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Drug Interactions

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they could shorten the estral period of mares. An I. U. or I. M. injection of 230 ugm given during the fourth to thirteenth day of diestrus for two days brought the mares into estrus in three days, and ovulation occurred in seven to twelve days peaking at ten days. If given before three days old, the CL is not susceptible.

There are many clinical possibilities for the use of prostaglandins in the mare. Using prostaglandins, one could control and shorten the cycle of the mare by decreasing the time spent in diestrus. They could be of particular importance on the breeding farm where many mares are booked to one stallion so that the estrus periods could be planned to prevent concurrent estrus periods. Where A. I. is practiced prostaglandins would prove invaluable. In Thoroughbred mares whose breeding season is restricted and A. I. not allowed by the breed registration authorities prostaglandins could shorten estral cycles from 22 to 14 days, thus increasing the number of possible cycles per season. As a final touch, they provide a means of treating the "problem mare" with a persistent CL which prevents normal cycling. This category could include early abortion, resorption, barren or lactating mares.

Although the main emphasis in research has been on reproduction, prostaglandins show promise in various other areas of research relating to man and animals.1

ULCERS—Certain prostaglandins decrease gastric acid secretion in the dog, possibly relating to peptic ulcers in man.

HYPERTENSION—The A and E groups decrease blood pressure by dilating peripheral vessels, while PGE types increase blood pressure.

KIDNEY DISEASE—PGF1, PGF2, and PGA, effect the kidney causing an increased renal blood flow, urine volume and sodium excretion. Possibly congenital heart disease and kidney failure are related to a lack of natural PGF2 production.

THROMBI—PGE1 inhibits thrombus formation while PGE2 stimulates it.

RESPIRATORY DISEASE—PGE1 and PGF2 relax the smooth muscle of bronchioles in animals and man. It has been shown to be a more potent bronchodilator than isoproterenol.

Prostaglandins have also been implicated as causes of various pathological conditions, including glaucoma, tumors and inflammation. The research information increases daily and the day is near that we will have prostaglandins as therapeutic agents. Only time will tell if they will live up to their expectations.

REFERENCES

Drug Interactions

Rapid advances in research in basic pharmacology and the productivity of the pharmaceutical industry have resulted in the introduction of many new drugs for the veterinary profession. The availability of large numbers of drugs has stimulated their concomitant use with the hope that maximum therapeutic effectiveness will be achieved. Indeed modern therapeutics in veterinary medicine often necessitates the simultaneous administration of several

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drugs. With the increased use of multiple drug therapy has come the problem of drug interactions which necessitates greater professional awareness and responsibility on the part of the veterinarian.

Recent studies indicate that hospitalized patients in human medicine receive an average of 14 different drugs during a typical stay in the hospital. It has also been shown that drug reactions increase geometrically as the number of drugs administered increases. Even though the average number of drugs administered to hospitalized animals has not been reported, drug interactions are certainly of great importance to the veterinary practitioner.

Drug interaction in its narrowest sense refers to the reaction between two or more therapeutic agents administered concurrently or in close sequence which results in an altered response of one or more drugs. Thus the expected effect of each agent administered may be increased or diminished or a new or toxic reaction may occur. This definition must be expanded to include an interplay between drugs and other exogenous chemical agents—food, feed additives, environmental pollutants, insecticides, and pesticides.

A particularly important potential interaction exists between prescription and non-prescription drugs. Non-prescription drugs are freely available to the public without professional control from a variety of outlets. It is thus advisable for the veterinarian to inquire about possible previous medication on the part of the animal owner.

An equally important consideration is the prevention of drug residues in meat and milk. It is well to remember that withdrawal times may change as a result of interaction in the animal body when two or more drugs are used together.

Although the untherapeutic and adverse consequences of drug interactions are emphasized in this paper, the beneficial side of drug interaction should be made apparent. It is often noted that today's side effect may be tomorrow's therapeutic effect. A well known beneficial drug interaction exists in the kidney between pro-

*benecid* and *penicillin*. Both of these agents compete for the same renal tubular organic acid transport system with resulting longer therapeutic blood levels of *penicillin*. *Phenobarbital*, one of the most powerful inducers of nonspecific hepatic drug metabolizing enzymes, is used in the dairy cow which has ingested ample quantities of chlorinated hydrocarbons. The extremely lipid soluble nature of these agents results in a lengthy milk discard time on the part of the dairy farmer. When a daily series of *phenobarbital* injections is given, the chlorinated hydrocarbon is more rapidly removed from the body through enhancement of hepatic drug-metabolizing enzymes. From these examples it is apparent that drug interactions, once recognized, understood, and controlled may become therapeutically beneficial.

Since the list of known drug interactions is too overwhelmingly long to commit to memory (one such tabulation lists 1300 interactions), it is important that the practicing veterinarian have a basic understanding of the mechanisms by which interactions may develop. Such an understanding will aid in anticipating and managing drug interactions when they do occur.

Several excellent discussions of the mechanisms of drug interaction have recently been published for the medical practitioner. Many of these contain numerous listings of interactions.

Modifications of drug response due to drug interaction may occur at any site of drug passage through the body, e.g., administration, absorption, distribution, receptor site, metabolism, and excretion.

*Direct Drug Interactions*

Direct interactions result from chemical or physical incompatibility or inactivation and may occur *in vitro* or *in vivo*. For example many acidic drugs interact directly with basic drugs. In many cases *in vitro* interaction results in the precipitation of one or both agents. A vivid demonstration of this is simultaneous mixing in one syringe of a local anesthetic such as *lido*...
caine with a barbiturate anesthetic such as sodium pentobarbital. Most incompatibilities in practice arise from placing two or more drugs in the same syringe or I.V. fluid bottle. An in vivo illustration is the treatment of excessive anticoagulation due to heparin, an acid drug, with the intravenous use of protamine, a strong base.

**Interactions Affecting Drug Absorption**

Since a large number of drugs are administered orally, most drug interactions altering absorption occur in the gastrointestinal tract. Interactions may not only increase or decrease the relative rate of absorption, but also may increase or decrease total bioavailability of drugs. Conditions responsible for altered availability can be pH changes, physical or chemical binding of two or more drugs, and alterations in mobility and contents of the gut.

The great majority of drugs are passively transported across the lipid containing membrane of cells lining the gastrointestinal tract. A basic principle of pharmacology is that drugs, being weak acids or bases, are more readily absorbed in the unionized form than the ionized form. Intraluminal pH changes brought on by one drug can influence the amount of unionized form and thus the amount of another drug which is absorbed. It would be expected that antacids would diminish the rate of absorption of acidic drugs such as sulfonamides, phenylbutazone, nitrofurantoin, aspirin, and phenobarbital.

Complexation reactions within the GI tract may significantly lower absorption. *Tetracyclines* can combine with polyvalent ions such as calcium, magnesium, aluminum and iron to form complexes which are poorly absorbed. Milk products and certain antacids can significantly reduce the absorption of this class of antibiotics.

Antidiarrheal combinations are capable of adsorbing drugs administered concurrently. For example, a *kaolin-pectin* mixture can produce erratic absorption of *lincomycin* when the two are given simultaneously.

It is also recognized that antibiotics are capable of enhancing the anticoagulant action of the coumarins by reducing vitamin K synthesizing bacterial flora in the intestine.

**Interactions Affecting Drug Metabolism (Biotransformation)**

The principle site of drug metabolism, usually to inactive ionized metabolites, is the smooth endoplasmic reticulum (microsomal enzyme fraction) of liver cells. This system is rather non-specific and can handle most drugs and other exogenous compounds. The clinical significance of metabolism is that polar metabolites are more readily excreted.

Animal studies in recent years have shown that many drugs and other foreign agents have the capability of increasing or decreasing the rate of metabolism of other drugs or foreign compounds. Virtually all pharmacological classes of drugs used in veterinary medicine contain numerous examples of this type of interaction. Enhanced metabolism is brought on by "enzyme induction" whereby liver cells are stimulated by a drug to synthesize greater quantities of microosomal metabolizing enzyme protein. The clinical significance is that when a second drug is administered it may be metabolized rapidly resulting in minimum therapeutic effect. The mechanism of drug interaction due to inhibited drug metabolism is less understood. An explanation may be competitive inhibition at the same site on metabolizing liver enzymes.

**Interactions Affecting Renal Excretion**

The urine constitutes the major route of excretion of unmetabolized drugs. Alkaline urine increases the ionization of acidic drugs, thereby reducing drug reabsorption from the nephron. *Sodium bicarbonate* accelerates the excretion of *phenobarbital* and *salicylate* which can be of clinical significance following overdosage of these two drugs. In a similar way acidification of the urine by *ammonium chloride* increases the excretion of weak bases.

Some drugs are actively secreted into the urine rather than passively excreted.
Competition of two or more drugs for active transport systems represents another major type of drug interaction. Decreased excretion rates of *penicillin* and *oxphenylbutazone* when given together are explained by this mechanism.

**Interactions Affecting Drug Distribution**

Many drugs become reversibly bound to plasma and tissue proteins. When bound they are pharmacologically inactive. Certain drugs may compete for the same binding sites on the plasma proteins. Clinically significant responses may result when the unbound level (active form) is increased by displacing it from its binding sites with a second drug. Displacement of *sulfonamides* by drugs such as *phenylbutazone* will greatly increase *sulfonamide* tissue concentration with possible toxic results.

**Interaction at the Site of Action**

The pharmacological effect of one drug may be modified at the site of action by another drug through competition for the receptor site, alteration of the receptor site or specific components and effects on a different biological system which has similar or opposite effects. In veterinary medicine documented examples of adverse drug interactions at this site are uncommon. A well known beneficial interaction is the use of *atropine* in the therapeutic management of excessive endogenous *acetylcholine* resulting from organic phosphate toxicity.

**Conclusion**

The mechanisms of drug interactions have been discussed. Predispositions for adverse drug interactions certainly exist in veterinary medicine today and may in large part be responsible for adverse drug reactions in general, including lack of efficacy. Prevention and management of adverse drug interactions in veterinary medical practice clearly dictates continuing education in clinical pharmacology of the potent therapeutic agents available to veterinarians today.

**References**


**Collection Development for the New Veterinary Medical College Library**

by Sally Peterson *

The Iowa State University Veterinary Medical Library was the recipient this past year of an $83,000 grant awarded to aid in providing library materials for the new veterinary medical college complex now under construction approximately two miles from the central campus. The National Library of Medicine resource project grant funded by the National Institutes of Health extends for a three-year period. A variety of books and journals are now being purchased and processed for inclusion

* Mrs. Peterson is the Veterinary Medical Librarian at Iowa State University.