Clinical Considerations Regarding Drug Interactions in the Bovine Patient

John W. Paul, *D.V.M., M.S.*
Pharmaceutical Research & Development Div.
Fort Dodge Laboratories
Fort Dodge, Iowa 50501

The subject of drug interactions should embrace at least three facets: (1) Interaction of two or more drugs resulting in an unexpected response in the patient. This is often an antagonistic response; however, occasionally a synergistic response may occur; (2) Interaction of one or more drugs with physiological processes in the patient often considered to be adverse reactions; (3) An interaction of one or more drugs with laboratory tests, either *in vivo* as a result of the drug(s) altering physiological and/or enzyme systems, or *in vitro* as a result of the drug(s) interfering with the chemical reaction of the test.

At least 1,300 drug interactions have been documented (21) and there are undoubtedly more that have not been reported or recognized. Obviously, it is improbable to remember all drug interactions that are known to have occurred in the bovine species. However, with the benefit of an awareness and understanding of drug interactions, one can formulate a conceptual perspective of the subject.

In an attempt to focus attention on the categories of drugs most commonly used in the bovine patient, reference is made to a report of a drug usage survey conducted in the Veterinary Ambulatory Service at the University of Minnesota in 1967 (19):

Table 1
Drug Usage Survey

Class of Drug	% of Total Use	
Antibiotics	38	
Sulfonamides	6	
Nitrofurans	4	
Total antimicrobials:		48
Anthelmintics		15
Hormones		12
Topicals		7
Analgesics	2	
Tranquilizers	2	
Anesthetics	2	
Total psychotropics:		6
Gastro-intestinal		5
Antihistamines & autonomic		2
Others		5
Total		100

Considering the above reported drug usage patterns, this paper will discuss drug interactions in the bovine involving antimicrobials, antiparasitics and hormones of the corticosteroid variety.

Physical and Chemical Aspects of Combining Drugs in vitro

In vitro drug incompatibilities may properly be classified as iatrogenic drug interactions. There may be some justifiable reasons for extemporaneous mixtures of drugs, including economy of time, convenience and avoiding multiple injection sites. However, the reasons for not mixing drugs *in vitro* should be given serious consideration. Certainly, an important reason for refraining from extemporaneous drug mixtures is the possibility of inactivating one or more of the active ingredients. Visible signs of *in vitro* incompatibility or inactivation include precipitation, colloidal formation, color changes or gas formation (20). It should be remembered that some reactions may occur that are invisible but nevertheless may render an active ingredient inactive. For instance, certain sulfonamides and penicillins are incompatible due to the fact that the high pH of sulfas will inactivate the penicillins (14,20). Unfortunately, this interaction is not grossly observable in the vial. It would be advantageous to consult with a pharmacist before mixing drugs *in vitro*.

Table 2 lists *in vitro* incompatibilities of some of the drugs more commonly used in bovine therapeutics (1,8,20).

Drug Interactions with Laboratory Tests

An extremely important and often overlooked aspect of drug interaction involves the alteration of blood chemical, hematological and urological tests. These abnormal test results may be due to pathology or enzyme alteration induced by a drug(s). For instance, Amphotericin B is known to be nephrotoxic and elevated BUN values could be expected to occur. A recent report (22) describes pronounced elevation of blood glucose following treatments of cattle with xylazine. Another source of abnormal test results is a chemical interaction of a drug with the test procedure. Mia, et al. (12), have reported the variance of several blood chemistry determinations as related to the different anticoagulants used to treat the blood sample. In essence, sound clinical judgment must be applied to the interpretation of laboratory

Table 2
In Vitro Drug Incompatibilities

Drug	Incompatible with
Ampicillin	Do not mix with other drugs.
Acepromazine	Chloramphenicol, phenylbutazone, sulfonamides
Calcium gluconate	Sodium bicarbonate, tetracyclines phenylbutazone, sulfonamides
Chloral Hydrate	Alkaline solutions
Chloramphenicol	Erythromycin, hydrocortisone, tetracycline, procaine, vitamin B complex
Erythromycin	Hydrocortisone, penicillin G, streptomycin, chloramphenicol
Hydrocortisone	Chloramphenicol, erythromycin, kanamycin, promazine, tylosin, tetracyclines
Levamisole	Neomycin, phenylbutazone, sulfonamides, tetracyclines
Penicillin G	Sulfonamides, erythromycin
Sulfonamides	Acepromazine, calcium gluconate, dextrose, kanamycin, penicillin G, procaine, tylosin
Tetracyclines	Many solutions
Tylosin	Hydrocortisone, tetracycline, streptomycin, sulfonamides
Vitamin B Complex	Many solutions, esp. antibiotics

test results when the patient is under medication or when the blood sample has been treated with substances such as anticoagulants.

Much of the present knowledge concerning interactions of drugs with laboratory tests is derived from the human literature. More work is needed to investigate possible interactions with some of the drugs more commonly used in veterinary therapeutics. Some commonly used drugs and their interactions with some laboratory tests are tabulated (Table 3). For additional information please see the indicated references (1,10,11,12).

Interactions of Antimicrobial Drugs

Combinations of Antimicrobial Drugs: Several years ago Jawetz (6,7) proposed a scheme whereby antimicrobial drugs were placed in one of two groups: (1) bacteriocidal agents, including penicillins, streptomycin, neomycin, bacitracin and polymixin, or (2) bacteriostatic agents, including tetracyclines, chloramphenicol, erythromycin, novabiocin and sulfonamides. Synergism was found to occur *in vitro* rather frequently among members of Group 1, but infrequently among members of Group 2. Also, if an organism was killed rapidly by a member of Group 1, addition of a Group 2 drug could result in antagonism. But if an organism was killed slowly by a Group 1 drug, the addition of a drug from Group 2 might result in synergism.

Since Jawetz proposed his scheme, regrettably many have taken it as a law. Jawetz never intended the scheme to be a clinical guide for combined antimicrobial therapy, but only as a laboratory framework. In reality, synergism or antagonism of

Table 3:
Effect of Drugs on Laboratory Tests

Drug	Laboratory Tests
Anabolic Steroids	Increased: Alkaline phosphatase, BSP, calcium, bilirubin, SGOT, SGPT, prothrombin time, cholesterol Decreased: Glucose
Ampicillin	Increased: SGOT, leukocyte count Decreased: None
Chloral Hydrate	Increased: BUN, urine glucose Decreased: Prothrombin time
Chloramphenicol	Increased: Alkaline phosphatase, bilirubin, SGOT, SGPT Decreased: Erythrocyte, leukocyte and thrombocyte counts, urobilinogen
Corticosteroids	Increased: Bilirubin, glucose, cholesterol, sodium, urine RBC, chloride Decreased: Uric acid, coagulation time, leukocyte count, prothrombin time
Erythromycin	Increased: Alkaline phosphatase, bilirubin, prothrombin time, SGOT, SGPT, leukocyte count Decreased: None
Furosemide	Increased: BUN, glucose, uric acid Decreased: Sodium, potassium, leukocyte count
Neomycin	Increased: BUN, urine casts, urine protein Decreased: Cholesterol
Penicillin	Increased: Alkaline phosphatase, potassium, protein, Coomb's test, urine glucose, urine protein Decreased: Erythrocyte and leukocyte counts
Phenothiazines	Increased: Alkaline phosphatase, bilirubin, cholesterol, SGOT, SGPT, leukocyte count, urine bilirubin, reddish urine Decreased: Protein bound iodine
Phenylbutazone	Increased: Bilirubin, chloride, sodium, prothrombin time, urine hemoglobin and erythrocyte count Decreased: Protein bound iodine, uric acid, erythrocyte, leukocyte and thrombocyte counts
Sulfonamides	Increased: Amino acids, bilirubin, SGOT, leukocyte count, prothrombin time, urine crystals, brownish urine, urine glucose, urine protein, urine erythrocytes Decreased: Protein bound iodine, erythrocyte and thrombocyte counts
Tetracyclines	Increased: BUN, phosphate, coagulation time, leukocyte count, prothrombin time, urine glucose, urine protein Decreased: Calcium, potassium
Thiabendazole	Increased: Chloride, glucose, SGOT Decreased: Leukocyte count
Xylazine	Increased: Glucose, urine glucose Decreased: Unknown

combinations of antimicrobial drugs depends upon the specific organism and the specific combination of drugs.

Finally, one must consider the duration of therapeutic activity of the components of a drug combination. For example, if procaine penicillin G has a therapeutic duration of 24 hours and dihydrostrepto-

mycin provides therapeutic blood levels for 12 hours (23), one must ponder this question: At what interval should this particular drug combination be administered?

Bacterial Resistance to Antimicrobial Drugs: The emergence of organisms resistant to various antimicrobial agents is of serious concern. The frequency of occurrence of resistance to a particular antimicrobial drug usually reflects the extent of usage of that compound (14). Indiscriminate use of antimicrobial drugs has surely contributed to the prevalence of resistant bacteria. Some of these indiscretions include: extensive prophylactic use, less than adequate doses, excessive intervals between doses, too short a duration of therapy and failure to rotate antimicrobial drugs in therapy (14,18). The low level use of antimicrobial drugs in animal feeds is a controversial subject, but has probably played a role in the development of bacterial resistance. Siegel, et al. (17), have reported a marked increase in incidence of resistant bacteria isolated from Illinois livestock that had been fed medicated feed as compared to the low incidence of resistant bacteria originating in range-fed Montana stock that had not received medicated feed.

Tetracycline: The tetracyclines are inhibitors of protein synthesis. This action can result in an antianabolic effect with an elevated BUN and impaired synthesis of various endogenous proteins such as prothrombin (4,14). Hence, interactions of tetracyclines with other drugs, such as anticoagulants, could produce serious impairment of blood-clotting mechanisms. Some suspicion exists as to inhibition of antibody synthesis. However, this has yet to be proven.

Tetracyclines are chelated by various bivalent and trivalent cations, such as calcium, magnesium, aluminum and iron. Milk products, antacids, calcium gluconate and other compounds containing these cations can render tetracycline inactive (4,14).

A neuromuscular blocking effect and reduced cardiac output accompanied by hypotension can occur as a result of tetracycline therapy. This is probably due to an interaction with calcium (2).

Oral administration of therapeutic doses of tetracycline can cause an alteration of gastrointestinal flora and hence interfere with rumen function. There is an indication that even after parenteral administration, tetracycline can exert an effect on gastrointestinal flora. Suprainfections are known to occur as a result of tetracycline therapy (4,18).

In general, solutions of oxytetracycline are irritating to tissue, and, following intramuscular injection, severe tissue damage may occur. Rapid intravenous administration of oxytetracycline can cause muscular weakness and collapse.

Chloramphenicol: Although this chemotherapeutic agent is not approved by the Food and Drug Administration for use in food-producing animals, there is good reason to believe that a considerable quantity of this antibiotic is used in the bovine animal. With that in mind, it may be worthwhile to mention a few points regarding chloramphenicol.

Certain hepatic microsomal enzymes are inhibited by chloramphenicol. These same enzymes are responsible for the bio-transformation of several other drugs, notably the barbiturates. The interaction of chloramphenicol and the barbiturates has been shown to result in prolonged activity of the barbiturates (2).

Chloramphenicol interferes with protein synthesis (14) and there is a suggestion that antibody synthesis is retarded (4). If this is true (all of the answers are not known as yet), chloramphenicol would be a poor choice of drug to use preceding or concurrently with immunization procedures.

It has been reported that chloramphenicol is inactivated by rumen contents (5). Therefore, oral administration of chloramphenicol to a ruminant that has developed a functional rumen would appear to be unwise.

Aminoglycosides (Neomycin, Streptomycin, Kanamycin, Gentamicin): The aminoglycosides are neuro-muscular blocking agents. This occurs via inhibition of calcium and competitive blockade of skeletal muscle receptors (2). This effect is additive among members of this group of antibiotics. Other drugs which possess neuro-muscular blocking effects are also additive in this respect to the aminoglycosides. Due to a probable inhibition of calcium, the aminoglycosides are capable of exerting cardiovascular depression resulting in decreased cardiac output and hypotension (2).

The aminoglycosides are not absorbed to any extent from the gastrointestinal tract (4,14). Therefore, one would not expect significant systemic activity following oral administration of this group of antibiotics.

Penicillins (Procaine Penicillin G, Benzathine Penicillin G, Ampicillin, etc.): The penicillins are known to induce anaphylactoid reactions in hypersensitive individuals of many species, including the bovine. Occasionally a single treatment may serve as the sensitizing as well as the shock dose. This reaction will persist longer following injection of the long-lasting benzathine salt as compared to the shorter acting forms of penicillin. This is an important consideration in treating the shock condition.

The possibility of suprainfection caused by overgrowth of organisms not susceptible to penicillin should be recognized (18). An example would be fungal infections of the gastrointestinal tract following long-term oral penicillin therapy.

Several of the newer, semi-synthetic penicillins, such as nafcillin, methicillin, cloxacillin, etc., are relatively resistant to inactivation by penicillinase (4,14). However, most of the other members of the penicillin family are quite susceptible to penicillinase. *Staphylococcus* species are notorious for their ability to produce penicillinase. Culture and

sensitivity testing would aid in selecting proper therapy when treating infections caused by penicillinase-producing bacteria.

Sulfonamides: As mentioned in the introduction to this paper, some drug interactions result in beneficial or synergistic responses. Certain sulfonamides in combination with trimethroprim is an example. Each of the components of this particular combination exert their action at different steps of bacterial metabolism, namely PABA and folic acid metabolism. However, sulfonamides can be antagonized by PABA and local anesthetics (14).

Due to low solubility, especially of the older sulfas, crystalluria can occur. This is especially true in the presence of low urine pH and low urine volume. Combining drugs is useful in this situation. Different sulfonamides may be combined, such as triple sulfa, resulting in an additive antibacterial effect without adding to the insolubility. In other words, the solubility of each sulfonamide remains independent.

Rapid intravenous administration or excessive doses of sulfonamides can cause muscular weakness, collapse, and, in some cases, death. Prolonged oral therapy can cause an alteration of the rumen flora and interfere with rumen function (14).

Interactions of Corticosteroids

The corticosteroids have been extensively used in all domestic animals, including cattle, in recent years. However, there are some significant interactions associated with corticosteroids that are worthy of consideration.

Corticosteroids are inducers of certain hepatic microsomal enzymes. Consequently, other drugs that undergo bio-transformation by these same enzymes are affected. For example, corticosteroids shorten the duration of action of Thiamylal (16).

The corticosteroids can cause abortion when administered during the last trimester of pregnancy. This method is often used to induce parturition. Adverse reactions associated with this technique are retained placenta and metritis, especially if parturition is induced too early. Also, if induced parturition or abortion occurs a month or more prior to term, calf mortality rates are high due to weakness and respiratory complications (9,13).

Corticoids can interfere with immune responses by inhibiting tissue macrophages and lymphocytes. This is probably significant only with massive doses or prolonged therapy. In the face of an infectious process or in the case of a susceptible patient, corticoid therapy should be covered with antimicrobial therapy. There is some work reported which demonstrates that bacteriocidal drugs should be used with corticoids rather than using bacteriostatic agents (1).

Short-term corticoid therapy seldom causes hypoadrenalism in domestic animals. However, abrupt cessation of long-term therapy of high doses of corticosteroids could result in hypocorticism. Therefore, gradual withdrawal of long-term corticoid therapy should be practiced (14).

Experimental studies have demonstrated that corticosteroids can cause a recrudescence of viruses, especially the virus of infectious bovine rhinotracheitis (I.B.R.). The activation or shedding of viruses may occur after vaccination for or natural infection of I.B.R. This event may occur up to several months following vaccination or active infection (3,15).

The corticosteroids may mask signs of disease. Musculoskeletal inflammatory disorders are a good example. Lame animals treated with corticosteroids may appear sound and are pressed back into service too early only to experience an exacerbation of the primary disturbance.

The use of corticoids in the presence of a fungal infection can be disastrous. Corticosteroids often intensify the disease and promote spreading of the infection throughout the body.

Antiparasitics

The organophosphorous compounds possess an inherent toxic potential via their ability to inhibit cholinesterase in the parasite as well as the host. When adversity is reported, there is often a history of product misuse. Typical signs of organophosphorous toxicity can be expected if (1) other compounds which inhibit cholinesterase are used concurrently or have been used in the recent past, (2) the product is overdosed, and (3) the product is used to treat severely stressed or debilitated animals. Each quarter the Food and Drug Administration publishes adverse drug reactions which have been reported in animals. Levamisole consistently appears on this list with reports of anaphylaxis, local irritation, tremors and paralysis. In many of these cases there is evidence of product misuse. The misuses include concurrent therapy with organophosphorous drugs, various antibiotics and biologicals.

In general, the antiparasitic drugs approved for use in cattle are relatively safe compounds when used as directed. Reasonable caution should be exercised to avoid or minimize possible drug interactions.

Conclusion

Several examples of various types of drug interactions have been presented and discussed. With many of these interactions, the clinical significance is admittedly questionable. However, in the critically ill or borderline patient, the slightest adverse drug interaction could mean the difference in recovery or death. Relatively high doses, particularly of antimicrobial drugs, are often administered to critically ill patients in hope of effecting a cure. Also, it is more likely that multiple drug therapy is practiced in such a patient. These two factors, high doses and multiple drug treatments, favor the likelihood of drug interactions. It would be prudent to consider the possibility of drug interaction when selecting modes of therapy, evaluating adverse reactions and evaluating laboratory test results.

Bibliography

1. Aronson, A.L.: Clinical Significance of Drug Interactions. Sylabbi of California, Vet. Med. Assn. Meeting, 1976. - 2. Adams, H.R.: Acute Adverse Effects of Antibiotics. JAVMA 166:983, 1975. - 3. Darcel, C. leQ., and Dorward, W.J.: Recovery of Infectious Bovine Rhinotracheitis Virus Following Corticosteroid Treatment of Vaccinated Animals. Can.Vet. J. 16:87, 1975. - 4. Davis, L.E.: Newer Antibacterial Drugs. Clinical Pharmacology and Therapeutics, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, Colorado, 1976. - 5. Davis, L.E. and Jenkins, W.L.: Some Considerations Regarding Drug Therapy in Ruminant Animals. Bovine Pract. No. 9:57, 1974. - 6. Jawetz, E.: The Use of Combinations of Antimicrobial Drugs. Ann. Rev. Pharmacol., 8:151, 1968. - 7. Jawetz, E.: Synergism and Antagonism Among Antimicrobial Drugs. West. J. Medicine, 123:87, 1975. - 8. Kramer, W., Inglott, A., Clinton, R.: I.V. Additive Review. Drug Intelligence and Clinical Pharmacology, 5:211, 1971. - 9. Kunesh, J.P.: Clinical Use of Glucocorticoids in Large Animals. Proc. Drug Usage by the Practitioner, Iowa State University, Ames, Iowa, 1976. - 10. Lubran, M.: Drug Effects on Blood Chemistry. Provided by Boehringer Manheim Corporation, New York. - 11. Martin, E.L., et al.: Hazards of Medication: A Manual on Drug Interactions, Incompatibilities, Contraindications and Adverse Effects. J.B. Lippincott, Philadelphia, 1971. - 12. Mia, A.S., Jacobs, A.R., and Koger, H.D.: Effects of Anticoagulants on Blood Chemistry Tests. Practicing Veterinarian 48:15, 1976. - 13. O'Farrell, K.J., and Crowley, J.P.: Some Observations on the Use of Two Corticosteroid Preparations for the Induction of Premature Calving. Vet. Rec. 94:364, 1974. - 14. Powers, T.E.: Antimicrobial Therapy in Veterinary Medicine, Ohio State University, Columbus, Ohio, 1976. - 15. Sheffy, B.E., and Rodman, S.: Activation of Latent Infectious Bovine Rhinotracheitis Infection. JAVMA 163:850, 1973. - 16. Short, C.E., and Paddleford, R.R.: The Inter-Relationships of Hormones/Steroids and Ultrashort-Acting Barbiturates, VM/SAC 71:746, 1976. - 17. Siegel, D., Huber, W.G., and Enloe, F.: Continuous Non-Therapeutic Use of Antibacterial Drugs in Feed and Drug Resistance of the Gram-Negative Enteric Florae of Food-Producing Animals. Antimicrob. Ag. Chemotherapy, 6:697, 1974. - 18. Stamp, G.L.: Antibacterial Prophylaxis in Veterinary Medicine. Southwestern Vet. 29:140, 1976. - 19. Stowe, C.M.: Antibiotic Therapy in Veterinary Medicine, Uses and Misuses. Pharmacology in the Animal Health Sector. Edited by L.E. Davis and L.C. Faulkner, Colorado State University Press, Ft. Collins, Colorado (1976): 199-219. - 20. Stowe, C.M.: Indications, Compatibilities and Incompatibilities of Antibiotics and Sulfonamides. Proc. Drug Usage by the Practitioner. Iowa State University, Ames, Iowa, 1976. - 21. Swidler, G.: Handbook of Drug Interactions, Wiley-International, New York, 1971. - 22. Symonds, H.W.: The Effect of Xylazine upon Hepatic Glucose Production and Blood Flow Rate in the Lactating Dairy Cow. Vet. Rec. 99:234, 1976. - 23. Teske, R.H., Rollins, L.D., and Carter, G.G.: Penicillin and Dihydrostreptomycin Serum Concentrations After Administration in Single and Repeated Doses to Feeder Steers. JAVMA 160:873, 1972.