

# Antihistamine Toxicosis

by

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Antihistamines are H<sub>1</sub>-receptor antagonists widely used in human and veterinary medicine to provide symptomatic relief of allergic signs caused by histamine release, including pruritus and anaphylactic reactions. Antihistamines are also commonly used as sedatives and antiemetics.<sup>1</sup> Antihistamines can be divided into first and second-generation (also called nonsedating) agents (*Table 1*). First-generation antihistamines are small lipophilic molecules, so they may cause adverse effects because of their cholinergic activity and their ability to cross the blood-brain barrier. Second-generation antihistamines are more lipophobic than first-generation antihistamines and are thought to lack central nervous system (CNS) and cholinergic effects when given at therapeutic doses.<sup>2</sup> Antihistamines are often found in combination with other ingredients in many over-the-counter cold, sinus, and allergy medications (*Table 2*); liquid products sometimes contain large amounts of alcohol as well.

Since 1998, veterinarians at the ASPCA Animal Poison Control Center (ASPCA APCC) have consulted on more than 2,000 cases involving antihistamine ingestion. Most cases have involved cats and dogs. Findings show that individual animals may vary greatly in their response to both therapeutic doses and overdoses of antihistamines (ASPCA APCC Database: Unpublished Data, 2001). This article briefly discusses antihistamine toxicoses in animals and how to treat them.

## Mechanism of Action

Antihistamines are reversible, competitive inhibitors of most of the pharmacologic actions of histamines. One exception is the stimulation of gastric acid secretion, which is mediated by H<sub>2</sub>-receptors. Most antihistamines do not chemically inactivate or physiologically antagonize histamine, nor do they prevent histamine release.<sup>3</sup> The exceptions are cetirizine hydrochloride (Zyrtec-Pfizer) and loratadine (Claritin-Schering), which decrease histamine release from basophils.<sup>4</sup> Actions of histamine inhibited by H<sub>1</sub>-antagonists include constriction of respiratory smooth muscle, increased capillary permeability, and edema and wheal formation.<sup>3</sup> Since the basic ethylamine group common to antihistamines is also common to anticholinergics, ganglionic- and adrenergic-blocking agents, local anesthetics, and antispasmodics, some antihistamines may exhibit some of the activities of these other classes of drugs. H<sub>1</sub>-receptor antagonists induce and may facilitate their own metabolism.

## Reported Adverse Effects

The adverse effects of antihistamines in people and animals have been associated with many different body systems (*Table 3*). Adverse cardiovascular effects, including ventricular fibrillation and death from prolonged QT interval and atypical ventricular tachyarrhythmias, have been associated with astemizole (Hismanal-Janssen Pharmaceutical) and terfenadine (Seldane-Hoechst Marion Roussel; no longer commercially available in the United States) in people. This specific cardiovascular syndrome has not been recognized in animals or seen with other antihistamines.<sup>3</sup>

The effects of antihistamine overdose vary with the dose ingested and the specific agent involved. In people, children appear to be more likely to develop excitatory signs after antihistamine overdose, while adults seem to experience sedation.<sup>5</sup> In contrast, cases from the ASPCA APCC database suggest that clinical signs are dose-related, with lower doses causing sedation and higher doses causing hyperactivity and seizures. Deaths have been reported to the ASPCA APCC after antihistamine overdose. For example, a 9-month-old dachshund that ingested 25 mg/kg of chlorpheniramine exhibited ataxia, tremors, bradycardia, coma, and cardiac arrest and died within 10.5 hours of ingestion.

Many over-the-counter antihistamine products, particularly cold, sinus, and allergy formulations, contains several ingredients. Many of these ingredients can cause serious clinical signs and often become more of a

concern than the antihistamine component of the product (Table 2). Ask clients to bring in the specific products their animals have ingested to verify all potentially harmful ingredients.

### **Ethanolamine-derivative antihistamines**

Ethanolamine-derivative antihistamines are a group of first-generation agents including bromodiphenhydramine hydrochloride, carbonoxamine, clemastine, dimenhydrinate, diphenhydramine, doxylamine succinate, and phenyltoloxamine citrate. Most calls in the ASPCA APCC database about this antihistamine class have involved diphenhydramine. Diphenhydramine is well absorbed after oral administration in people. But it appears to undergo first-pass metabolism in the liver, and only 40% to 60% of the dose reaches the systemic circulation as unchanged drug.<sup>5</sup> Diphenhydramine should not be given subcutaneously, intradermally, or perivascularly because of its irritating effects. Local necrosis has been reported with subcutaneous and intradermal administration of parenteral diphenhydramine.<sup>5</sup> Topical preparations can cause hypersensitivity reactions; topically applied antihistamines generally do not penetrate intact skin unless the stratum corneum is disrupted. Using topical diphenhydramine in addition to other preparations that contain diphenhydramine can lead to increased serum concentrations and systemic toxicosis. After intravenous administration of diphenhydramine in rats, the highest concentrations were attained in the lungs, spleen, and brain, with lower concentrations in the heart, muscle, and liver.<sup>5</sup> Peak plasma concentrations of Ethanolamine-derivative antihistamines are reached within one to five hours,<sup>5</sup> and elimination half-lives vary from 2.4 to 10 hours.<sup>1,5,6</sup>

Atropine-like activity and CNS depression may be more pronounced with this group of antihistamines compared with others,<sup>3</sup> although CNS stimulation may still be seen in overdose situations.<sup>1</sup> Adverse gastrointestinal effects are thought to occur less frequently with this group of antihistamines in comparison with the other groups.<sup>3</sup> The margin of safety seems relatively narrow within this class of antihistamines, with adverse effects occurring at or less than 1 mg/kg above therapeutic doses (ASPCA APCC Database: Unpublished data, 2001). Hyperactivity or depression, hypersalivation, tachypnea, and tachycardia are the most common adverse signs reported to the ASPCA APCC, generally occurring within one hour of exposure.

### **Ethylenediamine-derivative antihistamines**

This class of first-generation antihistamines includes antazoline, methapyrilene, pyrilamine, and tripeleennamine. Intravenous tripeleennamine has been used as a CNS stimulant in cases of downer cow syndrome. In animals, tripeleennamine crosses the placenta and is distributed into milk; it is distributed into bile primarily as metabolites and undergoes enterohepatic recirculation.<sup>5</sup> Peak plasma concentrations are usually reached two or three hours after oral administration of Ethylenediamine-derivative antihistamines. Small amounts of these agents are excreted unchanged in the urine, most appearing there as metabolites.<sup>3</sup> Even though tripeleennamine is distributed into bile, only small amounts are excreted in feces.<sup>5</sup> Adverse gastrointestinal effects and sensitivity reactions are common with Ethylenediamine-derivative antihistamines in people.<sup>3</sup> Depression, tachycardia, mydriasis, decreased bowel sounds, and urinary retention may occur even after therapeutic doses;<sup>6</sup> signs may last between three and six hours.<sup>3,5</sup>

### **Piperazine-derivative antihistamines**

This class of antihistamines includes the first-generation agents' buclizine hydrochloride, chlorcyclizine hydrochloride, cyclizine, hydroxyzine, and meclizine hydrochloride and the second-generation drug cetirizine, an active metabolite of hydroxyzine. Buclizine, cyclizine, and meclizine are used to treat and prevent motion sickness, with the antiemetic effect of meclizine thought to be mediated through the chemoreceptor trigger zone. Hydroxyzine is commonly used in veterinary medicine as a tranquilizer, sedative, antipruritic, and antiemetic.<sup>1</sup> Peak plasma concentrations generally occur within two or three hours of oral administration of Piperazine-derivative antihistamines.<sup>3</sup> The second-generation antihistamine cetirizine is largely excluded from the brain given in therapeutic doses.<sup>3</sup> But based on our observations of adverse neurological signs after second-generation antihistamine exposures (ASPCA APCC Database; Unpublished data, 2001), we speculate that cetirizine may cross the blood-brain barrier in overdose situations, leading to adverse neurological signs. Distribution of most antihistamines is not well characterized, but cetirizine appears to be widely distributed in animals, with the highest concentrations obtained in the liver, kidneys, and lungs. In lactating beagles, about 3% of a cetirizine dose was distributed

into milk. Cetirizine is also known to undergo low degree of first-pass metabolism in the liver, so individuals with a history of a liver disease may metabolize Piperazine-derivative antihistamines differently than normal individuals do.<sup>5</sup>

The first-generation Piperazine-derivative antihistamines are primarily excreted as metabolites in the urine. In contrast, cetirizine is primarily excreted in the urine in the unmetabolized form,<sup>3</sup> along with two unidentified metabolites. About 10% of cetirizine is excreted in feces, but it is not known whether this represents unabsorbed drug or excretion via biliary elimination.<sup>5</sup> Published half-lives vary greatly with Piperazine-derivative antihistamines; meclizine's reported serum half-life is six hours,<sup>1</sup> while hydroxyzine has a 20-hour elimination half-life.<sup>6</sup> Cetirizine may undergo biphasic elimination, with an initial distribution half-life of about three hours and a mean terminal elimination half-life of about 8.3 hours in healthy adult humans. The elimination half-life of cetirizine is 33% to 41% shorter in children and prolonged by about 50% in geriatric adults.<sup>5</sup>

Within this class of antihistamines, most cases reported to the ASPCA APCC have involved hydroxyzine and meclizine. In some cases, 5.9 mg/kg of hydroxyzine caused seizures in a 5-month-old puppy. But in other cases involving less than 33 mg/kg of meclizine, only mild hyperactivity or depression was seen. Depression and hyperactivity are the most common clinical signs reported to the ASPCA APCC after Piperazine-derivative antihistamine exposure. In canine cases of hydroxyzine overdose reported to the ASPCA APCC, signs seem to be somewhat dose-dependant. Lower doses tend to produce depression, while subsequently higher doses are more likely to cause hyperactivity and then seizures. The time of onset of adverse clinical signs seems to be highly variable in dogs and cats. Marked signs may be seen as early as 10 to 15 minutes after ingestion, while other cases have had a delayed onset of signs-as long as six to eleven hours after ingestion. In cases reported to the ASPCA APCC, signs typically last from six to 25.5 hours, but several cases have taken up to seven days to recover.

### **Piperidine-derivative antihistamines**

This group of second-generation antihistamines includes astemizole, levocabastine hydrochloride, loratadine, and terfenadine. Terfenadine is no longer commercially available in the United States because of its cardiotoxic potential<sup>5</sup> but may be available in other countries.<sup>6</sup> Loratadine is available as Claritin and in combination with pseudoephedrine as Claritin-D. These agents are rapidly absorbed from the gastrointestinal tract in monogastric animals, with peak plasma concentrations generally occurring within two or three hours of oral administration. The hepatic microsomal P450 system metabolizes these antihistamines to active metabolites.<sup>3</sup> Most antihistamines from other classes are excreted primarily as metabolites,<sup>3</sup> though many of the Piperidine-derivative antihistamines appear to be exceptions. Levocabastine is excreted as about 70% unchanged parent drug in the urine.<sup>7</sup> Loratadine's active metabolites are equally distributed between urine and feces; 55% to 75% is excreted unchanged in the urine. Terfenadine is predominantly eliminated unchanged and as metabolites through hepatic metabolism and biliary and renal excretion. In a study on terfenadine administration in rats, beagles, and rhesus monkeys, the fecal pathway of excretion was predominant, with nearly all the elimination occurring within 24 hours of administration<sup>8</sup>; the data suggest that biliary excretion plays a prominent role.<sup>9</sup>

In cases reported to the ASPCA APCC, this class of antihistamines usually causes signs within 30 minutes to seven hours; signs may persist 12 to 24 hours or more. The most typically reported signs after loratadine ingestions in dogs are hyperactivity, depression, and tachycardia at doses as low as 0.25 mg/kg; no deaths or serious effects have been reported to the ASPCA APCC, even at doses as high as 72 mg/kg. For terfenadine, vomiting, hyperactivity, and ataxia were the most common signs seen; depression and tremors were seen as often as no signs.

### **Propylamine-derivative antihistamines**

This class includes many first- and second-generation antihistamines also known as *alkylamines*. The first-generation agents include brompheniramine, chlorpheniramine, dexbrompheniramine maleate,

dexchlorpheniramine, dimethindene maleate, pheniramine maleate, and pyrrobutamine. The second-generation antihistamines in this group are acrivastine and triprolidine hydrochloride. Most cases in the ASPCA APCC database involving this class of antihistamines have involved chlorpheniramine. Absorption of chlorpheniramine in dogs is reported to be rapid and complete from the gastrointestinal tract, reaching peak plasma concentrations 30 to 60 minutes after oral administration.<sup>6</sup> Chlorpheniramine maleate undergoes substantial metabolism in the gastrointestinal mucosa during absorption and on the first pass through the liver.<sup>5</sup> This class of antihistamines is primarily excreted in urine as the parent drug and its metabolites. Urinary excretion of chlorpheniramine and its metabolites decreases substantially as urinary pH increases and urine flow decreases,<sup>5</sup> though acid diuresis is not recommended to enhance elimination in cases of chlorpheniramine overdose. About 50% of a chlorpheniramine dose is excreted within 12 hours in people, with 18% occurring as unchanged drug. The plasma half-life of chlorpheniramine in dogs is about 24 hours.<sup>6</sup>

Based on cases reported to the ASPCA APCC, the margin of safety for chlorpheniramine appears to be relatively wide for dogs, with only mild signs reported below 1 mg/kg. But 5.3 mg/kg caused moderate to severe signs in a 10-month-old terrier mix. After a single oral dose of chlorpheniramine in dogs, signs have been evident within six hours. Signs reported to the ASPCA APCC have included ataxia, tremors, depression, or hyperactivity, hypothermia, and seizures.

## **Other Antihistamines**

### **Cyproheptadine**

Cyproheptadine hydrochloride (Periactin-Merk) is a peripheral H<sub>1</sub>-antagonist<sup>6</sup> and nonspecific serotonin antagonist available as tablets or an oral solution. This first-generation antihistamine shares the actions and uses of other antihistamines, but is also useful in treating serotonin syndrome in people and animals.<sup>10</sup> Serotonin syndrome is a complex of clinical signs resulting from overstimulation of serotonin receptors in the central and peripheral nervous system. Neuromuscular effects such as tremors, hyperreflexia, and ataxia are the most commonly described signs in people with serotonin syndrome.<sup>10</sup> In cats, Cyproheptadine has been used as an appetite stimulant<sup>1</sup> and to control urine spraying.<sup>11</sup> Cyproheptadine has also been used to treat Cushing's disease in horses.<sup>12</sup> Cyproheptadine is well absorbed after oral administration, with peak plasma concentrations occurring six to nine hours later.

Distribution into body tissues and fluids has not been characterized in people, but it seems to cross the blood-brain barrier since it is able to exert CNS effects. It is not known whether the drug is distributed into milk.<sup>5</sup> Cyproheptadine appears to undergo extensive and almost complete metabolism<sup>5</sup> with its metabolites excreted primarily in urine, almost completely as conjugates. The elimination half-life for the metabolites of Cyproheptadine has been reported as 16 hours in people<sup>6</sup>; after oral administration of 8 mg in cats, the mean elimination half-life was 12.8+/-9.9 hours.<sup>13</sup> In a review of ASPCA APCC cases between 1995 and 2001, no deaths were reported involving Cyproheptadine. Signs were seen within 30 minutes to seven hours, and in a limited number of cases in which information was available, signs lasted between 30 minutes and 2.5 hours.

### **Fexofenadine hydrochloride**

Fexofenadine hydrochloride is a prescription second-generation antihistamine available as Allegra (Aventis) or Allegra-D, which contains 120 mg of pseudoephedrine. Fexofenadine is rapidly absorbed from the gastrointestinal tract after oral administration, with peak plasma concentrations occurring within 1.4 to 2.6 hours in people.<sup>5</sup> At therapeutic doses, Fexofenadine does not readily cross the blood-brain barrier and distributes more extensively into plasma than into blood or saliva. In animals, the drug is distributed into the small and large intestines, stomach, pancreas, liver, and kidneys after oral administration. It is unknown whether fexofenadine crosses the placenta or is distributed into breast milk. Only about 5% of a single dose of fexofenadine is metabolized in people, with about 80% of the unchanged drug eliminated in the feces. It is unknown whether this represents unabsorbed drug or whether it is the result of biliary excretion.<sup>5</sup> Half-lives of 14.4 and 18 hours have been reported in adults and children, respectively.

The literature reports that no evidence of toxicosis was observed in dogs receiving oral fexofenadine doses up to 2 g/kg.<sup>5</sup> Out of 44 canine cases in the ASPCA APCC database, only five dogs showed signs. Dose ranges of 6.5 to 9.2 mg/kg were associated with only mild to moderate depression in four of these dogs. The other case involved a West Highland white terrier that received 6.6 mg/kg of fexofenadine and displayed moderate to severe tachycardia, tachypnea, and dyspnea, ataxia, and hyperthermia within seven to 10 hours of exposure. These signs were more likely due to an ingestion of Allegra-D (equivalent to 13.2 mg/kg pseudoephedrine for this dog). Of the seven cases involving cats with doses of 10.2 to 20 mg/kg of fexofenadine, no signs were reported. One ferret was found moderately depressed and hypothermic at the same time the owner discovered two capsules (200 mg/kg) of fexofenadine were missing.

### **Contraindications**

Because of their anticholinergic activity, use antihistamines with caution in patients with prostatic hypertrophy, bladder neck obstruction, severe cardiac failure, angle-closure glaucoma, pyeloduodenal obstruction, and chronic obstructive pulmonary disease if secretions are a problem.<sup>1</sup> Certain drugs that inhibit the hepatic microsomal enzyme system may substantially reduce the metabolism of antihistamines and lead to the accumulation of potentially toxic concentrations of unchanged antihistamines (Table 4). Antihistamine metabolism and clearance may be affected in individuals with a history of liver disease for the same reason.<sup>5</sup> Concomitant administration of erythromycin or ketoconazole has been shown to increase fexofenadine plasma concentrations in people.<sup>5</sup> Alcohol, barbituates, tranquilizers, and other CNS depressants may potentiate the depressant effects of antihistamines. Other anticholinergic drugs may cause additive anticholinergic effects.<sup>1</sup>

### **Differential diagnoses**

Differential diagnoses for antihistamine toxicosis include other CNS stimulants (*i.e.* amphetamines, ivermectin, pseudoephedrine, caffeine) or depressants (*i.e.* alcohol, barbituates, tranquilizers, marijuana). Blood, plasma, or serum antihistamine concentrations can be evaluated, but are generally only useful for confirming antihistamine exposure.

### **Treatment**

#### **Asymptomatic patients**

Vomiting may be induced with 3% hydrogen peroxide (1 to 5 ml/kg orally; 45 ml maximum) or a conjunctival solution of apomorphine hydrochloride followed by rinsing.<sup>14</sup> Even though cyproheptadine may exert a marked antiemetic effect, emesis may still be effective if induced early before toxic or antiemetic effects appear; centrally acting emetics may be of limited value.<sup>5</sup> After nausea is resolved, administer 1 g/kg of activated charcoal with a cathartic such as 70% sorbitol (3 ml/kg orally).<sup>14</sup> In cases of massive overdose perform gastric lavage. Monitor the patient's electrocardiogram, blood pressure, and body temperature. Further treatment should be supportive and directed toward specific signs.

#### **Symptomatic patients**

As with any emergency situation, address life-threatening signs first. Diazepam (0.5 to 1 mg/kg intravenously to effect)<sup>1</sup> is probably the most practical first-choice anticonvulsant to control seizures associated with antihistamine overdose in animals. Give diazepam slowly intravenously or intramuscularly to avoid the adverse paradoxical CNS excitement sometimes associated with its administration, particularly in dogs.<sup>1</sup> Barbituates or isoflurane may also be needed to control signs in animals refractory to diazepam. Vasopressors such as dopamine or norepinephrine may be needed for some patients with unresponsive hypotension,<sup>6</sup> but avoid epinephrine because it may lower blood pressure further. Phenothiazines such as acepromazine maleate should probably be avoided or used with caution for the same reason.

There is some evidence that guaifenesin may be useful in controlling seizures. A 59-lb (27-k) dog exhibiting moderate to severe generalized muscle tremors, hyperthermia, and hyperesthesia that had ingested about 67 mg/kg of diphenhydramine and was unresponsive to intravenous diazepam (0.7 mg/kg) rapidly responded to an intravenous guaifenesin bolus (30 ml of 5% solution mixed into 5% dextrose in water) followed by a constant-rate infusion of guaifenesin (5% solution mixed into 5% dextrose in water at 1 ml/kg/hr for three hours, then 0.5 ml/kg/hr for another six hours). The dog was discharged 24 hours after

admission and had no apparent residual effects two days after discharge. Methocarbamol (55 to 220 mg/kg intravenously; not to exceed 330 mg/kg/day)<sup>1</sup> may help control seizures, though its potential effectiveness in this situation is currently unknown.

Monitor the patient's electrocardiogram, blood pressure, and body temperature, and treat abnormal signs appropriately. While cardiac arrhythmias may resolve spontaneously when antihistamines are discontinued, therapy for ventricular tachyarrhythmias may be needed. Patients with severe tachycardia resulting in hemodynamic compromise or ischemia may benefit from B-blocking agents such as propranolol (0.02 mg/kg slowly intravenously).<sup>1</sup> Artificial respiration may be necessary for severely affected animals; avoid respiratory depressants, if possible.<sup>1</sup> Fluid support may be helpful, especially with ingestions of products that combine antihistamines with other drugs. When combination products several ingredients are involved, you may need to direct treatment toward controlling a variety of signs being caused by more than one agent. Continue treatment until all clinical signs resolve.

### Conclusion

The prognosis of any given case of antihistamine toxicosis depends on the animal's history, the amount of antihistamine ingested, the severity of signs that develop, and whether additional agents were involved in the exposure. Early decontamination can prevent serious signs.

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**Table 1**

**Examples of Common Antihistamines Used in Human and Veterinary Medicine**

<b>Antihistamine Class</b>	<b>First-Generation Agents</b>	<b>Second-Generation (Nonsedating) Agents</b>
Ethanolamine derivatives	Clemastine (Tavist-Novoartis Consumer Health, Sandoz); Dimenhydrinate (Dramamine-Pharmacia and Upjohn, Searle); Diphenhydramine (Benadryl-Parke-Davis, Warner-Lambert)	None
Ethylenediamine derivatives	Pyrilamine (Histavet-P-Burns-Biotec); Tripelennamine (Pelamine-Major Pharmaceuticals; PBZ-Geigy Pharmaceuticals; Re-Covr-Solvay Animal Health)	None
Piperazine derivatives	Hydroxyzine (Atarax, Vistaril-Pfizer); Meclizine hydrochloride (Antivert-Pfizer; Dramamine II-Pharmacia and Upjohn)	Cetirizine hydrochloride (Zyrtec-Pfizer)
Piperidine derivatives	None	Astemizole (Hismanal-Janssen Pharmaceutica); Loratadine (Claritin-Schering); Terfenadine (Seldane-Hoechst Marion Roussel)
Propylamine derivatives	Brompheniramine (Dimetapp Allergy Liqui-Gels Gelcaps-A.H. Robins); Chlorpheniramine (Chlor-Trimeton Allergy-Schering Plough Healthcare Products)	Triprolidine hydrochloride (Actifed Cold and Allergy-Warner-Lambert) *
Other Antihistamines	Cyproheptadine hydrochloride (Periactin-Merck)	Fexofenadine hydrochloride (Allegra-Aventis)

\*Only available as a combination product.

**Table 2**

**Ingredients Commonly Found in Combination with Antihistamines**

Acetaminophen  
Aspirin  
Caffeine  
Codeine  
Dextromethorphan  
Ephedrine  
Hydrocodone  
Phenylpropanolamine  
Pseudoephedrine

**Table 3**

**Adverse Effects Reported in Animals and People in Association with Antihistamines\***

<b>System</b>	<b>Reported Effects</b>
Neurologic	Restlessness, muscle tremors, insomnia, nervousness, delirium, seizures, depression, mydriasis, hyperesthesia
Gastrointestinal	Abdominal pain, decreased bowel signs, anorexia, hypersalivation, dry mouth, nausea, vomiting, diarrhea, constipation, increased appetite and weight gain
Hepatic	Cholestasis, hepatitis, jaundice (all rarely reported)
Genitourinary	Cystitis, dysuria, hematuria, polyuria, urinary incontinence, urinary retention, glomerulonephritis
Cardiovascular	Tachycardia, palpitations, electrocardiographic changes, arrhythmias, hypotension, hypertension, edema, thrombophlebitis, cardiac arrest
Respiratory	Bronchodilation, thickened bronchial secretions, tachypnea, dyspnea, coughing
Sensory	Blindness, conjunctivitis, ocular pain, glaucoma, ocular hemorrhage, periorbital edema, deafness, otalgia, ototoxicity
Dermatologic	Local irritation, hypersensitivity reactions, dermatitis, dry skin, urticaria, purpura, bullous eruption, hyper keratosis, alopecia, pruritus, photosensitivity reactions
Reproductive	Teratogenicity
Hematologic	Leukopenia, agranulocytosis, hemolytic anemia (very rare)
Fluid-electrolyte	Acid-base disturbances

\*Source: References 1,3,5, and 15.

**Table 4**

## **Drugs That Inhibit the Hepatic Microsomal Enzyme System**

Certain azole-derivatives- fluconazole, itraconazole, ketoconazole, metronidazole

Certain macrolide antibiotics-clarithromycin, erythromycin, troleandomycin

Mibefradil dihydrochloride

Certain human immunodeficiency virus protease inhibitors-indinavir sulfate, nelfinavir mesylate, ritonavir, saquinavir mesylate

Possibly some serotonin-reuptake inhibitors-fluoxetine, fluvoxamine, nefazodone hydrochloride, paroxetine hydrochloride, sertraline hydrochloride

Zileuton (Zyflo Filmtab-Abbott Laboratories)

Quinine

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