Drug Interactions in the Bovine Animal

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I. Introduction

The subject of drug interactions should embrace at least three facets: (1) an interaction of two or more drugs resulting in an unexpected response; (2) an interaction of one or more drugs with physiological processes in the patient, often referred to as 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 systems or *in vitro* as a result of the drug(s) interfering with the chemistry of the test.

Many papers dealing with drug interactions approach the subject from a physiological-pharmacological basis. In that concept the problem is attacked from the point of view of basic functions involving drug kinetics such as dosage form, absorption, distribution, receptor site activity, biotransformation and elimination. This certainly is a logical and probably the best scientific approach to the subject of drug interactions. However, for practical consideration, I have chosen to depart from that classical format and look at various examples of drug interactions that have been reported within the various classifications of drugs. At least 1300 drug interactions have been documented 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 understanding an an awareness of drug interaction, we can formulate a conceptual perspective of the subject.

Dr. C. M. Stowe has reported the results of a drug usage survey conducted in the Veterinary Ambulatory Service at the University of Minnesota in 1967 (Table 1).

Table 1

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

II. Physical and Chemical Aspects of Combining Drugs in Vitro

In vitro drug incompatabilities may properly be classified as iatrogenic drug interactions. There may be some justifiable reasons for extemporaneous mixtures including economy of time, convenience and avoiding multiple injection sites. However, the reasons for not mixing drugs *in vitro* should be given serious consideration. Undoubtedly, an important reason for refraining from extemporaneous mixing of drugs is the possibility of inactivating one or more of the active ingredients. Visible signs of *in vitro* incompatability or inactivation include precipitation, colloidal formation, color changes or gas formation. It should be remembered that some reactions may occur that are invisible but nevertheless may render an active ingredient inactive. For instance, sulfonamides

Table 2
In Vitro Incompatibilities (From Kramer, et al.)

Drug	Incompatible with
Ampicillin	Do not mix with other drugs
Acepromazine	Chloramphenicol, Phenylbutazone, Sulfonamides
Calcium gluconate	$NaHCO_3$, Phenylbutazone, Sulfonamides, Tetracyclines
Chloral hydrate	Alkaline Solutions
Chloramphenicol	Erythromycin, Hydrocortisone, Tetracyclines, Procaine, Vit. B complex
Erythromycin	Hydrocortisone, Penicillin G, Streptomycin, Chloramphenicol
Hydrocortisone	Chloramphenicol, Erythromycin, Kanamycin, Promazine, Tylosin, Tetracyclines
Levamisole	Neomycin, Phenylbutazone, Sulfas, 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 drugs, especially antibiotics

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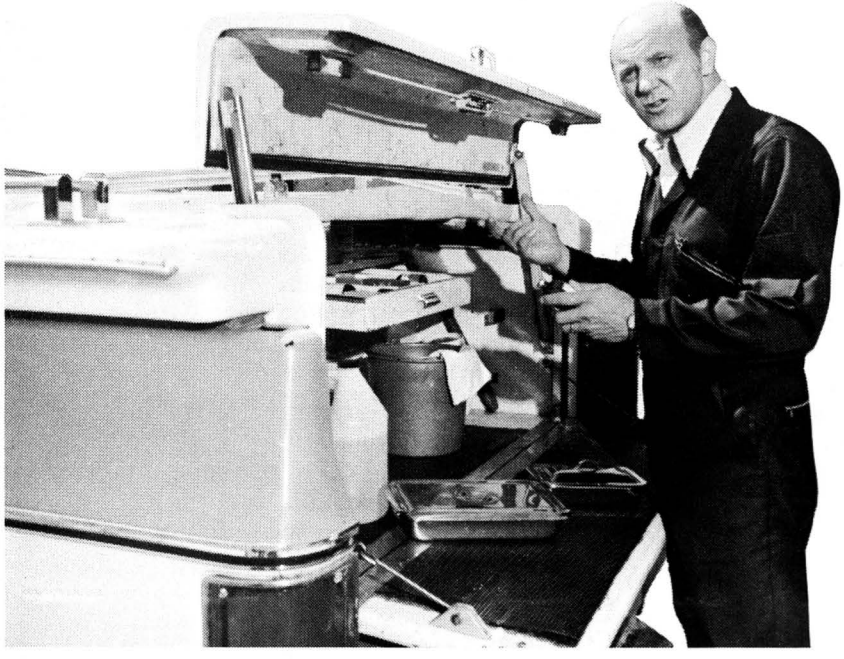

and penicillin are incompatable due to the fact that the high pH of the sulfas will inactivate penicillin. It would be advantageous to consult with a pharmaceutical chemist before mixing drugs *in vitro*.

III. Drug Interactions with Laboratory Tests

An extremely important aspect of drug interactions involves the alteration of blood chemistry, hematological and urological tests. These abnormal test results may be due to pathology or enzyme alteration induced by a drug(s) or may be a false reading due to chemical interaction of the drug(s) with the test procedure. The list of possible drug interactions is far too voluminous to deal with in this paper. Several references on this subject are available through your local clinical pathology laboratory. Sound clinical judgment must be applied to the interpretation of laboratory test results when the patient is under medication.

IV. Interactions of Antimicrobial Drugs

A. Combinations of Antimicrobial Drugs.

Several years ago Dr. Ernest Jawetz proposed a scheme whereby antimicrobial drugs were placed in two groups: (1) bacteriocidal agents including penicillins, streptomycin, neomycin, bacitracin, polymixin, and (2) bacteriostatic agents including tetracyclines, chloramphenicol, erythromycin, novabiocin, sulfonamides. Synergism was found to occur *in vitro* rather frequently among members of Group I but infrequently among members of Group II. Also, if an organism was killed rapidly by a member of Group I, addition of a Group II drug could result in antagonism. But if an organism was killed slowly by a Group I drug, the addition of a drug from Group II 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 essence, synergism or antagonism of 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 instance, if procaine penicillin G has a therapeutic duration of 24 hours and it is combined with dihydrostreptomycin which possesses a duration of 12 hours, does one treat with this combination once a day or twice a day?

B. 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 agent usually reflects the extent of usage of that compound. Indiscriminant use of antimicrobials has certainly contributed to the prevalence of resistant organisms. Some of the indiscriminant uses of antimicrobials include: extensive prophylactic use, less than adequate doses, excessive intervals between dosing, too short a duration of therapy and failure to rotate antimicrobial agents in therapy. The low level use of antimicrobials in feed is a controversial subject but has probably played a role in the development of resistant organisms.

C. Antimicrobial Drug Residues in Edible Animal Tissues.

The subject of residues in edible animal tissues should not be restricted to antimicrobial drugs. However, due to the frequency of use of this group of drugs, illegal residue has become a common problem. Drugs that are approved for use in the bovine will have specific withdrawal times published. The veterinarian should be knowledgeable of these withdrawal times and has a *legal* responsibility to inform the client of this information. It is true that a veterinarian may use any drug that can be legally purchased to treat a given disease entity. Unfortunately, tissue depletion times may not be known for unapproved drugs in the bovine. Nevertheless, the veterinarian must accept the legal responsibility to warn the client to withhold the animal from slaughter or discard milk from that animal for a sufficient period to allow for tissue depletion of that unapproved drug. Normally 30 days is considered an adequate withdrawal time. However, there is a possibility that some drugs would not be cleared from certain animal tissues by 30 days.

D. Tetracycline.

1. The tetracyclines are known to inhibit protein synthesis. This action can result in an antianabolic effect with an elevated BUN and impaired synthesis of various endogenous proteins such as prothrombin. Some suspicion exists as to inhibition of antibody production.

2. The tetracyclines are chelated by various bivalent and trivalent cations such as Ca, Mg, Al, Fe. Milk products, antacids, calcium gluconate and other compounds containing these cations can render tetracycline inactive.

3. 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.

4. Oral administration of therapeutic levels of tetracyclines can cause alteration of gastrointestinal flora and, hence, interfere with rumen function. There is some indication that, even after parenteral administration, tetracyclines can exert a significant effect on the gastrointestinal flora. Superinfections are also known to occur as a result of alteration of the G.I. flora.

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

E. Chloramphenicol.

Although this chemotherapeutic agent is not approved for use in food-producing animals in the United States, there is good reason to believe that a considerable amount of this drug is used in the bovine. With that in mind, it may be worthwhile to mention a couple of points regarding chloramphenicol.

1. Certain hepatic microsomes 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 and there is a strong suggestion that antibody synthesis is retarded. If this is true (all the answers are not in as yet), chloramphenicol would be a poor choice of drug to use preceding and at the time of immunization procedures.

3. It has been reported that chloramphenicol is inactivated by rumen contents. Therefore, oral administration of chloramphenicol to an animal that has developed a functional rumen would appear to be unwise.

F. Aminoglycosides (Neomycin, Streptomycin, Kanamycin, Gentamycin).

1. Aminoglycosides are neuro-muscular blocking agents. This occurs via inhibition of calcium and competitive blockage of skeletal muscle receptors. This effect is additive among the members of this group. Other drugs which have neuro-muscular blocking effects are also additive in this respect to the aminoglycosides.

2. The cardiovascular effects of the aminoglycosides are expressed as myocardial depression, decreased cardiac output and hypotension. Inhibition of calcium is a probable mechanism.

3. The aminoglycosides are not absorbed to any extent from the gastrointestinal tract.

G. Penicillins (Procaine Penicillin G, Benzathine Penicillin G, Ampicillin, etc.).

1. Anaphylactoid reactions can occur in hypersensitive individuals. Occasionally a single treatment can 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 duration forms. This is an important consideration in treating the shock condition.

2. Superinfection by non-susceptible organisms can occur with penicillin therapy.

H. Sulfonamides.

1. Certain sulfonamides are potentiated by trimethoprin via a two-step sequential inhibition of bacterial metabolism (PABA ▸ Folic Acid).

2. Sulfas can be antagonized by PABA and local anesthetics.

3. Due to low solubility, especially of the older sulfas, crystalluria can occur. This is particularly true in the presence of low urine pH and low urine volume.

4. Rapid intravenous administration or excessive doses of sulfas 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.

V. Corticosteroids

The corticosteroids have enjoyed extensive use in all species, including the bovine, in recent years. However, there are some significant interactions associated with corticosteroids that are worthy of consideration.

1. Corticosteroids are inducers of certain hepatic microsomes. Consequently, other drugs that undergo bio-transformation by these same enzymes are affected. For instance, corticosteroids shorten anesthetic time of Thiamylol Na.

2. Recrudescence of viruses, especially the IBR virus, can be triggered by corticosteroids. This can occur months after an active viral infection.

3. The corticosteroids can cause abortion when administered during the last trimester of pregnancy. This is often used advantageously to induce parturition. Adverse reactions often 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 is high due to weakness and respiratory complications.

4. Corticoids can interfere with immune responses by inhibiting tissue macrophages and lymphocytes. This is probably significant only with massive doses or extended therapy. In the face of an infectious process or a susceptible patient, corticoid therapy should be covered with antimicrobial therapy.

5. Short-term corticoid therapy seldom causes hypoadrenalism. However, abrupt cessation of long-term corticoid therapy could result in hypocortism. Therefore, gradual withdrawal of long-term corticoid treatment should be adhered to.

6. Corticosteroids should not be used when corneal ulceration is present. The topical use of corticoids in the eye with an ulcerated cornea quite likely delays healing of the ulcer and may lead to rupture allowing prolapse of the iris.

7. The corticosteroids are known to mask signs of disease. Musculo-skeletal inflammations are a good example. Lame animals treated with corticoids may appear sound and are pressed back into service too early only to have an exacerbation of the primary etiology.

8. The gluconeogenic effect of the corticoids is at the expense of protein. In other words, the corticoids are catabolic in nature and promote a negative introgen balance.

9. The use of corticosteroids in the face of a fungal infection can be disastrous. The corticoids

often intensify the disease and promote spreading of the organism throughout the body.

VI. Antiparasitics

1. The organophosphorous compounds possess an inherent toxic potential. When used in accordance with label direction, few if any adverse reactions occur. When adverse reactions are reported, there is usually a history of product misuse. Typical signs of organophosphorous toxicity can be expected if (1) other pesticides or other drugs which inhibit cholinesterase are used concurrently or have been used in the recent past, (2) the product is overdosed, (3) the product is used to treat severely stressed or debilitated animals.

2. Each quarter the FDA publishes adverse drug reactions which have been reported in animals. Levamisole consistently appears on this list with reports of various signs including anaphylaxis, local irritation, tremors, paralysis. In many of these cases there is evidence of mis-use of the product. The misuses include concurrent treatment with organophosphorous compounds, various antibiotics and vaccines.

In general, the antiparasitic drugs approved for use in the bovine are relatively safe compounds. However, reasonable caution should be exercised to avoid or minimize possible drug interactions.

VII. Conclusion

Several examples of various types of drug interactions have been presented. With several of these interactions the clinical significance is admittedly questionable. However, in the critically ill or borderline patient, they could possibly make the difference in recovery or death. It would be advantageous to consider the possibility of drug interaction when selecting modes of therapy, evaluating adverse reactions and results of laboratory tests.

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