-inflammatory activity of aspirin may be due to its inhibitory effect on prostaglandin synthetase (27) has stimulated renewed interest in the therapeutic properties of this drug. Because of its potential therapeutic value in combating the effects of endotoxins associated with gram-negative infections, aspirin has been suggested as a part of the therapeutic regimen in coliform mastitis (22). Comparative pharmacokinetic analyses of salicylates in various domestic species clearly indicate, however, that the "therapeutic" dosage of aspirin is vastly different from species to species (12). Indeed, pharmacokinetic data extrapolated from the pony and the goat would suggest that aspirin could not possibly be of therapeutic benefit in the cow because of the likelihood of very poor absorption from the rumen and because of its predictably short plasma half-life.

Clinical realities, however, suggested otherwise, which stimulated interest in the following studies conducted at the Ohio State University Veterinary Hospital (17):

Suitable Concentration: The minimum plasma salicylate concentrations which result in relief of minor aches and pains in man are 30 to 60 μg/ml (13). Since there is little reason to doubt that the tissue/plasma ration and receptor sensitivity would differ significantly in cattle as compared to other species, 30 μg/ml in serum was chosen as a therapeutic goal.

At the Site of Action: The working hypothesis accepted for these studies was that the pharmacologic effects of salicylates depend on the concentration of the drug at some site(s) of action and that the concentration at these sites is related to its concentration in serum. Achieving therapeutic concentrations of

salicylates in serum, therefore, would result in suitable concentrations at the receptor site(s).

For a Suitable Period of Time: Plasma salicylate concentrations vs. time following administration of different dosages by different routes to cattle were analysed to determine the duration of effect of a single treatment and to calculate a proper dosage interval.

When sodium salicylate was given to six normal cows intravenously at a dosage of 50 mg/kg, the salicylate was eliminated very rapidly from the serum (Figure 1). The mean serum half-life, T½, was 32 minutes which is even shorter than that found in goats (12). Salicylate concentrations in excess of 30 μg/ml did, however, persist in serum for around 90 minutes.

Single oral dosages of aspirin tablets given to three normal cows at the rate of 100 mg/kg resulted in serum salicylate concentrations above 30 μg/ml within 1½ hours, whereas dosages of 50 mg/kg resulted in plasma concentrations consistently below this minimum (Figure 2). From these data, an apparent elimination half-time of 3.7 hours was calculated.

After repeated oral administration of aspirin at 12-hour intervals in cows, steady-state concentrations of salicylate in serum were achieved which exceeded 30 μg/ml when 100 mg/kg were given but consistently fell short of 30 μg/ml when 50 mg/kg were given (Figure 3).

Conclusions From Aspirin Studies: If aspirin is to be given to cows as a part of the therapeutic regimen for mastitis, 100 mg/kg (70 gr/100 lb.) given orally at 12-hour intervals is an appropriate dosage. Steady-state serum concentrations in excess of 30 μg/ml will be maintained by this regimen despite the slow absorption and rapid elimination of the drug.

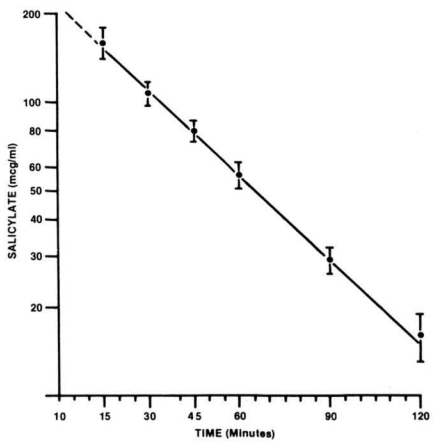

Figure 1: Semilogarithmic plot of salicylate concentration (mean ± 1 standard deviation, n = 6) in serum after rapid intravenous injection of sodium salicylate at a dosage of 50 mg/kg in normal cows. (Figures 1, 2 and 3 were reproduced from Gingerich, D. A., Baggot, J. D., and Yeary, R. A., JAVMA, 167:945-948, 1975, with permission.)

Tylosin

Tylosin is an antibiotic of the macrolide group which is a highly lipid-soluble organic base (pKa = 7.1) with only a moderate degree of protein binding. These properties would suggest that the drug would be widely distributed in the body and may, therefore, show promise as a systemically administered drug for the treatment of mastitis (16).

Suitable Concentration: As a first approximation in the determination of a suitable concentration of tylosin, a modified Kirby-Bauer disc susceptibility survey was conducted using cultures of various microorganisms isolated from clinical patients at the Ohio State University Veterinary Hospital. Organisms which showed zones of inhibition around the 30 μg discs included β hemolytic streptococci, *Staphylococcus aureus, Pasteurella spp.,* and *Corynebacterium pyogenes.* Disc-susceptible organisms were then tested by the tube dilution method to determine the minimum inhibitory concentration (MIC). All disc-susceptible organisms were found to be sensitive to tylosin at <1 μg/ml except for *Pasteurella spp.* for which the MIC was 12.5 μg/ml (Figure 4). On the basis of the MIC data, 1 μg/ml was tentatively selected as a suitable concentration of tylosin, with *Pasteurella spp.* eliminated from the list of susceptible organisms and *Mycoplasma spp.* (shown in other studies to be highly susceptible to tylosin (21) added to the list.

Pharmacokinetics of Tylosin in Cows: The concentration-time curve following a single intravenous dosage of tylosin at the rate of 12.5 mg/kg illustrates a distribution phase followed by an elimination phase (Figure 5). From data obtained from six cows, a mean T½ of 1.62 ± 0.17 hours and a mean apparent specific volume of distribution (V'd) of 1.10 ± 0.45 L/kg were calculated (5). These values indicate that tylosin is rapidly eliminated from the serum and suggest that the drug is widely distributed in the body.

Following intramuscular injection at a dosage of 12.5 mg/kg, concentrations of tylosin in serum seldom reached 1 μg/ml in serum and declined to very low levels within 12 hours (Figure 6).

Tylosin Concentrations in Milk: Tylosin was detected in milk within 15 minutes after intravenous

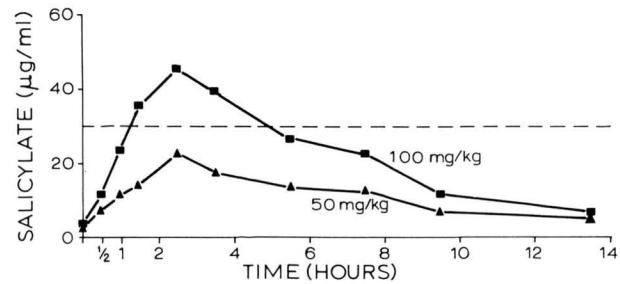

Figure 2: Mean salicylate concentration in serum after oral administration of aspirin tablets at a dosage of 50 mg/kg (▲) to 3 cows and at a dosage of 100 mg/kg (■) to 3 cows. Broken line indicates estimated minimum effective concentration.

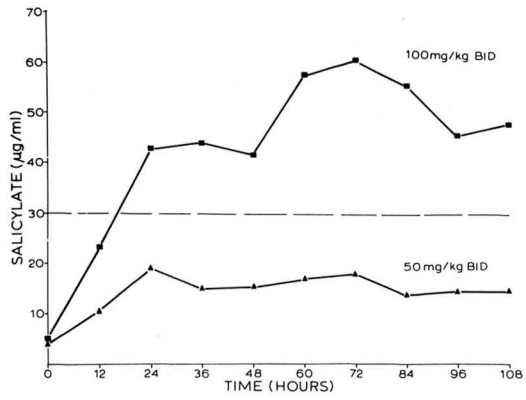

Figure 3: Mean salicylate concentration in serum after oral administration of aspirin tablets at a dosage of 50 mg/kg (▲) every 12 hours to 3 cows and at a dosage of 100 mg/kg (■) every 12 hours to 3 cows. Broken line indicates estimated minimum effective concentration.

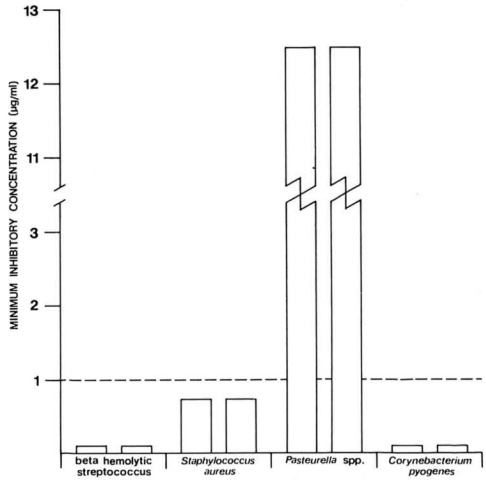

Figure 4: Minimum inhibitory concentration of tylosin for representative cultures of various disc-susceptible microorganisms isolated from cattle. (Figures 4, 6, 7 and 8 were reproduced from Gingerich, D. A., Baggot, J. D., and Kowalski, J. J., Can. Vet. J. 18:96-100, with permission.)

dosage in a lactating, non-mastitic cow (Figure 7). Drug concentration in milk exceeded its concentration in serum at 90 minutes after dosage and remained approximately fivefold higher throughout the sampling period. In subsequent studies, tylosin administered intramuscularly at the rate of 12.5 mg/kg at 12-hour intervals to three lactating cows resulted in progressively higher concentrations in milk following each dosage (Figure 8).

Conclusions From Tylosin Studies: The antimicrobial spectrum of tylosin includes some of the major pathogens of the bovine udder: β hemolytic streptococci, *Staphylococcus aureus, Corynebacterium pyogenes,* and *Mycoplasma spp.*, all of which are susceptible at concentrations <1 μg/ml. Tylosin diffuses readily into milk and achieves concentrations several-fold higher in normal milk than in serum. If high concentrations of antibiotic in milk are of therapeutic significance, then adequate doses of tylosin given intramuscularly at 12-hour intervals, would be a rational choice of antibiotic for the treatment of mastitis due to the above pathogens, although clinical studies in support of this statement are lacking.

Erythromycin

Erythromycin, another macrolide antibiotic, is a lipid-soluble organic base (pKa = 8.8) which is only moderately bound by serum proteins and thus, like tylosin, would be expected to be widely distributed in the body.

Suitable Concentration: The author is unaware of quantitative data on the sensitivity of animal pathogens to erythromycin. However, erythromycin is said to be effective against many gram-positive organisms (18) and a drug sensitivity survey of frequently isolated bacteria compiled at the University of Illinois Diagnostic Laboratory by Dr. H. E. Rhodes (1976) suggested that erythromycin has the same general susceptibility pattern as tylosin. A minimum concentration of 1 μg/ml serves as a tentative estimate of suitable concentration.

Pharmacokinetics of Erythromycin in Cows: The general shape of the concentration-time curve following single intravenous dosage of erythromycin at the rate of 12.5 mg/kg (Figure 9) was similar to the tylosin curve. From data obtained in six cows, a mean T½ of 3.16 ± 0.44 hours and a mean V'd of 0.79 ± 0.18 L/kg, were calculated (5) which suggests that erythromycin is somewhat more slowly eliminated than is tylosin but is also widely distributed. Intramuscular injection at the rate of 12.5 mg/kg resulted in erythromycin concentrations of around 1 μg/ml in serum throughout most of the 24 hours following treatment (Figure 10).

Erythromycin Concentrations in Milk: Erythromycin activity was detected in milk within two hours after intramuscular injection of 12.5 mg/kg to three normal lactating cows (Figure 11). Drug concentrations in milk were several-fold higher than the concentrations measured in serum at the same sampling times. A 24-hour dosage interval was sufficient to maintain erythromycin concentrations in excess of 1 μg/ml in milk.

Conclusions From Erythromycin Studies: Erythromycin is concentrated in the milk of normal cows and has the distinct advantage over tylosin in that its slower elimination permits maintenance of reasonable concentrations in milk for 24 hours following each intramuscular dosage. However, quantitative data on its antimicrobial activity is lacking and, as in the case of tylosin, the therpeutic value of systemically administered erythromycin for the treatment of mastitis has not been tested in clinical trials.

Kanamycin

Kanamycin is one of the drugs of the aminoglycoside group of antibiotics (others include streptomycin, neomycin, gentamycin, etc.). Interest in kanamycin in cows was based on the fact that it is an organic base (pKa approximately 7.8) that is less than 10% bound by serum proteins (32).

Suitable Concentration: Recently published data on the susceptibility of gram-negative organisms to kanamycin indicate that concentrations of 25 μg/ml or more are required to inhibit a significant proportion of cultures of *E. coli* (30). In studies of a limited number of isolates at the Ohio State University, it was found that the MIC of kanamycin was less than 6.25 μg/ml for a few strains of *E. coli* and most strains of staphylococci and klebsiellae studied. These findings indicate that kanamycin may have some therapeutic promise in the treatment of mastitis due to the above udder pathogens **if** concentrations of 5 to 25 μg/ml can be achieved.

Pharmacokinetics of Kanamycin in Cows: To determine the half-life and volume of distribution, a single dosage of kanamycin *(Kantrim*, Bristol Myers, Inc., Syracuse, N.Y. Supplies of the drug and financial support through Dr. George J. Christie of the Bristol Myers Company is gratefully acknowledged.)* was given by rapid intravenous injection at the rate of 10 mg/kg to six normal cows. Blood samples were collected at intervals after dosage and, at a later time, were analysed for kanamycin activity microbiologically by the cylinder cup method (1). The kanamycin concentration-time curve following intravenous administration, in comparison with tylosin and erythromycin curves, shows a less pronounced distribution phase (Figure 12). A mean T½ of 2.9 ± 0.7 hours and a mean V'd of 0.30 ± 0.09 L/kg were calculated. The diminished distribution phase in the concentration-time curve together with the rather low calculated volume of distribution suggests that kanamycin is not widely distributed in cows.

Single intramuscular injections of the same dosage to six cows resulted in rapid absorption to a mean peak of nearly 16 μg/ml within one hour, followed by a steady decline in concentration to barely detectable levels within 12 hours (Figure 13). Multiple intramuscular injections at 12-hour intervals to three cows resulted in progressively higher peak concentrations of kanamycin with each succeeding dose but the drug was completely eliminated within each 12-hour time period (Figure 14).

Kanamycin Concentratoins in Milk: In one lactating cow given a single intravenous dose of kanamycin at the rate of 10 mg/kg, low concentrations of the drug were detected in milk two hours after dosage. Drug concentrations in milk peaked at only 1.32 μg/ml at 4½ hours. Kanamycin was barely detectable in milk samples collected after intramuscular injection at 12-hour intervals. Neglibible concentratoins of kanamycin in milk following parenteral dosage are not surprising in light of the similar results found by other workers in cows and ewes (33). The best explanation for this finding is that kanamycin, like other aminoglycosides, is not lipid-soluble and therefore does not readily penetrate intact biological membranes.

Conclusions on Kanamycin Studies: Since kanamycin does not really penetrate the blood-milk

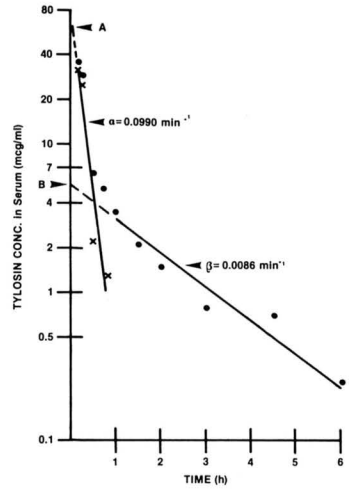

Figure 5: Semilogarithmic plot of tylosin activity in serum following intravenous administration at a dosage of 12.5 mg/kg in 1 cow. Calculations of various kinetic parameters are shown. (Figures 5 and 9 were reproduced from Baggot, J. D., and Gingerich, D. A., Res. Vet. Sci., 21:318-323, 1976, with permission.)

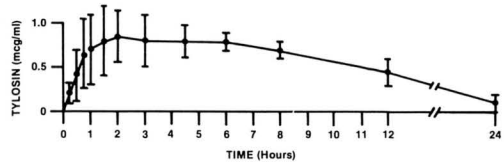

Figure 6: Tylosin activity in serum (mean ± 1 standard deviation) following intramuscular injection at a dosage of 12.5 mg/kg in 6 cows.

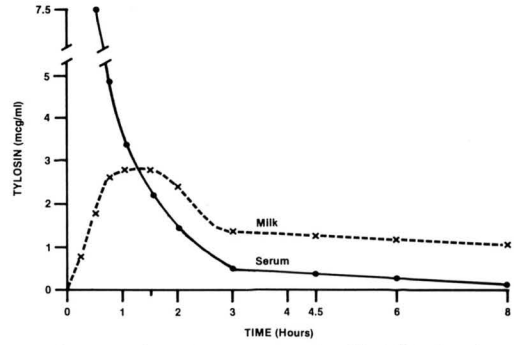

Figure 7: Tylosin activity in serum and milk following intravenous injection at a dosage of 12.5 mg/kg in 1 cow.

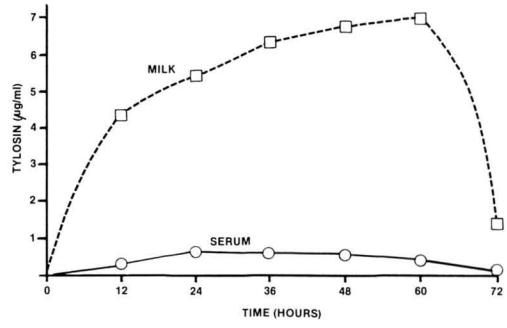

Figure 8: Tylosin activity in serum and milk following intramuscular injection at a dosage of 12.5 mg/kg at 12-hour intervals for 48 hours (mean data from 3 cows).

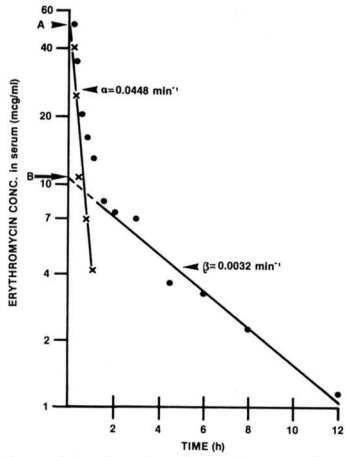

Figure 9: Semilogarithmic plot of erythromycin activity in serum following intravenous administration at a dosage of 12.5 mg/kg in 1 cow. Calculations of various kinetic parameters are shown.

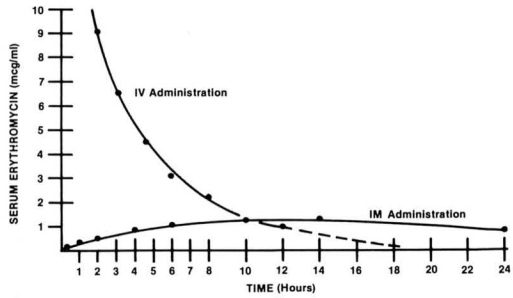

Figure 10: Erythromycin activity in serum following intravenous administration at a dosage of 12.5 mg/kg in a cow and following intramuscular administration of the same dosage at a later time to the same cow.

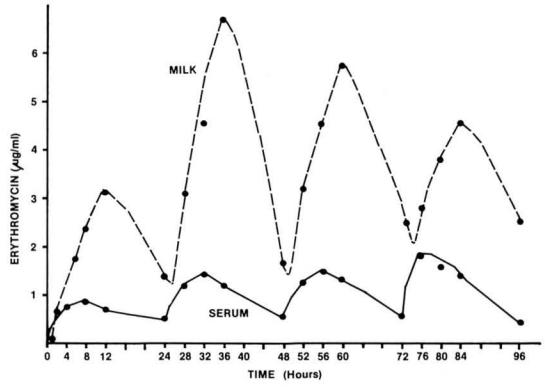

Figure 11: Erythromycin activity in serum and milk following intramuscular injection at a dosage of 12.5 mg/kg at 24-hour intervals for 72 hours (mean data from 3 cows).

barrier (at least in normal cows), it would appear to be a very poor choice of antibiotic for the systemic treatment of mastitis. Any therapeutic value of kanamycin as well as other aminoglycosides in mastitis therapy would likely be derived only from the intramammary infusion of the antibiotics in appropriate vehicles.

Other Antimicrobial Drugs

Other drugs which are frequently used systemically in the treatment of mastitis include the sulphonamides, tetracyclines and less commonly, chloramphenicol.

The sulphonamides generally behave as weak organic acids (9) and therefore, according to the nonionic passive diffusion theory, tend to achieve lower concentrations in normal milk than in plasma (26,24). Different sulphonamides vary with regard to their pK as well as degree of protein binding, which results in differences in distribution characteristics. A serious shortfall in current knowledge of sulphonamide clinical pharamcology stems from the fact that the value of 5 mg/100 ml which is accepted as the "therapeutic level" of sulphonamides has remained unchallenged, despite the introduction of new sulphonamides with widely differing chemical and biological characteristics. It is difficult to know whether "suitable concentrations" of sulphonamides can be achieved in the mammary gland following systemic administration since updated, quantitative data on the susceptibility of udder pathogens to the various sulphonamides is lacking.

The tetracycline antibiotics are generally rather well distributed to the mammary gland following systemic administration. The exact mechanism for their passage into milk is not known and analyses are complicated by the fact that tetracyclines are amphoteric and that different tetracycline derivatives differ with respect to their lipid solubility and extent of protein binding (31). Concentrations of tetracylcine in milk which are approximately equivalent to those achieved in serum can be expected following parenteral dosage.

Chloramphenicol is also an organic base (3) which is apparently widely distributed in ruminants as well as other species (11). Whether or not chloramphenicol is concentrated in extravascular compartments of the body in a therapeutically useful form is uncertain (23). One case of acute coliform mastitis was treated successfully by the author by intravenous injection of chloramphenicol at a dosage of 30 mg/kg at eight-hour intervals. (This cow was also given aspirin orally at a dosage of 100 mg/kg every 12 hours.) In light of the prohibitive costs of such high dosages, the lack of FDA approval for use in cattle, and the uncertainties regarding distribution, chloramphenicol should probably be avoided as a systemically administered drug for mastitis therapy.

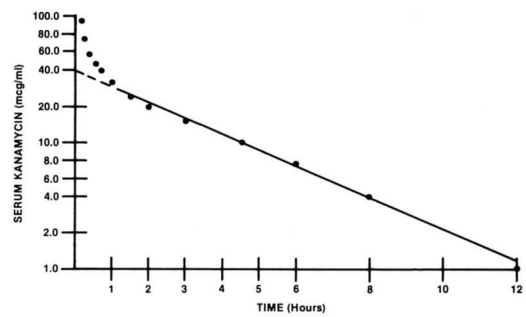

Figure 12: Semilogarithmic plot of kanamycin activity in serum following intravenous administration at a dosage of 10 mg/kg (mean data from 6 cows).

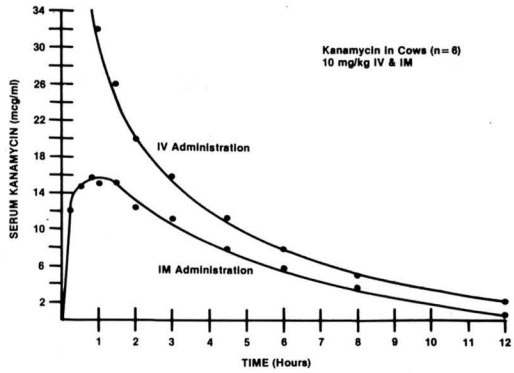

Figure 13: Mean kanamycin activity in serum following intravenous administration at a dosage of 10 mg/kg in 6 cows and following intramuscular administration at the same dosage at a later time to the same 6 cows.

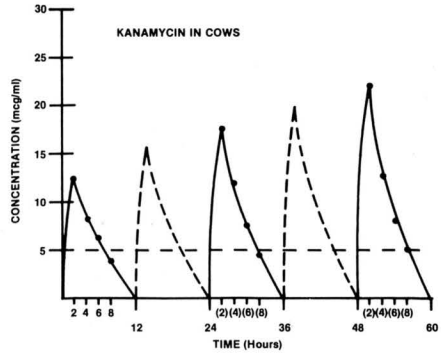

Figure 14: Kanamycin activity in serum following intramuscular injection at a dosage of 10 mg/kg at 12-hour intervals for 48 hours (mean data from 3 cows). Dotted portions indicate presumed shape of curves during times when actual measurements were not made. Milk samples were also assayed and kanamycin activity was found to be negligible at all sampling times.

Discussion and Conclusions

In the foregoing discussion, emphasis has been placed only on the efficacy of the drugs presented. It must be remembered that toxicity to the host animal is another equally important component of the therapeutic equation. Adhering to the dosage schedules recommended on the labels of marketed products may not always achieve the desired therapeutic effects, but will almost invariably ensure safety to the animal and compliance with drug withdrawal requirements. The use of non-approved products or altering the dosage or route of administration of approved products, as we have done experimentally, must be approached with due caution, particularly in food-producing animals.

Drugs are distributed to the extravascular spaces of the body according to physico-chemical laws of non-ionic, passive diffusion of drug molecules across biological membranes. Drugs differ with respect to their ability to penetrate biological membranes such as the blood-milk barrier, largely because of their differing chemical properties. Generally speaking, those drugs which are highly lipid-soluble, largely non-ionized at the pH of plasma and not extensively bound by plasma proteins, diffuse readily into milk. The key to successful systemic therapy for bovine mastitis is likely to be in the use of drugs which are adequately distributed to the mammary gland.

The macrolide antibiotics, including tylosin, erythromycin, etc., are lipid-soluble, weak organic bases which tend to achieve higher concentration in normal milk than in plasma under equilibrium conditions. Although they would not theoretically concentrate to such a great extent in mastitic milk of higher pH, the macrolides would, from a pharmacologic point of view, be a rational choice of antibiotic for the systemic treatment of mastitis due to susceptible pathogens.

Drugs of the penicillin family and of the sulphonamide family behave as weak organic acids and, therefore, tend not to achieve high concentrations in normal milk. These drugs also vary tremendously with respect to their degree of protein binding and other chemical characteristics which affect distribution. Organic acids would, however, theoretically achieve higher concentrations in mastitic milk of higher pH than in normal milk. The penicillins should be avoided as systemic treatment for mastitis, although their therapeutic value in intra-mammary infusion is undisputed. Certain sulphonamides may have some therapeutic potential for mastitis therapy but concentration in the udder is not one of their favorable pharmacologic attributes.

The tetracyclines are amphoteric compounds which distribute quite well to the mammary gland, for reasons which are not entirely clear.

The aminoglycosides (streptomycin, kanamycin, neomycin, gentamycin, etc.) are organic bases but are very poorly distributed to the mammary gland probably because of their low lipid solubility. Any therapeutic value derived from these antibiotics would likely depend on local intramammary infusion rather than systemic administration.

References

1. Arret, B., Johnson, D. P., and Kirshbaum, A.: Outline of Details for Microbiological Assays of Antibiotics: Second Revision. J. Pharmac. Sci. 60 (1971):1689. - 2. Baggot, J. D.: An Introduction to Principles of Veterinary Clinical Pharmacology: General Principles. New Zealand Vet. J. 21 (1973):207. - 3. Baggot, J. D.: Disposition and Fate of Drugs in the Body. In Veterinary Pharmacology and Therapeutics. 4th ed. Edited by L. Meyer Jones, Nicholas H. Booth and Leslie E. McDonald. The Iowa State University Press, Ames, Iowa (1977):43. - 4. Baggot, J. D.: Principles of Drug Distribution. Aust. Vet. J. 50 (1974):111. - 5. Baggot, J. D., and Gingerich, D. A.: Pharmacokinetic Interpretation of Erythromycin and Tylosin Activity in Serum After Intravenous Administration of a Single Dose to Cows. Res. Vet. Sci. 21 (1976):318. - 6. Bailey. W. R., and Scott, E. G.: Diagnostic Microbiology. 4th Ed. The C. V. Mosby Company, St. Louis, Missouri (1974):314. - 7. Barker, C. A. V.: Observations on the Use of Penicillin in the Treatment of Bovine Mastitis. Can. J. Comp. Med. 9 (1945):235. - 8. Barker, C. A. V., and Dussault, H. P.: Observations on the Permeability of the Lactating Mammary Gland to Penicillin. Can. J. Comp. Med. 9 (1945):332. - 9. Bevill, R. F., and Huber, W. G.: Sulphonamides. In Veterinary Pharmacology and Therapeutics, 4th ed. Edited by L. Meyer Jones, Nicholas H. Booth, and Leslie E. McDonald. The Iowa State University Press, Ames, Iowa (1977):894. - 10. Bryan, C. S., Horwood, R. E., and Huffman, C. F.: A Preliminary Report on Penicillin in the Treatment of Chronic Streptococci Mastitis. Vet. Med. 40 (1945):87. - 11. Davis, L. E., Neff, C. A., Baggot, J. D.,

and Powers, T. E.: Pharmacokinetics of Chloramphenicol in Domesticated Animals. Am. J. Vet. Res. 33 (1972):2259. - 12. Davis, L. E., and Westfall, B. A.: Species Differences in the Biotransformation and Excretion of Salicylate. Am. J. Vet. Res. 33 (1972):1253. - 13. Davison, C.: Salicylate Metabolism in Man. Ann. N. Y. and Acad. Sci., 149 (1971):249. - 14. Dodd, F. H., Westgarth, D. R., and Griffin, T. K.: Strategy of Mastitis Control. JAVMA, 170 (1977):1124. - 15. Food and Drug Administration: Standardized Disc Susceptibility Test. Fed. Reg. 37 (1972):20527. - 16. Gingerich, D. A., Baggot, J. D., and Kowalski, J. J.: Tylosin Antimicrobial Activity and Pharmacokinetics in Cows. Can. Vet. J. 18 (1977):96. - 17. Gingerich, D. A., Baggot, J. D., and Yeary, R. A.: Pharmacokinetics and Dosage of Aspirin in Cattle. JAVMA 167 (1975):945. - 18. Huber, W. G.: Streptomycin, Chloramphenicol, and Other Antimicrobial Agents. In Veterinary Pharmacology and Therapeutics 4th ed. Edited by L. Meyer Jones, Nicholas H. Booth, and Leslie E. McDonald. The Iowa State University Press, Ames, Iowa (1977):953. - 19. Kakavas, J. C.: Penicillin in the Treatment of Bovine Mastitis, A Preliminary Report. North Amer. Vet. 25 (1944):408. - 20. Linton, A. H.: The Antibiotic Sensitivity Testing of Pathogens Commonly Found in Veterinary Practice. Vet. Rec. 99 (1976):370. - 21. McGuire, J. M., Boniece, W. S., Higgins, C. E., Hoehn, M. M., Stark, W. M., Westhead, J., and Wolfe, R. N.: Tylosin, a New Antibiotic: I Microbiological Studies. Antibiot. Chemother. 11 (1961):320. - 22. Mercer, H. D., and Teske, R. H.: Special Consideration for the Development of Drugs for Acute Clinical Mastitis. JAVMA 170 (1977):1190. - 23. Pilloud, M.: Pharmacokinetics, Plasma Protein Binding and Dosage of Chloramphenicol in Cattle and Horses. Res. Vet. Sci. 15 (1973):231. - 24. Rasmussen, F.: Mammary Excretion of Sulphonamides. Acta. Pharamcol. Toxicol. 15 (1958):139. - 25. Seely, H. W., Anderson, E. O., Plastridge, W. N., and Pearson, P.: Non-Permeability of the Lactating Bovine Mammary Gland to Penicillin. Science, 102 (1945):44. - 26. Stowe, C. M., and Sisodia, C. S.: The Pharmacologic Properties of Sulfadimethoxine in Dairy Cattle. Am. J. Vet. Res. 24 (1963):525. - 27. Vane, J. R., Inhibition of Prostaglandin Synthesis As a Mechanism of Action for Aspirin-like Drugs. Nature New Biol. 231 (1971):232. - 28. Watts, P. S., and McLeod, D. H.: The Estimation of Penicillin in Blood Serum and Milk of Bovines After Intramuscular Injection. J. Comp. Path. 56 (1946):170. - 29. Welsh, M., Langer, P. H., Burkhart, R. L., and Schroeder, C. R.: Penicillin Blood and Milk Concentrations in the Normal Cow Following Parenteral Administration. Science, 108 (1948):185. - 30. Ziv, G.: Comparative Clinical Pharmacology of Amikacin and Kanamycin in Dairy Calves. Am. J. Vet. Res. 38 (1977):337. - 31. Ziv, G., and Sulman, F. G.: Analysis of Pharmacokinetic Properties of Nine Tetracycline Analogues in Dairy Cows and Ewes. Am. J. Vet. Res. 35 (1974):1197. - 32. Ziv, G., and Sulman, F. G.: Binding of Antibiotics to Bovine and Ovine Serum. Antimicrob. Agents Chemother. 2 (1972):206. - 33. Ziv, G., and Sulman, F. G.: Distribution of Aminoglycoside Antibiotics in Blood and Milk. Res. Vet. Sci. 17 (1974):68.