Drug Interactions

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Introduction

Adverse drug reactions are becoming increasingly important to the veterinary practitioner as a basis for malpractice litigation. Drug interactions are often overlooked as a cause of adverse drug reactions or failure of therapeutic response. To the veterinarian the problem is further complicated when animals are previously exposed to pesticides and OTC drugs of which he has no knowledge. For example, there are documented cases of adverse reactions to succinylcholine when horses had been previously exposed to organophosphate anthelmintics. The following article is a general review with suggested reading on the subject of drug interactions.

It is a well known fact that all drugs are potential poisons relative to dosage, species and other factors. A factor that is often overlooked is the phenomenon of drug interaction. The magnitude of the problem of drug interaction is unknown and it is probable that the clinician is unaware of many drug interactions. Some interactions are of unknown or little clinical significance while others are of considerable importance. Those that are known will be reviewed according to mechanism of action.

The basic mechanisms of drug interaction include: 1) displacement from carrier sites and protein binding, 2) competition for renal tubular secretion, 3) enzyme induction or inhibition, 4) interactions at tissue sites, 5) interactions controlled by drug pKa and pH, 6) physical incompatibilities of drugs in intravenous solution, 7) effects secondary to change in intestinal flora by antimicrobials, and 8) antagonism of bacteriostatic and bacteriocidal antimicrobials used in combination.

Displacement of one drug from albumin carrier sites by a second drug may cause either a deleterious or desirable effect. Coumarins such as warfarin which are nearly 100% protein bound can be displaced by the sulfonamides which will increase the free coumarin levels and intensify the bleeding syndrome. Bilirubin may be displaced by sulfonamides resulting in kernicterus. Sulfonamides may be displaced by phenylbutazone and aspirin increasing the sulfonamide activity. Penicillin is known to be displaced by probenicid which can be used advantageously to increase penicillin activity.

Competition for renal tubular secretion is best exemplified by the effects of probenicid and phenylbutazone, both of which can compete with penicillin and cause increased serum levels and decreased urine levels of penicillin.

Enzyme induction or inhibition is a phenomenon controlled by the microsomal-hepatic-enzyme system or cytochrome P-450 system. A drug may either stimulate and induce hepatic enzymes causing increased metabolism of a second drug, or some drugs may inhibit or repress the hepatic enzymes causing decreased metabolism and toxic levels of a second drug to occur (Table 1).

Table 1

Interactions Involving Enzyme Induction or Repression

Drug Affected	Affected By	Result
Diphenylhydantoin	Sulfonamides Chloramphenicol	Diphenylhydantoin toxicity
Coumarins	Sulfonamides Chloramphenicol	Bleeding syndrome
Bilirubin	Novobiocin Chloramphenicol	Jaundice in newborn
Griseofulvin	Barbiturates Diphenylhydantoin	Inhibition of griseofulvin
Gen. Anesthetics	Chloramphenicol Polymyxins Neomycin Streptomycin Other aminoglycoside-antibiotics	Enhanced anesthesia

Interactions occurring at tissue sites are listed in Table 2.

It should also be noted that succinylcholine which is metabolized by plasmacholinesterase can cause serious problems when used following drugs which inhibit acetylcholinesterase or plasmacholinesterase. These drugs include phenothiazine derivatives, carbamates, organophosphates, and high levels of Vitamin A.

Interactions controlled by pH are of primary concern with antimicrobials such as sulfonamides which are more prone to cause crystalluria in an acid urine and agents like methenamine which requires an acid urine to be effective.

Physical incompatibilities are very common as there is a tendency to mix drugs in the same syringe or infusion bottle. A few of the more common physical incompatibilities include tetracyclines mixed with

Table 2
Interaction at Tissue Sites

Drug Affected	Affected By	Effect
Aminoglycoside Antibiotics	Polymyxins	Nephrotoxicity
Methoxyflurane	Tetracycline	Nephrotoxicity
Aminoglycoside Antibiotics	Ethacrynic Acid	Ototoxicity
Succinylcholine	Aminoglycosides Polymyxins	Myasthenia and Apnea

lactated ringers, penicillins mixed with dextrose or sucrose with a pH 8 or greater, amphotericin mixed with saline, and most antibiotics mixed with Vitamin B complex solution.

Effects secondary to change in intestinal flora have been demonstrated following prolonged use of oral antibiotics. Suppression of Vitamin K_1 production, malabsorption of glucose, iron and Vitamin B_{12} can occur following prolonged therapy with neomycin, tetracyclines, sulfonamides and the aminoglycoside antibiotics.

Antimicrobial combinations are used with the hope of controlling infection more effectively. However, a single agent often will accomplish as much as a combination of drugs, and at times adverse reactions will follow the use of several antimicrobial agents. Indications advanced for the use of antimicrobial combinations are: 1) synergic effect, 2) delayed emergence of resistant organisms, 3) prevention of superinfection, 4) treatment of intracellular bacteria, 5) treatment of mixed infections, 6) initial treatment of overwhelming undiagnosed infections, and 7) decreased untoward effects.

It has been shown that antibiotic combinations, particularly bacteriocidal and bacteriostatic agents used simultaneously may be antagonistic. Antimicrobial combinations may also increase the chances for adverse effects such as drug fever which mimics the progression or persistence of infection.

It is not enough that the clinician must be aware of the dosage, route of administration, mechanism of action, toxicity and side effects of individual drugs; rational drug therapy also requires the clinician to be cognizant of potential drug interactions.

There are many other drug interactions of clinical importance that could not be included in the scope of this paper. They may be found in the references and suggested reading.

References

1. Azarnoff, D. L. and Hurwitz, A. Drug Interactions. Pharmacology for Physicians. W. B. Saunders Co., Vol. 4:2, Feb. (1970). – 2. DiPalma, J. R. Drug Interactions. R. N. Magazine. Litton Publications, July, 1970. – 3. Kabins, S. A. Interactions among Antibiotics and Other Drugs. J.A.M.A. 219:2, 206-212, Jan., 1972. – 4. Teske, R. H. Effect of Chloramphenicol on Pentobarbital Induced Anesthesia in Dogs. J.A.V.M.A. 159:6, 777-780, Sept., 1971. – 5. Caldwell, J. R. and Leighton, E. C. The Real and Present Danger of Antibiotics. Pharmacology for Physicians. W. B. Saunders Co., Vol. 7:1, Jan. (1973). – 6. Conney, A. H. Microsomal Enzyme Induction by Drugs. Pharmacology for Physicians. W. B. Saunders Co., Vol. 3:12, Dec. (1969). – 7. Swidler, G. Handbook of Drug Interactions. Wiley-Interscience. New York (1971).

Book Review: Handbook of Veterinary Drugs; Rossoff

The veterinary profession has been in dire need of a pharmacology compendium for many years. Irving S. Rossoff's *Handbook of Veterinary Drugs*, containing some 1800 old and new drugs, provides easily accessible and clinically relevant information.

This publication can be recommended to veterinarians throughout the world since it is international in its application and is cross-indexed with foreign as well as American generic and trade names. This first edition contains valuable information regarding drug dosages for domestic as well as exotic animals.

This compendium does not contain detailed pharmacological information on each of the drugs listed nor does it provide references regarding therapeutic indications or dosages. However, it does contain a great deal of information relative to uses, warnings and dosages for a multitude of compounds. The handbook is very well indexed, concisely written and easy to use for review and quick reference.

By: Irving S. Rossoff, Springer Publishing Co., Inc., 200 Park Avenue South, New York, New York 10003. 1974. 730 pp. $42.50.

(This review was prepared by Dr. W. C. Edwards, Dept. of Physiological Sciences, Oklahoma State University.)