Chapter 69

# Effects of Food on Pharmacokinetics

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*"Give me a lever long enough and a fulcrum on which to place it, and I shall move the world."*
*Archimedes*

## INTRODUCTION

When the effects of veterinary pharmaceuticals are evaluated and standardized doses are determined, researchers typically use relatively healthy, fasted animals that have been maintained on foods with acceptable nutrient balance. However, in clinical settings, animals receiving a drug often have variable food intake or specific nutrient imbalances, or they must be given a drug in conjunction with a meal, or some combination of these factors may occur. The patient's health status and the nutrient ingredient profile of the diet being consumed may greatly affect drug absorption, distribution, metabolism, elimination, efficacy and toxicity (**Table 69-1**). Concurrent food intake also may markedly affect drug availability and pharmacokinetics (**Tables 69-2** and **69-3**).

Veterinarians should be acquainted with the effects diet can have on drug disposition to anticipate adjustments in the food or drug dose, properly time administration of drugs and allow for changes in the margin for error between efficacy and toxicity of pharmaceutical agents.

## GENERAL TYPES OF FOOD AND DRUG INTERACTIONS

Food-drug interactions that occur as a result of the physical form or chemical properties of food may lead to drug binding, precipitation, inactivation or ionization, which alter gastrointestinal (GI) absorption. These interactions may occur in vitro after mixing the drug with food to make administration more convenient, to enhance palatability or to reduce GI irritation. Another concern is adsorption of drugs to synthetic surfaces of the equipment used for nutrient and drug administration (e.g., food containers, feeding syringes and tubing for assisted feeding). Physiochemical interactions may occur in vivo, whereby drug absorption from the GI tract is decreased because of chelation by dietary fiber or minerals, or increased because of favorable changes in ionization or solvent partitioning.

### Metabolic Interactions

Both nutrient and non-nutrient substances in foods can alter the metabolism of absorbed drugs. Nutrients are nourishing ingredients of food. Non-nutrient substances are chemicals without metabolic value, including naturally occurring phytochemicals and synthetic chemicals added inadvertently or purposely to food. Protein and energy malnutrition can alter the synthesis of plasma proteins, affecting drug distribution and pharmacokinetics. Individual dietary lipid, carbohydrate, protein, vitamin and mineral levels can effect changes in xenobiotic-metabolizing enzymes, resulting in altered clearance, circulating concentrations and resultant therapeutic efficacy and toxicity. Naturally occurring non-nutrient food ingredients and added synthetic preservatives may similarly

**Table 69-1.** Factors affecting the disposition of drugs that can be influenced by foods.

| |
|---|
| **Absorption** |
| GI transit time |
| GI luminal environment |
| Enterocyte function |
| Electrochemical gradient across the GI mucosa |
| pH gradient across the GI mucosa |
| **Distribution** |
| Drug-binding proteins |
| Blood cells that bind or metabolize drugs |
| **Metabolism** |
| Site of metabolism |
| Organ |
| Tissue |
| Cell type |
| Cell organelle |
| Biotransformation pathways |
| Phase I oxidative vs. phase II conjugative pathways |
| Cofactors required for metabolism |
| Vitamins |
| Minerals |
| Reducing agents |
| Non-nutrient enzyme inducers |
| Phytochemicals |
| Synthetic contaminants |
| Preservatives |
| **Excretion** |
| Route of excretion |
| Biliary |
| Fecal |
| Mammary |
| Pulmonary |
| Renal |
| Salivary |
| Sweat |
| Electrochemical gradient across mucosa of excretory organs |
| Rate of excretion |

**Table 69-2.** Selected factors that can determine the effects of nutrients on drug absorption.

| Factors | Examples |
|---|---|
| Physiochemical properties of drugs | Lipophilic or hydrophilic |
| Drug formulation | Tablet, capsule or liquid |
| Meal type | Volume, temperature, moisture |
| Drug dose | Amount and concentration |
| Route of administration | By mouth, gastric tube, etc. |
| Order of administration | Pre- vs. postprandial |
| Time interval between food and drug administration | Phase of digestion |
| Owner/patient compliance | Mixing drugs and food for ease of administration |

alter pharmacokinetics and apparent drug effectiveness.

### Indirect Physiologic Effects

The rate of drug elimination is also affected by changes in blood flow and drug delivery to the principal organs of metabolism for that particular agent. Thus, postprandial alterations in blood flow to the liver may affect drug clearance from the portal and systemic circulation, and altered blood flow to the kidneys may change the rate of urinary elimination. Likewise, changes in functional morphology or pathology due to specific nutrient deficiencies or excesses can affect drug clearance.

## GENERAL EFFECTS OF FOOD AND DRUG INTERACTIONS

### Ameliorating Potential Adverse Effects

The composition and volume of food consumed can modify the degree of GI irritation caused by concurrently administered oral drugs. Enteral and parenteral fluid intake can augment drug absorption and distribution and protect against renal damage induced by nephrotoxic agents. Supplementation with specific nutrients may prevent deficiencies secondary to adverse drug effects on nutrient absorption and metabolism.

### Potentiating Drug Action

Specific nutrients can increase drug effects by facilitating GI absorption, improving drug distribution or decreasing drug metabolism and excretion. Furthermore, some nutrients may be necessary for optimal drug effects (e.g., arginine for nitric oxide production, cysteine for nitroglycerin action and carnitine for optimal activity of cardiac glycosides).

### Impaired Drug Action

Impaired drug action is the adverse effect most often considered when evaluating nutrient-drug interactions that impair therapeutic efficacy. These adverse effects may result from decreased drug absorption, inadequate amounts of the drug reaching the site of action, or nutrient interference with the drug's action. Drug action may be impaired for variable periods of time after food composition and feeding behavior are altered, if target cell receptor numbers or affinity are suppressed or long-lived biotransforming enzyme systems have been induced.

### Adverse Side Effects

Pathologic reactions to nutrient-induced changes in drug distribution and metabolism can be of greater immediate consequence than loss of disease control following impaired drug action. Drug metabolism and excretion routes may be altered, resulting in accumulation of toxic quantities of the agent itself or the products of its biotransformation. This phenomenon is similar in principle to adverse interactions between concurrently administered drugs, but may be more difficult to identify because mental recollection and written records of nutrient intake are not usually as complete as for administration of pharmaceutical agents.

## EFFECTS OF NUTRIENTS ON DRUG ABSORPTION

### General Observations

The absorption of orally administered drugs may be: 1) decreased, 2) delayed, 3) unaffected or 4) enhanced by the con-

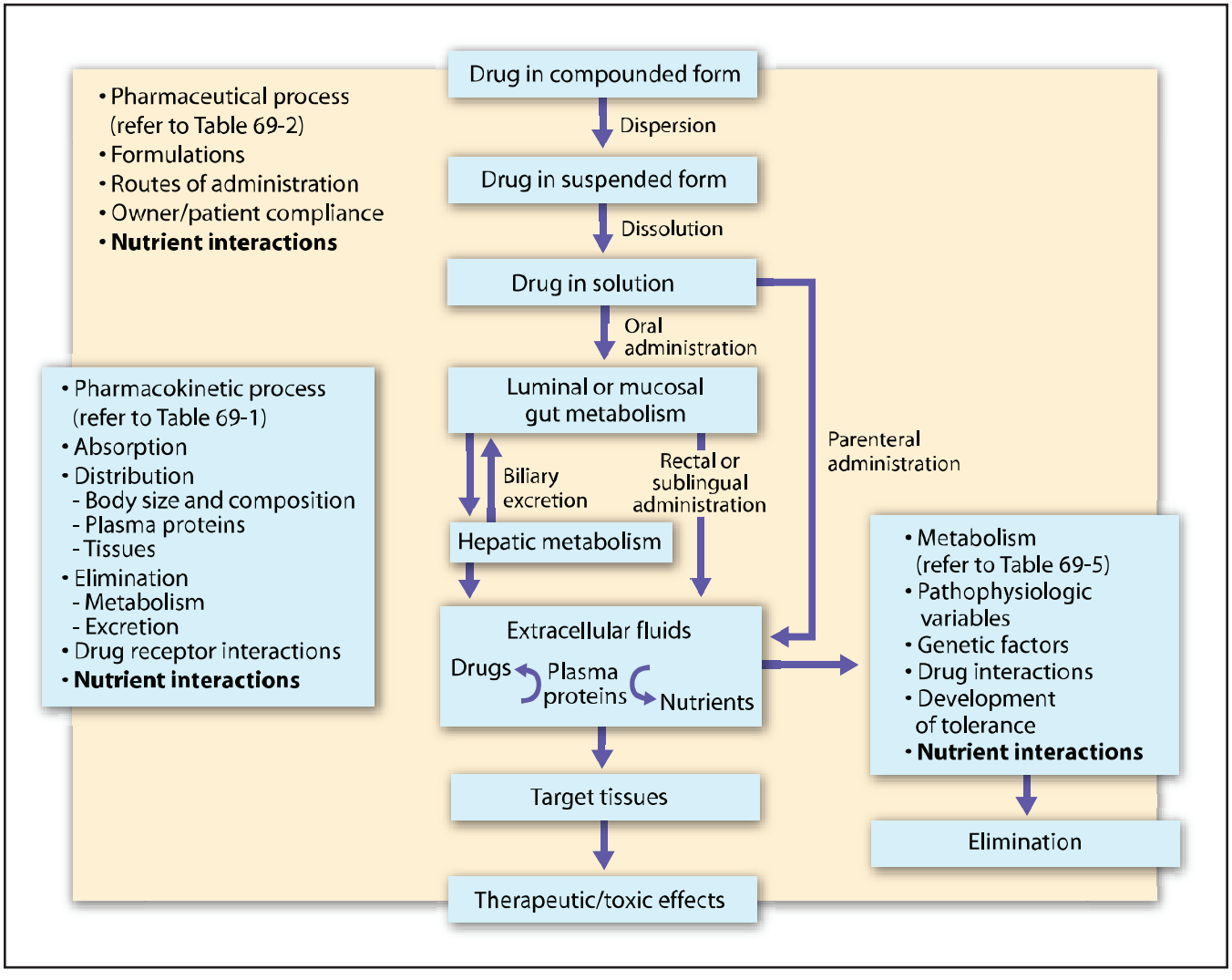


**Figure 69-1.** Determinants of drug absorption, distribution, metabolism and excretion that may be modified by nutrient interactions. (Adapted from Grahame-Smith DG, Aronson JK. In: The Oxford Textbook of Clinical Pharmacology and Drug Therapy. Oxford, UK: Oxford University Press, 1985.) Rectal absorption in dogs and cats is subject to first-pass hepatic metabolism due to the small relative size of the rectum and the lack of a hemorrhoidal plexus in these species. Transdermal could be substituted for rectal delivery (e.g., fentanyl patches in dogs and cats). A good example of a drug absorbed across oral mucous membranes is buprenorphine in cats.

comitant consumption of food (**Figure 69-1** and **Tables 69-2** and **69-3**). This interaction depends on the physical and chemical nature of the food and the drug, including such things as meal size and type, the formulation in which the drug is administered, the order in which the food and drug are ingested and the interval between their consumption (Roe, 1989).

Any food can reduce drug absorption by creating a barrier that prevents dispersion of the drug and dissolution of the active agent in GI luminal contents. Drugs are better absorbed in dilute vs. concentrated solution because of greater dissolution and more rapid gastric emptying. In people, absorption of erythromycin stearate is reduced by approximately one-half when taken with food or a small fluid volume, as compared with a large fluid volume (Toothaker and Welling, 1980). Absorption of acetylsalicylic acid (aspirin), cephalexin, metronidazole, digoxin, hydralazine and cimetidine are similarly affected (Toothaker and Welling, 1980).

Alternatively, food does not affect absorption of other drugs in people, including erythromycin estolate, oxazepam, propylthiouracil and enteric-coated aspirin granules in caplet form (Toothaker and Welling, 1980). In fact, food enhances the absorption of certain drugs (e.g., erythromycin ethylsuccinate, nitrofurantoin, hydrochlorothiazide and diazepam) (Toothaker and Welling, 1980). The rate and quantity of drug and nutrient delivery are important, as evidenced by studies of hydralazine absorption. A bolus of nutrients impairs hydralazine uptake whereas a constant infusion over several hours does not (Semple et al, 1991). Total hydralazine absorption, however, is similar in both cases, although absorption is delayed by a bolus meal.

Gastric emptying of drugs is delayed when they are administered with a meal. Gastric emptying of drugs is about 15 minutes for fasted dogs, but may take up to three hours if given to

dogs fed a full meal. Because the majority of drug absorption occurs in the small intestine, drug administration with food typically results in delayed drug absorption and may or may not affect the extent of absorption. Feeding also stimulates acid secretion in dogs, which markedly increases the absorption of drugs with low pKa (e.g., weak acids, ketoconazole). The rate and extent of absorption of cephalexin are decreased in dogs when this antibiotic is administered with food, but this decrease is clinically irrelevant (a similar example is amoxicillin). In contrast, the extent of absorption of cefadroxil is increased in fed dogs, but its rate of absorption is decreased. Because cefadroxil is a time-dependent antimicrobial, its efficacy is expected to increase when it is administered with food, but this increase may or may not be clinically relevant (Campbell and Rosin, 1998). Feeding also tends to increase GI tract blood flow, increasing both food and drug absorption.

Studies of penicillin absorption in dogs after oral administration have yielded conflicting results. In a study of greyhounds receiving 20 mg/kg body weight ampicillin or amoxicillin per os with no food, moist food or dry food, ampicillin absorption was impeded 60 to 80% by feeding, whereas amoxicillin absorption was unaffected (Watson and Egerton, 1977). In a more recent study involving a variety of breeds, absorption was impaired about 30% when ampicillin (20 mg/kg body weight) was administered immediately or two hours after feeding a dry food as compared with ampicillin administered to fasting dogs or one hour before feeding (Kung et al, 1995). Absorption of ampicillin (20 mg/kg body weight) administered immediately after feeding a moist food was similarly impaired, whereas administration two hours after feeding a moist food had a lesser effect on absorption.

In a comparative study of different penicillin preparations given to dogs, peak plasma concentrations of ampicillin, amoxicillin, penicillin V, phenethicillin and cloxacillin were decreased 40 to 50% by feeding immediately before drug administration; however, time to maximal concentrations was increased 0.5 to 1.5 hours only for ampicillin and amoxicillin (Watson et al, 1986). From these studies, it is recommended that ampicillin be given to fasted dogs and at least one hour before feeding to ensure adequate drug absorption.

**Table 69-3.** Recommendations for administering medications with or without food.*

**Drugs that can be administered with food**

| | | |
|---|---|---|
| Allopurinol | Hydrocortisone | Mitotane |
| Amantadine | Isotretinoin | Nitrofurantoin |
| Aspirin | Itraconazole (capsules) | Olsalazine |
| Azathioprine | Ketoconazole | Pancrelipase |
| Betamethasone | Ketoprofen | Paromomycin |
| Carprofen | Ketorolac | Pentoxifylline |
| Cefadroxil | Lithium | Phenylbutazone |
| Cimetidine | Lufenuron | Piroxicam |
| Clofazimine | Meclofenamate | Praziquantel |
| Clomipramine | Meloxicam | Prednisolone |
| Deracoxib | Metformin | Prednisone |
| Dexamethasone | Methocarbamol (not high fat) | Quinacrine |
| Diethylcarbamazine | Methylprednisolone | Sulfasalazine |
| Etodolac | Metoprolol | Tepoxalin |
| Flunixin | Mexiletine | Triamcinolone |
| Glyburide | Misoprostol | Ursodiol |
| Griseofulvin | | |

**Drugs that should not be administered with food (one hour before or three hours after)**

| | | |
|---|---|---|
| Acetaminophen | Digitoxin | Omeprazole |
| Ampicillin | Digoxin | Oxacillin |
| Bethanechol | Dipyridamole | Oxytetracycline |
| Captopril | Etidronate | Penicillamine |
| Carbenicillin | Itraconazole (suspension) | Penicillin V |
| Chlortetracycline | Levodopa | Procainamide |
| Cloxacillin | Levothyroxine | Quinidine |
| Codeine | Lincomycin | Rifampin |
| Cyclophosphamide | Minocycline | Tetracycline |
| Difloxacin | | |

**No effect = no *clinical* effect, can give to either fed or fasted animals (some of these drugs may have increased absorption in the fasted state but the clinical outcome is unaffected)**

| | | |
|---|---|---|
| Acepromazine | Diphenoxylate | Methotrexate |
| Aminophylline | Disopyramide | Metronidazole |
| Amitriptyline | Dolasetron | Mibolerone |
| Amlodipine | Doxepin | Milbemycin |
| Amoxicillin | Doxycycline | Moxidectin |
| Amoxicillin/clavulanate | Enalapril | Naltrexone |
| Amprolium | Enrofloxacin | Nandrolone |
| Atenolol | Ephedrine | Neomycin |
| Azithromycin | Epsiprantel | Nifedipine |
| Benazepril | Ergocalciferol | Ondansetron |
| Bismuth subsalicylate | Erythromycin | Orbifloxacin |
| Bromide | Famotidine | Ormetoprim/ sulfadimethoxine |
| Bunamidine | Felbamate | Pamidronate |
| Buspirone | Fenbendazole | Paroxetine |
| Busulfan | Finasteride | |

## Physical Incompatibilities

Specific nutrients (e.g., dietary fiber) can impede drug absorption across the GI mucosa by adsorbing the agent or increasing the unstirred water layer on the mucosal surface (Reppas et al, 1991). Some of these interactions are predictable, based on the behavior of fiber in binding substances such as bile acids or decreasing the absorptive rate of solutes such as monosaccharides. Psyllium mucilloid decreases the absorption of riboflavin, β-carotene, iron, zinc and other trace elements (Roe, 1989).

Both nutritive and non-nutritive cytoprotective agents adsorb drugs and inhibit their absorption. For example, sucralfate binds tetracycline, phenytoin, cimetidine, digoxin and levothyroxine (Havrankova and Lahaie, 1992; McCarthy, 1991). Antacids (e.g., aluminum hydroxide) can precipitate tetracyclines, iron salts, warfarin, digoxin, quinidine, phenothiazines, indomethacin, isoniazid, sulfadiazine, prednisone and levothyroxine (Roe, 1989; Liel et al, 1994). Mineral sup-

Butorphanol
Calcitriol
Carbimazole
Cefaclor
Cefdinir
Cefixime
Cefpodoxime
Cephalexin
Chlorambucil
Chloramphenicol
Chlorothiazide
Chlorpheniramine
Chlorpromazine
Ciprofloxacin
Clenbuterol
Clindamycin
Clonazepam
Clorazepate
Colchicine
Cyproheptadine
Danazol
Dantrolene
Dapsone
Dextromethorphan
Diazepam
Dichlorvos
Dichlorphenamide
Diclazuril
Diethylstilbestrol
Dihydrotachysterol
Diltiazem
Dimenhydrinate
Diphenhydramine
Firocoxib
Florfenicol
Flucytosine
Fludrocortisone
Fluoxetine
Fluconazole
Furosemide
Gabapentin
Granisetron
Hydralazine
Hydrochlorothiazide
Hydrocodone
Hydroxyurea
Hydroxyzine
Imipramine
Ipodate
Isosorbide
Ivermectin
Levamisole
Linezolid
Lisinopril
Loperamide
Marbofloxacin
Mebendazole
Meclizine
Megestrol
Melphalan
Mercaptopurine
Mesalamine
Metaproterenol
Methazolamide
Methenamine
Methimazole
Phenobarbital
Phenoxybenzamine
Phenylpropanolamine
Phytonadione (vitamin K)
Piperazine
Ponazuril
Potassium
Prazosin
Primidone
Promethazine
Propranolol
Pyrantel
Pyridostigmine
Pyrimethamine
Selegiline
Sotalol
Spironolactone
Stanozolol
Sulfadiazine
Sulfadimethoxine
Sulfamethazine
Sulfamethoxazole
Taurine
Terbutaline
Theophylline
Tocainide
Toltrazuril
Trimeprazine
Trimethoprim
Tripelennamine
Tylosin
Valproic acid
Vancomycin
Warfarin

**Prior to = administer 30 to 60 minutes before feeding**
Cisapride
Domperidone
Gemfibrozil
Glipizide
Liothyronine
Metoclopramide
Propantheline
Ranitidine
Sucralfate
Trimethobenzamide

**Consistent = can be given to fed or fasted animals, but give in a consistent manner**
Cyclosporine

**Unknown = data were not available for recommendation**
Acetylcysteine
*For no effects, although some of these drugs may have increased absorption in the fasted state, the clinical outcome may be unaffected.

plements, including iron salts such as ferrous sulfate, can decrease the absorption of methyldopa, penicillamine, tetracycline, levothyroxine and quinolone antibiotics (Roe, 1989; Campbell et al, 1992). When orbifloxacin was mixed with a vitamin-mineral supplement in vitro, within four days orbifloxacin concentration was decreased by about 50% of what was expected (KuKanich and Papich, 2003). Calcium salts and calcium-containing foods (e.g., milk, 1 to 2 mg calcium/ml) can precipitate insoluble tetracycline chelates (Williams et al, 1993). Foods of plant origin may contain phytic acid, which inhibits zinc and calcium absorption, and tannins, which inhibit iron uptake. Gelatinization of liquid drug formulations following mixing with enteral formulas has been observed for certain expectorants, elixirs, syrups, concentrates and suspensions.

The potential binding of pharmaceutical agents to equipment used for administration should also be considered. Adsorption of vitamin A and drugs such as phenytoin and insulin to plastic polymers used in nasogastric, gastrostomy and enterostomy tubing has been reported (Fleisher et al, 1990; Spence and Camishion, 1995). Furthermore, precipitation or gelatinization of drugs by nutrients can block feeding tubes. Diazepam binding to intravenous fluid lines is a good example of drugs binding to equipment (Parker and MacCara, 1980). Approximately 45% of diazepam will adsorb to fluid bags within two hours and about 48% of diazepam will bind to intravenous fluid lines during a constant rate infusion.

## Physical Factors Affecting GI Absorption of Drugs

The cephalic phase of digestion is normally initiated by the perception, visualization, smell and taste of food. This phenomenon contributes to normal GI motility, secretion, digestion and absorption of food and pharmaceutical agents. For example, when acetaminophen is administered by nasogastric tube postoperatively, its absorption is significantly reduced compared with its absorption following oral administration (Elfant et al, 1992). Decreased GI motility due to stress, pain, luminal obstruction and postsurgical ileus may also contribute to reduced absorption.

Commercial moist and dry foods similarly affect gastric emptying; however, solid food may decrease the emptying of liquids and liquids may decrease the rate and pattern of solid emptying (Burrows et al, 1985; Horowitz et al, 1989). Specific dietary components that affect the rate of GI transit can also alter oral drug assimilation. In dogs, meals containing cellulose or wheat bran increase the frequency of postprandial contractions; yet, only cellulose decreases duodenojejunal flow and prolongs transit time (Bueno et al, 1981). However, bran increases mixing and onward propulsion of ingesta. Addition of guar gum induces continuous low-amplitude contractions in dogs and increases jejunal flow, but still increases transit time because of water adsorption and luminal distention. Soluble fibers (e.g., methylcellulose) increase luminal viscosity, resulting in delayed gastric emptying and increased thickness of the unstirred water layer (Reppas et al, 1991). Thus, both delivery of drug to the intestine and contact with the mucosal surface are impeded.

Addition of fat to a meal changes intragastric distribution of solid material, induces segmental changes in antral and pyloric

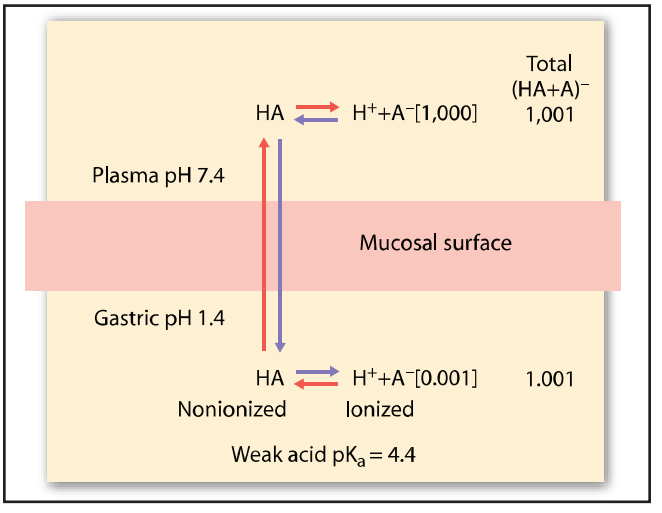


**Figure 69-2.** Influence of pH on the distribution of a weak acid between gastric contents and blood plasma across the gastric mucosa. The nonionized form of the drug predominates at low pH following gastric acid release. Only the nonionized form has sufficient lipid solubility to diffuse across the gastric mucosa. The ratio of ionized to nonionized drug may be calculated from the Henderson-Hasselbalch equation, and is determined by the pH on either side of the mucosa relative to the pKa of the drug. Dietary factors that increase or decrease gastric acid secretion will promote or inhibit acidic drug absorption. (Adapted from Benet LZ, Kroetz DL, Sheiner LB. The dynamics of drug absorption, distribution, and elimination. In: Hardman JA, Limbird LE, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed. New York, NY: McGraw-Hill, 1996.)

**Table 69-4.** Dietary factors that may affect drug metabolism and excretion, principally through induction of phase I biotransformation.

| Macronutrients | Micronutrients | Non-nutrients |
|---|---|---|
| Protein | Vitamins | Antioxidants (BHA, BHT) |
| Carbohydrate | Minerals | Coumarins |
| Fat | Essential fatty acids | Flavonoids |
| Fiber | | Indoles |
| | | Methylxanthines |
| | | Organonitriles |
| | | Phenols |
| | | Pyrolysis by-products |
| | | Terpenoids |
| **Examples of drugs whose metabolism and excretion is altered by these dietary factors** | | |
| Acetaminophen | | Morphine |
| Allopurinol | | Oxazepam |
| Aminophylline | | Penicillin |
| Cefoxitin | | Pentobarbital |
| Chloramphenicol | | Phenobarbital |
| Chloroquine | | Phenytoin |
| Diazepam | | Prednisolone |
| Estradiol | | Propranolol |
| Hexobarbital | | Theophylline |
| Isoniazid | | Zoxazolamine |
| Meperidine | | |

motility and retards gastric emptying (Heddle et al, 1989). Intraduodenal instillation of dilute glucose solutions at a rate in excess of approximately 2 kcal (8.4 kJ)/min., regardless of tonicity, stimulates both phasic and tonic pyloric contractions, thereby inhibiting gastric emptying and delaying oral drug absorption. Propranolol and metoprolol are affected in this manner (Chow and Lalka, 1993; Heddle et al, 1988). Enterohepatic cycling of drugs (e.g., doxycycline) may be affected by rate of passage and by portal blood flow and hepatic metabolism.

## Chemical Factors Affecting GI Absorption of Drugs

Beyond the effects of drug binding or precipitation, specific nutrients may compete for absorption by the intestinal mucosa. For instance, phenytoin absorption is impaired by concurrent administration of the B vitamins folic acid and pyridoxine (Roe, 1989). Concurrent food intake and particular food ingredients can alter gastric or intestinal pH, thereby altering drug dissolution, ionization and absorption. In addition to the effect of milk calcium content on tetracycline absorption, milk can increase gastric pH, inducing premature dissolution of enteric-coated tablets, resulting in gastric irritation, altered absorption or both.

Gastric acid secretion associated with food ingestion can assist in the dissolution and ionization of alkaline drugs. Gastric acid secretion, however, limits the rate of absorption of alkaline drugs, while promoting the absorption of dissolved, unionized acidic drugs (**Figure 69-2**). The subsequent release of bicarbonate-rich pancreatic secretions promotes ionization of acidic drugs, but facilitates absorption of dissolved, unionized alkaline drugs. Release of hydrochloric acid in the stomach typically leads to alkalinization of the blood and the postprandial "alkaline tide," establishing an ionization gradient that can affect diffusion of ionizable compounds across the GI mucosa.

By affecting the food's acidification potential, dietary cation-anion balance can alter mineral absorption and drug availability through changes in ionization. Concurrent consumption of fats can affect drug absorption, depending on the polarity and lipid solubility of the individual agent. For example, it has been well documented that lipid-soluble vitamins and the antifungal agent griseofulvin are better absorbed when taken with whole milk or a meal with fat. High-fat foods may promote the absorption of nitrofurantoin, chlorothiazide and riboflavin by delaying gastric emptying, which facilitates dissolution in the stomach before passage into the small intestine for uptake (Roe, 1989).

# TRANSPORT FROM THE GI TRACT TO THE SITE OF ACTION OR METABOLISM

Dietary factors that affect blood flow will alter the rate of delivery of absorbed drugs to their site of action or metabolism. Dehydration not only may reduce GI blood flow and absorption, but may also reduce the absorbed drug's subsequent delivery to or removal from particular tissues. Hypovolemia and reduced tissue perfusion may result in target tissue concentrations below the effective concentration. Decreased blood flow may reduce hepatic extraction for metabolism and excretion. Decreased urine formation may increase drug accumulation and toxicity in various organs; aminoglycoside accumulation in

the renal proximal tubules is an example. Other dietary ingredients may affect cardiac output (methylxanthines), renal blood flow (protein) or intestinal reperfusion following ischemia (antioxidants), thereby altering drug distribution.

Like many metabolites and hormones, drugs may be transported in the blood in free form or bound to plasma proteins. Thus, changes in nutritional status that affect plasma protein synthesis will likely affect drug binding and distribution. For example, hypoalbuminemia due to low dietary protein quantity or quality can affect the distribution of antibiotics, barbiturates, cardiac glycosides and analgesics. Drugs and nutrients may influence one another's disposition because binding to plasma proteins is competitive. Recent protein-binding interaction studies indicate that drug-drug competition for protein binding sites occurs rarely; the only drug expected to result in an adverse effect is lidocaine administered as an IV infusion (Benet and Hoener, 2002). However, hypoproteinemia may have marked effects that can result in toxicity due to increased free drug (e.g., lidocaine) or decreased efficacy (e.g., cefpodoxime) due to increased elimination by glomerular filtration (i.e., protein-bound drugs are excluded from glomerular filtration). High postprandial free fatty acid levels can displace anionic compounds from cationic binding sites on plasma proteins. Drugs and nutrients that are competitively transported into erythrocytes may be similarly affected. This effect has been documented for the interaction between folic acid and the loop diuretics furosemide and ethacrynic acid (Roe, 1989). Dietary factors that influence acid-base metabolism can alter blood pH and intraerythrocytic pH, thereby affecting drug ionization, protein binding and cell uptake.

## DIETARY EFFECTS ON DRUG METABOLISM

The clearance of many drugs from the circulation depends on their biotransformation in the liver, kidneys and other organs with xenobiotic-metabolizing enzymes (**Table 69-4**) (Williams et al, 1993; Anderson and Kappas, 1991). For drugs that are metabolized rapidly, extraction is determined principally by organ blood flow. For example, the rate-limiting step for clearance of indocyanine green and sulfobromophthalein sodium is hepatic blood flow. Lidocaine and fentanyl are examples of currently used drugs, whereas sulfobromophthalein and indocyanine green are typically used for physiologic measurements. For drugs that are metabolized relatively slowly, clearance from the circulation is determined primarily by the quantity and affinity of enzymes responsible for their metabolism.

Hepatic drug metabolism occurs through two predominant biotransformation pathways: 1) phase I (oxidation, reduction and hydrolysis) and 2) phase II (glutathione or glucuronide conjugation, acetylation and sulfation). Phase I reactions are catalyzed principally by a family of cytochrome P-450 enzymes in the microsomal mixed-function oxidase system. Phase I reactions alter the functional groups of a compound (**Figure 69-3**). Phase I reactions increase water solubility. However, phase I reactions do not always alter functional groups (e.g., diazepam→nordiazepam, oxazepam). Furthermore, metabolism increases the conversion of prodrugs to active drugs (e.g., cyclophosphamide→4-hydroxyphosphamide→acrolein, phosphoramide mustard).

Phase II reactions are catalyzed by families of glutathione-S-transferase, glucuronyl transferase and N-acetyltransferase isoenzymes. Phase II reactions result in conjugation and altered water solubility (**Figure 69-4**). The outcome of phase I and II reactions is reduced activity and enhanced drug excretion. Phase I reactions may increase the activity or toxicity of drugs; phase II reactions may alter tissue distribution and subsequent target organs for toxicity or mutagenicity of the drug's metabolites (Guengerich, 1984; Parke and Ioannides, 1981).

### Macronutrient Effects on Drug Metabolism

Inappetence due to disease is a common cause of decreased macronutrient intake that can affect drug action. Furthermore,

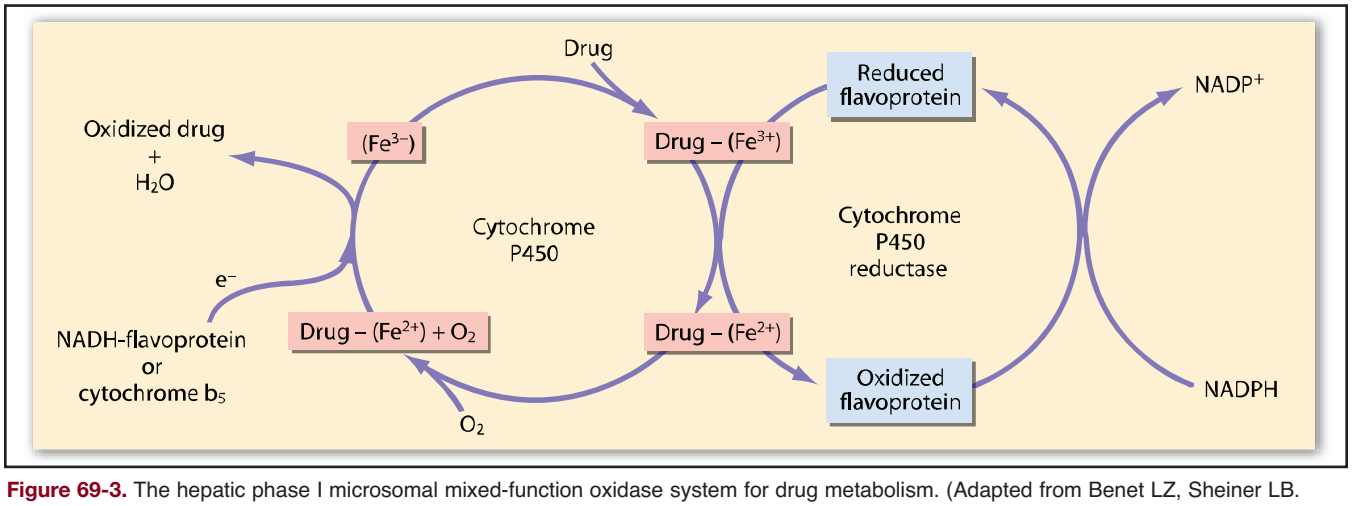


**Figure 69-3.** The hepatic phase I microsomal mixed-function oxidase system for drug metabolism. (Adapted from Benet LZ, Sheiner LB. Pharmacokinetics: The dynamics of drug absorption, distribution, and elimination. In: The Pharmacological Basis of Therapeutics, 7th ed. New York, NY: McGraw-Hill, 1985.) Key: Fe = iron, $NADP^+$ = the oxidized form of nicotinamide-adenine dinucleotide phosphate, NADPH = the reduced form of NADP.

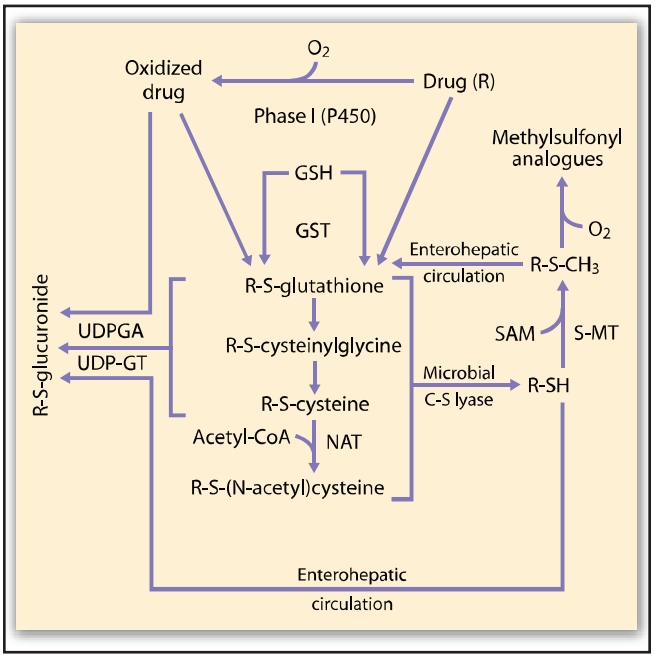


**Figure 69-4.** The hepatic phase II biotransformation system for drug metabolism. (Adapted from Fettman MJ, Butler RN, McMichael AJ, et al. Metabolic phenotypes and colorectal neoplasia. Journal of Gastroenterology and Hepatology 1991; 6: 81-90.) Key: P-450 = cytochrome P-450, GSH = reduced glutathione, GST = glutathione-S-transferase, acetyl-CoA = acetyl-coenzyme A, NAT = N-acetyltransferase, UDPGA = uridine diphosphoglucuronic acid, UDP-GT = UDP-glucuronyl transferase, SAM = adenosylmethionine, S-MT = S-methyltransferase.

changes in the macronutrient composition of the diet can significantly alter hepatic drug metabolism.

## Dietary Protein Intake

In experimental studies in rats, low dietary protein intake reduced the metabolism and increased the toxicity of pentobarbital, strychnine and zoxazolamine (Guengerich, 1984). The activities of the mixed-function oxidase enzymes flavoprotein reductase and cytochrome b5 are decreased by dietary protein restriction. Inducibility of cytochrome P-450 by phenobarbital in rats is also decreased by feeding less dietary protein (Guengerich, 1995).

High-protein (e.g., 44 vs. 10% of kcal, as fed), low-carbohydrate foods (e.g., 35 vs. 70% of kcal, as fed) enhance the hepatic metabolism and excretion of many different drugs in people, including acetaminophen, oxazepam, theophylline, propranolol and estradiol (Guengerich, 1995; Fagan et al, 1987; Pantuck et al, 1991). Conversely, consumption of protein-restricted foods for as few as 10 days significantly decreases elimination of these drugs.

Certain essential amino acids may stimulate hepatic protein synthesis and thereby induce the hepatic mixed-function oxidase system. Sulfur-containing amino acids can promote hepatic drug metabolism by increasing glutathione synthesis and subsequent conjugation reactions (Fettman, 1991). Starvation can reduce the activity of glutathione-S-transferase and the synthesis of glutathione for conjugation; events that also participate in the development of fasting hyperbilirubinemia.

Dietary protein-related changes in renal blood flow and renal tubular transport can simultaneously affect the clearance of drugs eliminated in urine (Park et al, 1989). Increased dietary protein intake in dogs (from 9.4 to 27.3% on a dry matter basis) increases the elimination of gentamicin and reduces the potential for nephrotoxicity, presumably by stimulating renal blood flow (Behrend et al, 1994; Grauer et al, 1994). In people, low-protein diets (19 vs. 268 g/day) decrease the hepatic metabolism of allopurinol to oxypurinol, and decrease renal excretion of oxypurinol (Berlinger et al, 1985). The pharmacokinetics of allopurinol and oxypurinol in dogs do not appear to be affected by dietary protein (Bartges et al, 1997).

One canine study determined the effects of various foods on the pharmacokinetics of phenobarbital and the interactive effects of changes in body composition and metabolic rate (Maguire et al, 2000). Phenobarbital pharmacokinetic studies were performed in 27 healthy, adult, sexually intact female beagles before and two months after they were fed one of three commercially available foods: 1) a maintenance food, 2) a low-protein veterinary therapeutic food for renal failure patients or 3) a low-fat veterinary therapeutic food for weight loss. Phenobarbital, 3 mg/kg body weight orally, twice daily was administered to all three groups. Volume of distribution, mean residence time and half-life ($t_{1/2}$) decreased significantly, whereas clearance rate and elimination rate increased significantly with time in all groups. Dietary protein or fat restriction induced significantly greater changes: $t_{1/2}$ (hours) was lower in dogs fed the renal food (25.9 ± 6.1) and the weight-loss food (24.0 ± 4.7) compared to results from dogs fed the maintenance food (32.9 ± 5.2). Phenobarbital clearance rate (ml/kg/min.) was significantly higher in dogs fed the weight-loss food (0.22 ± 0.05) compared to clearance rates in dogs fed the maintenance food (0.17 ± 0.03) or the renal food (0.18 ± 0.03). Induction of serum alkaline phosphatase activity (IU/l) was greater in dogs fed the renal food (192.4 ± 47.5) and the weight-loss food (202.0 ± 98.2) than in dogs fed the maintenance food (125.0 ± 47.5). The authors concluded that phenobarbital dosage should be reevaluated if a dog's diet, body weight or body composition changes during treatment. Veterinarians in clinical practice, researchers evaluating drug pharmacokinetics (phenobarbital and other drugs) and pet food companies that market veterinary therapeutic foods with nutrient profiles that differ from typical commercial maintenance foods should be aware that a dietary change may markedly affect the pharmacokinetics of concurrent drug therapy.

## Dietary Carbohydrate Intake

High carbohydrate intake (70 vs. 35% on a dry matter basis) in people depresses oxidative drug metabolism (Fagan et al, 1987). High dietary fructose, glucose and sucrose levels increase barbiturate sleeping time and decrease in vitro metabolism of barbiturates in mice (Guengerich, 1995). Parenteral glucose has the same effect in dogs and cats; thus, high dietary intake of these carbohydrates may likely modify barbiturate responses in these

species as well. Supplemental carbohydrate administration in rats increases liver weight, hepatic fat and glycogen deposition, but decreases hepatic mixed-function oxidase activities. Carbohydrate feeding in rats can similarly decrease the microsomal activation of carcinogens such as benzo(a)pyrene and aflatoxin $B_1$.

In people, long-term consumption of 70 vs. 35% carbohydrate diets depresses antipyrine and theophylline clearance (Pantuck et al, 1991). The proposed mechanism involves inhibition of the synthesis of d-aminolevulinic acid synthetase, a key enzyme in the synthesis of heme for cytochrome P-450 (Pantuck et al, 1991). However, carbohydrate is also required for UDP-glucuronyl transferase activity for glucuronidation of oxidized drug metabolites; short-term deprivation of carbohydrates can decrease rates of conjugation. This, too, contributes to the hyperbilirubinemia of fasting.

### *Dietary Fat Intake*

In addition to the effects of dietary fat intake on drug absorption and plasma protein binding, lipid intake can affect hepatic xenobiotic-metabolizing enzyme activities (Guengerich, 1995). Foods deficient in essential fatty acids result in decreased rates of drug metabolism. Dietary lipids have been reported to be essential for optimal induction of P-450 enzymes by phenobarbital. Rats fed a 20% corn-oil diet for four days had twofold increases in the activities of several hepatic P-450 isoenzymes (P-450 2, 2A1, 2B1, 2C11, 2E1 and 3A) as compared with enzyme activities in rats fed a fat-free diet (Yoo et al, 1992). However, there is an inverse relationship between lung P-450 2B1 activity and dietary fat intake. In one study in which rats were fed 6% dietary lipid for 40 days as coconut, peanut, corn or fish oil, cytochrome P-450 and epoxide hydrolase activities were highest in the fish-oil group (Mounie et al, 1986). In this same study, UDP-glucuronyl transferase type I activity was increased by fish-oil or corn-oil supplementation, but reduced by coconut oil.

In another study, rats fed 10% dietary lipid for two weeks as soybean oil, lard or fish oil were exposed to pentachlorobenzene (PECB). Blood concentrations of the metabolite pentachlorophenol were highest and tissue concentrations of PECB were lowest after feeding fish oil (Umegaki et al, 1995).

Fish oils are relatively high in polyunsaturated fatty acids, particularly of the omega-3 (n-3) family (eicosapentaenoic and docosahexaenoic acids), but contain relatively less omega-6 (n-6) fatty acids than other sources. Effects of fish-oil supplementation may be due to: 1) altered cell and organelle membrane fluidity, 2) increased propensity towards oxidative damage and/or 3) specific induction of enzyme synthesis. In people, the degree of dietary fatty acid saturation has had little effect on oxidation of antipyrine or theophylline; however, the principal cytochrome P-450 isoenzyme, 3A4, is sensitive to microsomal membrane characteristics (Guengerich, 1995). A dietary deficiency of labile methyl donors (e.g., choline or methionine) increases spontaneous and chemically induced hepatocarcinogenesis in rats because of decreased microsomal enzyme activity (Rogers, 1995). Lipotrope deficiency also impairs methylation of DNA and RNA; however, a considerable portion of microsomal lipid can be removed in vitro without adversely affecting P-450 activity.

Dietary fat restriction alters phenobarbital pharmacokinetics in dogs, as discussed in more detail in the Dietary Protein Intake section (above). Restriction of dietary fat resulted in a significantly shorter phenobarbital half-life, a significantly higher phenobarbital clearance rate and an increased induction of alkaline phosphatase activity vs. the fat levels in the control, maintenance type food (Maguire et al, 2000).

### *Effects of Feeding Route*

The route of nutrient administration may also affect hepatic drug metabolism. Decreased hepatic clearance of indocyanine green in pigs fasted for 12 days returns to normal after enteral feeding for 12 days (Waters et al, 1994). However, intravenous feeding with an identical formula did not improve hepatic clearance despite similar weight gains. Hepatic hydroxylation of pentobarbital and demethylation of meperidine by rats are significantly impaired following seven days of parenteral feeding with a formula that otherwise maintains hepatic drug clearance when administered enterally (Knodell et al, 1984). Lipid-free total parenteral nutrition depresses hepatic phase I and II drug metabolism. Parenteral lipid-free nutrition for 10 days in rats decreased the hepatic activities of cytochrome P-450 oxidase, p-nitroanisole demethylase and p-nitrophenol glutathione-S-transferase by one-half (Raftogianis et al, 1995). Thus, the intake of macronutrients, composition of the food and route of nutritional support interact to modify drug metabolism.

## Micronutrient Effects on Drug Metabolism

### *Dietary Vitamin Intake*

The hepatic mixed-function oxidase system requires several vitamins (Anderson and Kappas, 1991; Yang et al, 1992). Niacin and riboflavin participate directly as the principal components of the electron carriers $NADP^+$, $NAD^+$, FAD and FMN, which are coenzymes for cytochrome P-450 reductase, DT-diaphorase and NADH-cytochrome $b_5$ reductase (Anderson and Kappas, 1991). Dietary deficiency can lead to a generalized decrease in total P-450 and associated monooxygenase activities (Guengerich, 1984; Catz et al, 1970).

Folate deficiency blocks the induction of cytochrome P-450 by phenobarbital, and pyridoxine (vitamin $B_6$) deficiency may alter cysteine conjugate β-lyase activity (Guengerich, 1984). Excessive dietary folate can antagonize methotrexate activity, whereas increased pyridoxine intake can increase the metabolism of levodopa, thereby reducing its effectiveness. Thiamin deficiency increases the levels of cytochrome P-450 2E1, NADH-P-450 reductase and cytochrome b5, but decreases the oxidation of N-nitrosodimethylamine, acetaminophen, aminopyrine, ethylmorphine, zoxazolamine and benzo(a)pyrene (Anderson and Kappas, 1991).

The antioxidant vitamins (A, C and E) are required for normal membrane synthesis and stability. Vitamin A deficiency decreases hepatic mixed-function oxidase system activity and depresses oxidation of aminopyrine, ethylmorphine, aniline,

benzo(a)pyrene and 7-ethoxycoumarin (Anderson and Kappas, 1991). Vitamin C deficiency decreases NADPH-P-450 reductase activity and prolongs the half-life of antipyrine, acetaminophen and salicylamide. Vitamin E deficiency decreases microsomal metabolism of ethylmorphine, codeine and benzo(a)pyrene (Anderson and Kappas, 1991). Effects of vitamin E deficiency occur without decreases in cytochrome P-450 activity, and probably relate to the antioxidant properties of tocopherol, which may prevent oxidative damage to membrane lipids. Vitamins A and D are substrates for cytochrome P-450 and can competitively block the metabolism of other P-450 substrates.

### *Dietary Mineral Intake*

Many minerals modulate hepatic drug metabolism. Iron is required for heme synthesis in cytochromes and for metal ion-catalyzed oxidative reactions (Parke and Ioannides, 1981). Iron deficiency results in decreased metabolism of hexobarbital and aminopyrine (Anderson and Kappas, 1991). Selenium is a cofactor for glutathione peroxidase; selenium deficiency may promote oxidative damage to the microsomal system. Hypothyroidism resulting from iodide deficiency increases flavoprotein synthesis and cytochrome P-450 oxidative activity (Danforth and Burger, 1989). Deficiencies of zinc, magnesium and potassium decrease drug metabolism, whereas high concentrations of metals (e.g., cobalt and cadmium) may block heme synthesis and thereby lower cytochrome P-450 levels (Anderson and Kappas, 1991).

## Non-Nutrient Effects on Drug Metabolism

Non-nutrient dietary factors can profoundly influence drug metabolism by inducing the activity of many hepatic biotransformation enzymes (Guengerich, 1995). Phenols (e.g., hydroxycinnamic, dihydroxycinnamic and ferulic acids) are antioxidants that block chemical carcinogenesis. Methylxanthines, including caffeine, theobromine and theophylline, competitively bind to cytochrome P-450 to block oxidation of other compounds. Coumarin derivatives in vegetables and fruits induce glutathione-S-transferase activity. Organonitriles (1-cyano-2-hydroxy-3-butene, 1-cyano-3,4-epithiobutane) and indole derivatives (indole-3-carbinol, 3,3'-diindolmethane, indole-3-acetonitrile) in cruciferous plants (e.g., broccoli, cauliflower and cabbage) increase hepatic and renal glutathione concentrations and induce hepatic and renal glutathione-S-transferase activities (Fettman, 1991).

Excessive organonitrile exposure induces hepatic and renal toxicity, which may impair drug metabolism, whereas small amounts may have anti-carcinogenic properties (Guengerich, 1995; Fettman, 1991). Flavonoids and terpenoids from citrus fruits can either induce or block cytochrome P-450-related oxidative reactions, and can exert mutagenic or anti-tumorigenic effects, depending on the dose administered (Guengerich, 1995). Flavonoids in grapefruit juice can significantly prolong the half-life of dihydropyridine calcium channel blockers (e.g., nifedipine, felodipine and nisoldipine) and inhibit the metabolism of cyclosporin. St. John's wort is a potent inhibitor of cytochrome P-450 3 families (CYP3A); therefore, it can inhibit metabolism, cause toxicity or lead to decreased efficacy.

Butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) are added to certain processed food products to inhibit lipid oxidation (Guengerich, 1995). These food additives competitively inhibit cytochrome P-450-related oxidases, but induce other enzymes, including glutathione-S-transferase, glucuronyl transferase, DT-diaphorase and quinone reductase. In some experimental systems, they have demonstrated anti-carcinogenic properties, presumably by blocking activation of chemical carcinogens (DeLong et al, 1985). In other systems, a hydroperoxide derivative has been shown to have a tumor-promoting effect (Guyton et al, 1991). Polycyclic hydrocarbons and related pyrolysis products of charbroiling are reported to increase cytochrome P-450 oxidase activities and to increase the clearance of such drugs as theophylline, bufuralol, acetaminophen, tacrine and warfarin (Guengerich, 1995). Induction of cytochrome P-450 hydroxylase can lead to activation of arylamine and heterocyclic amines, which are also consumed with food, and have been linked to stimulation of carcinogenesis.

# DIETARY EFFECTS ON DRUG EXCRETION

Following P-450 hydroxylation, heterocyclic amines may subsequently undergo N-acetylation, the metabolic phenotype and activity of which affects the organ and route of excretion of the metabolite (Fettman et al, 1991). If there is "slow" N-acetyltransferase activity, most of the hydroxylated amine undergoes hepatic glucuronidation and is returned to the blood for excretion in the urine. In people, so called "slow acetylators" are predisposed to urinary bladder cancer. Those individuals with "fast" N-acetyltransferase activity appear to be predisposed to colorectal cancer, presumably through preferential colonocytic metabolism to mutagenic arylamides and acetoxyarylamines. Thus, metabolic phenotype as determined by genetics, or from enzyme induction due to dietary effects, can influence the site, route and rate of drug excretion. In veterinary patients, dogs are poor acetylators whereas cats are good acetylators.

Because many of the drugs excreted by the kidneys undergo active transport by anion- or cation-specific mechanisms in the renal tubular epithelium, their elimination can be altered through competitive inhibition by other charged solutes. Pharmacologically, this effect has been purposely employed by the co-administration of probenecid with penicillins to block elimination by the anion-specific renal tubular transport mechanism. Nutritionally, this effect may result from consumption of divalent cations (e.g., calcium and magnesium), which decreases renal tubular transport and accumulation of aminoglycosides such as gentamicin (Brinker et al, 1981; Quarum et al, 1984; Schumacher et al, 1991; Wong et al, 1989). As a result, urinary elimination of the antibiotic is increased and nephrotoxicity thereby reduced.

Furthermore, dietary alterations in urinary pH can affect the ionization and trapping of drugs secreted into the tubular lumina. The relatively common practice of formulating commercial feline foods to promote urinary acidification in the prevention and treatment of lower urinary tract diseases (e.g., struvite crys-

talluria and urolithiasis) may also affect the elimination of pharmaceutical agents excreted in the urine (Fettman et al, 1992). Examples include ion trapping in urine as a treatment for aspirin (salicylate) and amphetamine toxicities. Urine alkalinization increases the elimination of aspirin and urine acidification increases the elimination of amphetamine. However, acid/alkaline changes for these treatments typically occur through fluid and fluid supplementation.

Food ingredients that stimulate bile, fecal or urine flow may affect the excretion of drugs by these routes. For example, dietary fats with choleretic properties will enhance the excretion of drug metabolites in the bile and the return of enterohepatically recycled drugs such as doxycycline. Salts of divalent cations (e.g., magnesium oxide and magnesium hydroxide) can exert a laxative effect that may increase fecal elimination of poorly absorbed oral drugs and enterohepatically recycled drugs. High dietary salt content and other naturally occurring diuretics, including active loop diuretics, can enhance the excretion of drugs and their metabolites in urine.

## BENEFICIAL EFFECTS OF NUTRIENTS ON DRUG ACTION

The presence of food need not impair drug absorption, and within limits may be indicated to facilitate safe GI uptake of drugs (**Table 69-3**). Food may prevent GI irritation, modify drug-induced nausea or delay drug uptake, increasing the ultimate amount of drug absorbed (**Table 69-5**). For example, food can promote gastric acid secretion to enhance the uptake of an acidic drug such as aspirin while simultaneously protecting the mucosa from irritation by the drug.

Consumption of food can minimize nausea induced by the concurrent administration of hypertonic salt and carbohydrate solutions. In people, micronized preparations of phenytoin are actually better absorbed in the fed rather than the fasted state (Fleisher et al, 1990). In other cases, dietary supplementation with a specific nutrient may be indicated to counteract adverse drug side effects, to prevent drug-induced nutrient imbalances or to potentiate therapeutic effects.

### Provision of Nutrients to Prevent Drug-Induced Imbalances

Additional energy and protein may be indicated to combat alterations in drug metabolism associated with prolonged decreases in food intake. A critical example would be the provision of nutrients during enteral- or parenteral-assisted feeding of patients incapable of voluntary food consumption. Effects of individual nutrient deficiencies have already been described. In addition, studies of prolonged starvation and of kwashiorkor in people have demonstrated significant reductions in the metabolism of numerous drugs by phase I and phase II hepatic biotransformation systems (Guengerich, 1995). These drugs include chloroquine, isoniazid, penicillin, chloramphenicol, tobramycin and cefoxitin. In addition, hypoalbuminemia-related decreases in drug binding alter the clearance of cloxacillin, streptomycin, sulfamethoxazole, sulfadiazine, digoxin, thiopental and phenylbutazone (Roe, 1989). Malnutrition-related decreases in renal blood flow and glomerular filtration rate have caused gentamicin toxicity.

**Table 69-5.** Examples of the effects of nutrients on drug action.

| **Beneficial effects** | **Examples** |
|---|---|
| Enhanced GI drug absorption | Fatty foods enhance absorption of griseofulvin |
| Prevention of undesirable drug effects | Foods minimize nausea induced by metronidazole |
| Enhancement of desirable drug effects | Water enhances laxative effects of psyllium |
| Improved drug metabolism | Enteral feeding supports metabolism of cefoxitin |
| Altered drug excretion | Protein promotes renal excretion of gentamicin |
| **Detrimental effects** | **Examples** |
| Impaired GI drug absorption | Food interferes with absorption of ampicillin |
| Antagonism of desirable drug effects | Folate opposes chemotherapeutic effects of methotrexate |
| | Increased plasma potassium decreases digoxin activity |
| Potentiation of undesirable drug effects | Potassium increases potential toxicity of captopril |
| | Decreased plasma potassium increases digoxin activity |
| Impaired drug metabolism | Fish oil enhances hepatic oxidation of phenobarbital |
| Altered drug excretion | Calcium increases urinary excretion of gentamicin |
| | High-chloride diets increase bromide clearance and decrease its half-life |

Most commercial pet foods are adequately fortified with micronutrients; therefore, supplementation is not necessary unless a homemade food is fed, nutrient intake is decreased or a specific medical indication for prescription of a nutrient as a "neutraceutical" exists. Vitamin supplementation may be indicated to counteract the effects of drugs that specifically antagonize vitamin absorption or function. These include: 1) the use of folacin to manage deficiency induced by folic acid antagonists such as methotrexate, 2) vitamin K vs. antagonists in the coumarin family, 3) tocopherol, retinol and/or ascorbic acid to counter losses due to oxidative drug damage, 4) cholecalciferol for deficiency induced by anticonvulsants such as phenytoin, 5) thiamin to replace that lost to thiaminase activity in raw fish and 6) B vitamins to replace those lost following antibiotic-induced alterations in the GI microflora.

Specific minerals may also become deficient because of binding or precipitation in the GI tract, or following enhanced fecal losses due to laxatives or urinary loss due to diuretics. Urinary electrolyte losses due to loop diuretics can lead to significant physiologic abnormalities. Trace elements such as zinc may bind to fiber or be precipitated by phytates. Oral calcium supplements may block iron absorption. Excessive use of antacids, laxatives and binding resins can result in macroelement deficiencies.

Glutathione precursors (e.g., cysteine or N-acetylcysteine) may be indicated to counter the oxidative damage induced by pharmaceutical agents such as the: 1) analgesic acetaminophen (e.g., S-adenosyl-L-methionine [SAMe] is recommended for oxidative damage in cats caused by acetaminophen as well as hepatotoxicity due to other origins, although definitive efficacy is lacking), 2) urinary antiseptic methylene blue, 3) injectable anesthetic propofol and 4) antitumor agent doxorubicin (Fettman, 1991; Webb et al, 2003). Oxidative damage resulting from administration of oxidized lipid supplements or excessive use of omega-3 fatty acid sources may also necessitate treatment with glutathione precursors or antioxidant vitamins.

Provision of additional water may be indicated for the prevention or treatment of renal damage resulting from nephrotoxic drug administration. Examples of drugs whose administration should routinely be coupled to increased water intake include cisplatin, aminoglycosides, nonsteroidal antiinflammatory drugs, analgesics and diuretics.

### Provision of Nutrients to Enhance Drug Effects

Certain nutrients may be prescribed to facilitate a drug's intended effect or to synergistically promote the target physiologic functions. Additional energy or protein can generally facilitate therapeutic drug effects by promoting optimal distribution and hepatic biotransformation activities. These additions will tend to normalize pharmacokinetics to ensure the individual patient's dose response may more closely approximate the anticipated response.

Providing adequate energy and protein to patients receiving exogenous thyroid hormones plays an integral role in the physiologic response to that supplementation (Danforth and Burger, 1989). Undernutrition may result in reduced synthesis of thyroid-binding plasma proteins and subsequent changes in thyroid pharmacokinetics. Reductions in energy or protein intake suppress target tissue monodeiodination of thyroxine to the physiologically active triiodothyronine. Triiodothyronine levels decrease within 24 hours of fasting or caloric restriction, and may decline by 40 to 50% within three days. Should fasting induce increased adrenal glucocorticoid secretion, depressed target tissue triiodothyronine receptor levels may also be observed. Although these reductions in target-cell responsiveness to thyroid hormones represent an appropriate adaptation to conserve energy during starvation, the effect on exogenous thyroid hormone pharmacotherapy may be undesirable.

It is important to maintain a regular feeding schedule and consistent food for animals with diabetes mellitus to stabilize intermediary metabolism. The administration of exogenous insulin to insulin-dependent diabetics and the administration of oral hypoglycemic agents to non-insulin-dependent diabetics should be timed relative to feeding. For both forms of diabetes mellitus, specific dietary formulations are indicated to: 1) modulate GI carbohydrate uptake, 2) meet protein requirements without adversely affecting renal function and 3) moderate overall lipid metabolism to prevent ketoacidosis (Chapter 29).

Dietary intake of specific minerals that modulate hormonal axes should be considered, including calcium and phosphorus intake when cholecalciferol is administered for chronic renal failure, and sodium and potassium when mineralocorticoids are replaced in hypoadrenocorticism. The trace minerals chromium and vanadium may improve glucose tolerance and facilitate management of diabetics with insulin or oral hypoglycemic agents (Anderson et al, 1991; Boden et al, 1996). Specific omega-3 fatty acid therapy may be used to potentiate the effects of antiinflammatory drugs, anticoagulants and antineoplastic agents (Meydani, 1996). Arginine may be provided to improve nitric oxide production and to enhance immune function (Kirk and Barbul, 1990), glutamine to promote enterocyte metabolism (Hall et al, 1996), cysteine to enhance glutathione synthesis (Sellke et al, 1991), carnitine to improve digoxin responsiveness in congestive heart failure (Pepine, 1991) and antioxidant vitamins to protect against oxidative damage.

Dietary fiber may be indicated along with drug therapy for a number of diseases. Increased dietary fiber intake has proved beneficial in the treatment of insulin-dependent and non-insulin-dependent diabetes mellitus by moderating glucose absorption from the GI tract. Fermentable dietary fiber increases colonic short-chain fatty acid concentrations and decreases luminal pH. As a result, these fibers may be used as the primary treatment for canine and feline colitis or as an ancillary therapy to sulfasalazine or metronidazole treatment. Soluble fibers (e.g., psyllium mucilloid) may act in this way in conjunction with other antidiarrheal treatments, or as stool softeners for use with laxatives to treat constipation (Fettman, 1992). Hepatic cytochrome P-450 concentrations and UDP-glucuronyl transferase activities appear to be altered by the type and quantity of fiber in the food (Nugon-Boudon et al, 1996).

Dietary buffers may be indicated in conjunction with other therapies for chronic renal failure to correct metabolic acidosis or to facilitate activity of replacement pancreatic enzymes in exocrine pancreatic disease. They may be used to enhance alkaline drug absorption from the GI tract and to promote acidic drug excretion in the urine. Alkalinization of the urine has been used clinically to reduce the ionization, renal accumulation and toxicity of aminoglycosides (Brown and Riviere, 1991). Finally, buffers (e.g., sodium bicarbonate, aluminum hydroxide) can be used with $H_2$-receptor antagonists (e.g., cimetidine, ranitidine) or as laxatives (e.g., magnesium oxide, magnesium hydroxide).

## ADVERSE EFFECTS OF NUTRIENTS ON DRUG ACTION

In addition to ameliorating undesirable effects on drug absorption or metabolism, specific nutrients may antagonize desired drug effects (**Table 69-5**). Excess caloric intake will complicate weight management in obese patients. Excess protein intake can adversely affect renal handling of drugs by increasing renal blood flow and drug excretion, or by promoting intraglomerular hypertension and reducing glomerular filtration in chronic renal failure. High protein intake can increase the hepatic

metabolism of drugs such as the methylxanthines, resulting in reduced therapeutic efficacy.

High mineral intake can complicate drug therapy of specific disorders: 1) sodium and hypertension, 2) potassium and hypoadrenocorticism, 3) magnesium and feline lower urinary tract disease and 4) phosphorus and chronic renal failure.

Excessive dietary intake of iodine can lead to a paradoxical "iodine toxicosis goiter" through what is referred to as the "Wolff-Chaikoff effect." As iodide accumulation by the thyroid gland increases, so does iodination of tyrosyl residues of thyroglobulin. However, very high iodine levels appear to cause auto-inhibition of iodide organification and thyroglobulin proteolysis, leading to thyroid hormone deficiency. This phenomenon has been observed in foals born to mares that received excessive iodine supplementation during gestation, as well as in other species (Drew et al, 1975; Driscoll et al, 1978).

Naturally occurring non-nutritive dietary factors that may influence drug responses include methylxanthines, which may complicate aminophylline therapy, histamine in certain types of fish, which may interfere with antihistamine treatment and tyramine in chicken livers and aged cheeses, which confound the action of monoamine oxidase inhibitors. Alcohols and antioxidants added to certain nutrient sources as preservatives and humectants may have adverse effects as well. Benzoic acid and benzoyl alcohol in commercial fluid and drug preparations, propylene glycol in semi-moist commercial cat food and onion powder in commercial human baby foods may induce oxidative erythrocyte damage and Heinz body anemia in cats (Bedford and Clarke, 1971; Wilkie and Kirby, 1988; Christopher et al, 1989; Kaplan, 1995). These substances are no longer commonly used in commercial product manufacturing.

## EFFECTS OF OBESITY ON DRUG DISPOSITION

Although complicated by the metabolic effects of overnutrition during weight gain or restricted food intake during weight loss, numerous studies have documented a significant effect of obesity on drug metabolism in people and other animals (Reidenberg, 1977). Changes in the apparent volume of distribution have been observed because of alterations in the quantity of body fat. Obesity increases the volume distribution of lipophilic drugs such as alprazolam, carbamazepine, diazepam, methotrexate, oxazepam, sufentanil and vancomycin. Increased volume distribution for lipophilic drugs (e.g., thiobarbiturates) necessitates administration of a higher dose to achieve the desired clinical response. Sequestration in body fat may prolong the drug's action. Obesity decreases the volume distribution of polar compounds including acetaminophen, ciprofloxacin, furosemide, gentamicin, isoniazid, sulfisoxazole and tolbutamide (Ducharme et al, 1994; Dunn et al, 1991; Caraco et al, 1992; Abernethy et al, 1984; Shum and Jusko, 1984; Yuk et al, 1988; Fleming et al, 1991; Schwartz et al, 1991; Allard et al, 1993).

Drug clearance may be affected following changes in hepatic microsomal enzyme induction, as well as alterations in the predominant pathways used for phase II conjugation reactions. Several investigations have demonstrated enhanced biotransformation of volatile anesthetics in obese patients, resulting in increased production of the reactive intermediates typically responsible for organ toxicity (Bentley et al, 1982). Enhanced hepatic oxidative metabolism of halothane in obese people has resulted in increased serum levels of fluoride and bromide ions; the former is associated with increased hepatotoxicity. Half-life elimination of triazolam is prolonged in obese subjects, and clearance following oral administration is reduced, presumably because of decreases in hepatic extraction.

Drug toxicity may be enhanced when the dose administered is based on total body mass, but distribution is restricted to lean body mass, resulting in higher plasma drug concentrations and greater exposure to susceptible organs (Corcoran et al, 1989; Corcoran and Salazar, 1989). Obese rats appear to be at increased risk for gentamicin and furosemide nephrotoxicity by this mechanism (Corcoran et al, 1989; Corcoran and Salazar, 1989). Susceptibility to the toxic affects of these drugs remains even when the dose is decreased to reflect lean body mass and to equalize drug exposure. Studies of acetaminophen toxicity in rats have shown that when obese animals are dosed according to fat-free mass, toxicity is increased because of a metabolic shift toward less sulfation and more glucuronidation (Corcoran and Wong, 1987). Obesity likewise appears to increase drug glucuronidation in people. Furthermore, target organs may be predisposed to drug toxicity by pre-existing obesity-related lesions such as hepatic lipidosis.

Obesity increases steroid hormone clearance in people because of enhanced aromatization and interconversion of androgens to estrogens by adipose tissue (Dunn et al, 1991). Prednisolone and methylprednisolone succinate clearance in obese people is also increased, although potential contributions by increased cardiac output, hepatic blood flow, liver size and hydrolysis by extrahepatic carboxyesterases have not been resolved. On the other hand, methylprednisolone clearance appears to be decreased, suggesting that obesity may affect specific oxidative pathways very differently (Dunn et al, 1991).

Although similar studies have not been conducted in companion animals, certain generalizations can be made. Obesity will result in changes in the effective dose administered for drugs given according to total body weight, whether it is increased because of poor lipid solubility or decreased because of lipophilicity. Drug dose or dosing interval may need to be adjusted to maintain therapeutic effect and protect against toxicity. Alterations in body composition concurrent with drug administration may have significant effects on clinical efficacy and margin of safety, and must be considered whenever a patient's body weight changes markedly (Caraco et al, 1992).

## SUMMARY

Quantitatively and qualitatively, ingested nutrients have major effects on the biologic activity of pharmacologic agents. This is true not just for orally administered drugs in the GI tract, but also for drugs administered parenterally. Ingested nutrients may

modify hepatic and renal metabolic processes, thus altering the action of parenterally administered drugs. Inappetence associated with many chronic diseases may significantly modify drug absorption, metabolism and action.

Specific macronutrients and micronutrients not only support normal physiologic processes necessary for drug delivery and action, but may also modify specific metabolic processes integral to drug activity. For instance, dietary protein must be sufficient to ensure adequate plasma protein synthesis and maintenance of plasma volume for the delivery and action of most systemically administered drugs. Dietary protein may also specifically affect the hepatic metabolism of some drugs, the renal elimination of others and the modification by target tissues of yet others. Specific amino acids can play a role in drug metabolism and action as well. Food is a major modulator of drug activity and food-drug interrelationships must be considered when designing treatment regimens.

Because few studies to determine the effects of food on drug metabolism have been conducted in dogs and cats, it is difficult to delineate specific feeding recommendations for drugs commonly used in veterinary practice. However, it is important to consider potential nutrient-drug interactions whenever the expected action of a prescribed drug is not seen in an individual patient. One may alter the dosing schedule relative to meals or adjust the dietary composition or dose to correct overt nutrient imbalances. Alternatively, one may determine circulating drug concentrations to detect changes in pharmacokinetics and to establish the need for a change in drug type or dose. It is clear that a standardized food, consistent feeding schedule and balanced nutrient intake are prerequisites to successful pharmacologic management of disease.

## FOR MORE INFORMATION

See Chapters 25 and 26 for lists of drugs that may affect taste and smell perception, stimulate appetite, are incompatible with B-complex vitamins and are compatible with total nutrient admixtures.

## REFERENCES

The references for **Chapter 69** can be found at www.markmorris.org.

## CASE 69-1

### Epilepsy in a Dachshund

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### Patient Assessment

An 11-year-old, neutered female dachshund weighing 10 kg was presented for evaluation of poorly controlled seizures. Idiopathic epilepsy had been diagnosed when the dog was six months old. The dog had received phenobarbital, phenytoin or a combination of both drugs for the past nine years. During the past few months, the dog had been having clusters of seizures each month, despite treatment with phenobarbital. Trough serum phenobarbital concentrations (20.4 μg/ml) were within the therapeutic range (15 to 45 μg/ml).

The results of physical and neurologic examinations were normal. The dog's body condition was 3/5. Serum biochemistry analysis revealed increases in liver enzyme activity (alkaline phosphatase, gamma-glutamyl transferase) and abnormal pre- and postprandial bile acid concentrations. Abdominal ultrasonography revealed mild hepatomegaly with normal hepatic echogenicity. Two small cystic calculi were evident in the urinary bladder.

The presumptive diagnosis was subclinical anticonvulsant-associated hepatopathy. Treatment was initiated with another anticonvulsant, potassium bromide (20 mg/kg body weight, per os, q24h), to control the seizures and allow the dose of phenobarbital to be reduced. The dog had no seizures during the two months after initiation of potassium bromide treatment. Serum bromide concentration had reached 1,100 mg/l (therapeutic range 1,000 to 2,000 mg/l). Alkaline phosphatase and gamma-glutamyl transferase activities had decreased markedly.

On re-examination one month later, the dog was still free from seizures, but had persistent cystic calculi. In the past, the dog had been treated for recurrent struvite crystalluria and cystic calculi with antibiotics and a veterinary therapeutic food. A struvite calculolytic food (Prescription Diet s/d Canine[a]) and antibiotic (Clavamox[b]) were prescribed. Two weeks later, the dog had a cluster of five seizures over a 36-hour period.

### Assess the Food and Feeding Method

For the past three years, the dog had been fed a moist veterinary therapeutic food (Prescription Diet c/d Canine[a]) that contains reduced levels of struvite precursor substances and produces an acidic urinary pH. These nutritional characteristics help keep struvite crystalluria and urolithiasis from recurring. Because of the recurrent cystic calculi, the food was changed two weeks ago to a

moist veterinary therapeutic food (Prescription Diet s/d Canine[a]) shown to help dissolve struvite uroliths. Nutrient profiles of the two foods are summarized in **Table 1**.

## Questions

1. What potential food-drug interactions could be causing the recent increased seizure activity in this dog?
2. What other diagnostic tests should be performed in this patient?
3. How should the treatment and feeding plan be modified?

## Answers and Discussion

1. The most likely food-drug interaction in this dog is between the potassium bromide anticonvulsant and the dietary chloride load. Bromide is excreted slowly, but almost exclusively by the kidneys. The amount of bromide excreted depends on the total body halide (i.e., fluorine, chlorine, bromine, iodine) concentration. Bromide and chloride compete for renal tubular reabsorption. An increase in chloride load, in the form of dietary sodium chloride or ammonium chloride, will markedly increase urinary excretion of bromide in several species, including dogs. In addition, high-chloride foods fed experimentally to dogs will significantly shorten the elimination half-life of bromide and lead to decreases in serum bromide concentrations. The veterinary therapeutic food being fed to the dog to help dissolve the cystic uroliths contains increased levels of sodium chloride to increase urine volume thereby decreasing the concentration of struvite-forming constituents in the urine.

**Table 1.** Nutrient profiles of veterinary therapeutic foods fed to the patient.

| Nutrient (% DM) | c/d Canine, canned[a] | s/d Canine, canned[a] |
|---|---|---|
| Protein | 23.6 | 7.9 |
| Fat | 24.0 | 26.0 |
| Carbohydrate (NFE) | 46.6 | 58.9 |
| Crude fiber | 1.4 | 2.1 |
| Calcium | 0.68 | 0.31 |
| Phosphorus | 0.51 | 0.10 |
| Potassium | 0.62 | 0.45 |
| Magnesium | 0.08 | 0.02 |
| Sodium | 0.27 | 1.30 |
| Chloride | 0.65 | 2.41 |

Key: DM = dry matter, NFE = nitrogen-free extract.

2. Serum bromide concentrations can be measured to determine whether therapeutic levels are being maintained. In this patient, the serum bromide concentration the day after the seizures was 410 mg/l, which was much lower than the concentration measured one month earlier (1,100 mg/l) and below the normal therapeutic range (1,000 to 2,000 mg/l). The anticonvulsant dosage or formulation had not been changed, and the owner was adamant that doses of potassium bromide had not been missed.
3. Because high chloride intake enhances bromide elimination and may have reduced the serum bromide concentration, the owner was instructed to discontinue feeding the moist calculolytic food and to resume feeding the moist struvite-preventive food, with the lower chloride content. The dog was fed to maintain a weight of 10 kg (520 kcal [2.18 MJ]; 1.1 cans/day).

   Seven weeks after being fed the lower chloride food again and with daily potassium bromide treatment (20 mg/kg body weight), the dog's serum bromide concentration was 990 mg/l. If a change to a higher chloride food or a food of unknown chloride content is necessary, serum bromide concentrations should be monitored frequently during the weeks to months after the dietary change, and the dosage of potassium bromide should be adjusted as needed to maintain therapeutic bromide concentrations. Eradication of urinary tract infection and monitoring urinary pH to ensure that the urine is continuously acidic are required for successful treatment and prevention of struvite urolithiasis. Serial radiographs and urinalyses should be performed to monitor the cystic uroliths. Surgical removal of uroliths may be indicated if they persist, increase in size or cause clinical problems.

## Progress Notes

Serum bromide concentrations remained stable between 1,200 and 1,250 mg/l over the next 21 months. Seizures were not observed since the cluster of seizures that occurred after the change to the high-chloride food.

## Endnotes

a. Hill's Pet Nutrition, Inc., Topeka, KS, USA.
b. Pfizer Animal Health, West Chester, PA, USA.

## Bibliography

Shaw N, Trepanier LA, Center SA, et al. High dietary chloride content associated with loss of therapeutic serum bromide concentrations in an epileptic dog. Journal of the American Veterinary Medical Association 1996; 208: 234-236.
Trepanier LA, Babish JG. Effect of dietary chloride content on the elimination of bromide by dogs. Research in Veterinary Science 1995; 58: 252-255.

## CASE 69-2

### Hyperadrenocorticism in a Dachshund

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### Patient Assessment

An eight-year-old neutered female dachshund was examined for chronic dermatitis. The owners reported a slowly progressive, nonpruritic dermatopathy and polydipsia and polyuria of three to four months' duration. The dermatitis had been treated with antibiotics and griseofulvin with no response. To the owners' knowledge, the dog had received no corticosteroids.

Physical examination revealed an alert, active 10-kg dog with normal body condition (3/5), a dry coat and a "pot-bellied" appearance. The abdomen was distended and totally devoid of hair. The skin on the abdomen was markedly thinned. Bilateral alopecia and hyperpigmentation were evident on the dorsum, extending from the shoulders to the flank. Focal, circumscribed plaques with peripheral erythema were present in the inguinal and axillary regions. The remainder of the physical examination was normal.

Diagnostic evaluation included a complete blood count (lymphopenia, eosinopenia), serum biochemistry profile (hypercholesterolemia [1,414 mg/dl, normal = 125 to 250 mg/dl] and increased alkaline phosphatase activity [491 IU/l, normal <50 IU/l]), urinalysis (dilute urine with hematuria and bacteriuria) and thoracic and abdominal radiographs (calcification of subcutaneous tissues along the back). Subsequent urine culture yielded large numbers of *Escherichia coli*. Histologic evaluation of skin biopsy specimens confirmed calcinosis cutis. Water consumption in the hospital exceeded 120 ml/kg body weight/24 hours (normal = 40 to 60 ml/kg body weight).

The tentative diagnosis was pituitary-dependent hyperadrenocorticism with secondary calcinosis cutis and bacterial urinary tract infection. Hyperadrenocorticism was confirmed by excessive plasma cortisol response to intramuscular injection of ACTH gel (cortisol, pre 27 mg/dl and cortisol, two hours post-ACTH 60.0 mg/dl; normal pre-cortisol 0.5 to 4.0 mg/dl and post-ACTH 8.0 to 20.0 mg/dl).

### Assess the Food and Feeding Method

The dog was fed a combination of a commercial grocery store brand dry food and a grocery store brand moist food. The dry food was available free choice and the moist food was fed once daily in the morning.

### Question

Mitotane[a] (o,p'-DDD) was used to treat this patient's hyperadrenocorticism. What food-drug interactions are important to consider in the treatment and feeding plans?

### Answer and Discussion

Mitotane is a commonly used drug for treatment of canine hyperadrenocorticism. Mitotane exerts a direct cytotoxic effect on the adrenal cortex, resulting in selective, progressive necrosis and atrophy of the zonae fasciculata and reticularis.

The efficacy of mitotane therapy in patients with hyperadrenocorticism can be improved markedly by dosing with food. Studies have shown that the systemic availability of mitotane is very poor when intact tablets are administered to fasting dogs, whereas availability is much better from intact or powdered tablets given with food (**Table 1**). Mitotane is soluble in fat but poorly soluble in water. The presence of dietary fat during drug administration could assist in dissolution and absorption of lipophilic drugs such as mitotane. Based on these studies, mitotane should always be administered with meals.

The interaction between food and drug probably explains some of the variation in response of pituitary-dependent hyperadrenocorticism patients to mitotane, in relation to the time required to gain initial control with daily administration and the efficacy of weekly maintenance doses. Failure to administer the drug with food may contribute to the apparent "resistance" to the effects of the drug seen in some dogs with hyperadrenocorticism.

Interactions between drugs and ingested food are common. The most common outcome is reduced or delayed absorption of the drug, although absorption is sometimes increased or unaffected by food. In many instances the changes in drug availability are modest and their clinical significance is not great. However, the substantial effect of food on mitotane availability is almost certainly clinically important and should be considered when prescribing adrenolytic therapy with this drug.

Clinical signs that owners should monitor include the dog's attitude, appetite and water intake. A common, early adverse sign of mitotane toxicity is diminished appetite, which usually occurs before other adverse clinical signs develop such as vomiting, weakness and complete anorexia. Therefore, the owners should observe the dog's appetite closely before administering the daily mitotane dose. If the food is consumed rapidly, the owner should administer the mitotane immediately after the dog finishes the meal. If the food is consumed slowly or not at all, the owners should contact the veterinarian before administering the drug.

## Progress Notes

Therapy was initiated at home with an induction or loading dose of mitotane (42 mg/kg body weight/day for seven to 10 days). One 500-mg tablet was given each day following the morning meal of moist food. The dog ate the morning meal rapidly over the next 10 days; mitotane was administered each day. By Day 10 of treatment, daily water consumption had decreased from more than 120 ml/kg body weight/day to 31 ml/kg body weight/day. Daily mitotane administration was stopped and weekly therapy initiated. The dog was also treated with sulfisoxazole for the concurrent cystitis.

## Endnote

a. Lysodren. Bristol-Myers Oncology Division, Evansville, IN, USA.

## Bibliography

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Kintzer PP, Peterson ME. Mitotane (o,p'-DDD) treatment of 200 dogs with pituitary-dependent hyperadrenocorticism. Journal of Veterinary Internal Medicine 1991; 5: 182-190.

Watson ADJ, Rijnberk A, Moolenaar J. Systemic availability of o,p'-DDD in normal dogs, fasted and fed, and in dogs with hyperadrenocorticism. Research in Veterinary Science 1987; 43: 160-165.

**Table 1.** Availability of mitotane in dogs when given in various vehicles.*

| Dogs | Dosage method | Maximum plasma drug concentration (mg/l) |
|---|---|---|
| Normal | Tablets, fasting | 0.4 |
| | Pure drug in emulsion | 11.0 |
| | Ground tablets in oil with food | 15.4 |
| | Tablets in food | 13.0 |
| Hyperadrenocorticism | Tablets in food | 24.5 |

*Adapted from Watson ADJ, Rijnberk A, Moolenaar AJ. Systemic availability of o,p'-DDD in normal dogs, fasted and fed, and in dogs with hyperadrenocorticism. Research in Veterinary Science 1987; 43: 160-165.

# CASE 69-3

## Traumatic Injury in a Mixed-Breed Dog

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## Patient Assessment

A 10-year-old, female mixed-breed dog weighing 22.2 kg was presented after being attacked by two dogs. Physical examination revealed a temperature of 37.4°C (99.3°F), pulse of 120 beats/min. and a thready, respiratory rate of 140 breaths/min. (panting) and multiple bite wounds associated with severe tearing of the subcutaneous tissues and crushing injuries to the deep musculature of the flank, lumbar and cervical regions. The dog had a flail chest, rib fractures and subcutaneous emphysema over the flank, chest, neck and head. The abdomen was painful on palpation and bruising was noticeable throughout the wound regions. The dog's body condition score was normal (3/5).

Results of a complete blood count and biochemistry profile included marked leukopenia and neutropenia with a degenerative left shift. The dog had panhypoproteinemia and moderate thrombocytopenia, which were consistent with severe sepsis and a poor prognosis. A coagulation panel demonstrated increased activated partial thromboplastin and prothrombin times with a significant decrease in platelet numbers, suggesting disseminated intravascular coagulation. Thoracic radiographs revealed a pneumomediastinum, mild pneumothorax, contusion of the left cranial lung lobe, disseminated emphysema and fractures of the right 11th and 12th ribs. Abdominal radiographs were within normal limits. No fluid was aspirated during abdominocentesis.

Initial treatment consisted of 400 ml of hetastarch (50 ml/hr) followed by lactated Ringer's solution + 20 mEq KCl/l (IV, 80 ml/hr), eurofloxacin (IV, 5 mg/kg b.i.d.), ampicillin (IV, 22 mg/kg t.i.d.), metronidazole (IV, 10 mg/kg t.i.d.), plasma (IV, 36 ml/hr administered by pump), sodium heparin (SQ, 1,500 IU t.i.d.), diazepam (IV, 2.1 mg) and 250 ml morphine (3.0 ml/45.6 mg)/lido-

caine (27.4 ml/547.2 mg) in 0.9% NaCl at a constant infusion rate (IV, 10 ml/hr). Additionally, one dose of oxymorphone (IV, 1-mg vial) was administered; morphine (IV, 0.2 mg/kg) was provided as needed to control pain.

While the dog was anesthetized, its wounds were surgically débrided, explored and covered. Devitalized tissue and skin were removed, wounds were irrigated, suction tubing was placed in linear incisions over each wound and continuous suction applied. A 20-Fr., 16-in. Argyle thoracostomy tube was placed in the 11th intercostal space because one wound communicated with the thoracic cavity. During surgery, a percutaneous gastrostomy (PEG) tube was placed for nutritional support. The dog was placed in an oxygen cage in the intensive care unit.

## Assess the Food and Feeding Method

The dog had been NPO for three days before presenting to the hospital. The dietary goals were to feed a highly digestible, calorically dense diet, with high quality and quantity of protein and high fat content to support wound healing and immune cell function and decrease body catabolism. Because the patient had not eaten for the previous three days, enteral nutritional support was initiated at 75% of the dog's calculated resting energy requirement (510 kcal/day). One 6-oz. can of Maximum-Calorie[a] diet was blended with 60 ml of warm water, which provided 1.4 kcal/ml. The feeding schedule was initiated on Day 1; the dog was fed 63 ml of the blended diet q4h through the PEG tube. Four hours after the first feeding, but before the next scheduled feeding, more than 40 ml of a dark brown granular material was aspirated from the feeding tube. Enteral feeding was discontinued.

## Questions

1. What food-drug interaction in this patient resulted in discontinuation of enteral feeding?
2. What alternative feeding route could be used to feed this dog?

## Answers and Discussion

1. Morphine is a plant-derived alkaloid of opium and is the most widely used opioid throughout the world. Oxymorphone is produced by modifying the morphine molecule. Both of these opioids produce multiple, major effects on the central nervous, respiratory, cardiovascular and gastrointestinal (GI) systems. Opioids are excellent analgesics but poor to moderately effective sedatives and muscle relaxants. Central nervous system depression occurs in dogs after systemic administration of morphine.

   The dog's first response to morphine is to empty the GI tract. Opioid receptors are found in the myenteric plexus of the GI tract and when stimulated result in constipation. Opioids induce GI stasis, which is associated with increased tone of smooth muscle throughout the GI tract. Morphine decreases biliary and pancreatic secretions, resulting in delayed digestion in the small intestine. Propulsive contractions are markedly decreased throughout the intestinal tract.

   The opioids used to control severe pain in this patient were responsible for GI tract stasis. The enteral feeding route was unsuitable for this patient because food was retained within the stomach and digestion was delayed. The dog may have had GI bleeding as evidenced by the dark brown color of the aspirated material from the PEG tube.
2. Parenteral feeding was selected for this patient.

## Progress Notes

Three days after presentation, the dog underwent cardiac arrest and died. Necropsy findings revealed massive trauma, congestion of the heart and lungs and myocardial necrosis. The bite wounds caused severe sepsis that likely led to the death of this patient.

## Endnote

a. The Iams Company, Dayton, OH, USA.

## Bibliography

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