**Human Medications: Your dog ate what?**
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**Aspirin**

Aspirin (acetylsalicylic acid, ASA) is the salicylate ester of acetic acid and is a weak acid derived from phenol. It is available as tablets and capsules (65, 81, 325, and 500 mg), powders, effervescent tablets and oral liquid preparations. Aspirin reduces pain and inflammation by reducing prostaglandin and thromboxane synthesis through inhibition of cyclooxygenase. At very high doses, aspirin and other salicylates uncouple oxidative phosphorylation leading to decreased ATP production. Salicylates also affect platelet aggregation.

Aspirin is rapidly absorbed from the stomach and proximal small intestines in monogastrics. Absorption of large doses may be slower than therapeutic doses partly due to the effect of aspirin on gastric emptying. Aspirin is metabolized in the liver and excreted through the urine. The elimination half life increases with the dose. Cats are deficient in glucuronyl transferase and have prolonged excretion due to decreased metabolism. Elimination is also slower in neonates and geriatric animals.

Aspirin should be used with caution in patients with hypoproteinemia or pre-existing hepatic or renal disease and is contraindicated in patients with bleeding GI ulcers. In dogs, single doses of 150 - 300 mg/kg should be decontaminated. Doses of 325 mg twice a day were lethal to cats.

Signs may include vomiting (+/- blood), hyperpnea, respiratory alkalosis, metabolic acidosis, gastric hemorrhage, central lobular liver necrosis, and bleeding diathesis. Fever and seizures may be seen due to the uncoupling of oxidative phosphorylation. Renal insufficiency is uncommon with salicylate toxicoses.

Emesis can be performed in the asymptomatic animal, unless contraindicated. Activated charcoal adsorbs aspirin and repeated doses may be used with large ingestions. A cathartic should be used, unless the animal is dehydrated or has diarrhea. Liver values, glucose, acid base status and electrolytes should be monitored. Maintain hydration and start GI protectants (sucralfate, H2 blockers, +/- misoprostol, +/- omeprazole). Gastric protectants should be continued for 5 - 7 days, longer in the symptomatic patient. Metoclopramide can be used to control vomiting.

Alkalization of the urine results in ion trapping of salicylate in the kidney tubule and increases its secretion. Ion trapping should only be used in cases where the acid base balance can be monitored. Assisted ventilation and supplemental oxygen may be required if the animal is comatose. Seizures should be treated with diazepam. Fluids, whole blood, and electrolytes may be needed to control hypotension and hemorrhage, manage acute bleeding ulcers, and correct electrolyte abnormalities. Acid base imbalances should be corrected. Hyperpyrexia should be treated conservatively as aggressive cooling (ice baths or cold water enemas) may result in hypothermia.

Prognosis is good if the animal is treated promptly and appropriately. The development of hepatic necrosis is considered to have a poor prognosis. With hepatic damage, treatment may need to be continued for weeks.
Other Salicylates

Salicylates are found in many products. Bismuth subsalicylate (Pepto-Bismol®, Kaopectate®) contains 9 mg of salicylate in 1 ml (2 tablespoons = 325 mg aspirin). Topically applied salicylates (arthritis, psoriasis, teething, wart removal) can be absorbed through the skin and cause systemic problems. Oil of wintergreen is used as a flavoring for candy and contains approximately 98% methyl salicylate.

Acetaminophen

Acetaminophen (Tylenol®, non-aspirin pain reliever, APAP) is a synthetic non-opiate derivative of p-aminophenol. It is available in tablets, liquid preparations, and long-acting compounds. Tablet strengths vary from 80 to 650 mg. Liquids are available in 160 mg/5 ml, 100 mg/ml, and 120 mg/2.5 ml. APAP's exact mechanism of action is unknown but it is believed to block production of prostaglandins from arachidonic acid by inhibiting COX-3. APAP acts primarily in the CNS to increase the pain threshold and may also inhibit chemical mediators that sensitize the pain receptors to mechanical or chemical stimulation. The antipyretic activity of APAP is achieved by blocking the effects of endogenous pyrogens by inhibiting prostaglandin synthesis.

Acetaminophen is rapidly and almost completely absorbed from the GI tract. Peak plasma levels are seen at 10-60 minutes (60-120 min for extended release). APAP is distributed into most body tissues with the highest concentrations in the peri-portal zone of the liver and the renal medulla. Elimination is capacity-limited. Two major conjugation pathways are used to metabolize APAP by most species (P-450 metabolism followed by glucuronidation or sulfation). Acetaminophen-induced hepatotoxicity and nephrotoxicity is due to the formation of the oxidative metabolite, N-acetyl-para-benzoquinoneimine (NAPQI). Glutathione can conjugate and neutralize NAPQI, but when glutathione stores are depleted, NAPQI binds to sulfhydryl groups on the hepatic cell membrane and damages the lipid layer. Another metabolite, PAP (para-aminophenol), appears to be responsible for methemoglobinemia and Heinz body formation.

Methemoglobin values increase within 2-4 hours, followed by Heinz body formation. Clinical signs include depression, weakness, hyperventilation, icterus, vomiting, methemoglobinemia, hypothermia, facial or paw edema, death, cyanosis, dyspnea, and hepatic necrosis. Liver necrosis is less common in cats than in dogs. Clinical signs of methemoglobinemia may last 3-4 days. Hepatic injury may not resolve for several weeks. Hepatotoxicity has been reported in dogs at 100 mg/kg and 200 mg/kg caused clinical methemoglobinemia in 3 out of 4 dogs. Therapeutic doses have resulted in KCS 72 hours after ingestion. Cats develop clinical signs at doses > 40 mg/kg. No dose is safe in cats since they are deficient in glucuronyl transferase. Ferrets are considered to be as sensitive as cats.

Early decontamination is most beneficial. Emesis can be performed in the asymptomatic animal, unless contraindicated. Activated charcoal adsorbs APAP and may need to be repeated, due to enterohepatic recirculation. A cathartic should also be used, unless the animal is dehydrated or has diarrhea. Monitor liver values and for the presence of methemoglobinemia. ALT, AST and bilirubin may rise within 24 hours after ingestion and peak within 48 to 72 hours. Serum albumin concentrations decrease.
significantly after 36 hours and continue to decrease during liver failure, providing a true index of liver function.

Symptomatic patients need initial stabilization, including oxygen if dyspneic. Treatment involves replenishing the glutathione stores and converting methemoglobin back to hemoglobin. N-acetylcysteine (Mucomyst®, NAC) is a precursor in the synthesis of glutathione or can be oxidized to organic sulfate which provides sulfhydryl groups that bind with APAP metabolites to enhance elimination. NAC may be given orally or IV. An initial oral loading dose of 140 mg/kg (dilute to 5% in dextrose or sterile water) is given, followed by 70 mg/kg QID for 7 treatments. With ingestion of massive quantities some authors suggest using 280 mg/kg for a loading dose and continuing treatment for 12 to 17 doses. A two-to-three hour wait between activated charcoal and PO administration of NAC is needed, since activated charcoal will adsorb NAC. Adverse effects of the oral route include nausea and vomiting. If using the IV routes, give slowly over a period of 15 to 20 minutes. Fluid therapy is used to correct dehydration and for maintenance needs, not for diuresis. Whole blood transfusions or oxyglobin may be necessary to increase oxygen carrying capacity.

Ascorbic acid provides a reserve system for the reduction of methemoglobin back to hemoglobin; however, ascorbic acid has questionable efficacy and may irritate the stomach. Cimetidine is an inhibitor of cytochrome p-450 oxidation system but takes several days to become effective and should be avoided in cats. For hepatic injury, s-adenosylmethionine (SAMe, Denosyl-SD4®) at 20 mg/kg/day shows a positive effect for treatment of APAP toxicosis. Prognosis is good if the animal is treated promptly. Animals with severe signs of methemoglobinemia or with hepatic damage have poor to guarded prognosis.

Ibuprofen

Ibuprofen (Motrin®, Advil®, Midol®, etc.) is a nonsteroidal anti-inflammatory agent. It is available over the counter in 50, 100, 200 mg tablets and 100 mg/5 ml suspension. Prescription strength tablets are 400, 600, and 800 mg. Ibuprofen inhibits prostaglandin synthesis by blocking the conversion of arachidonic acid to various prostaglandins. Ibuprofen decreases secretion of the protective mucous layer in the stomach and small intestine and causes vasoconstriction in gastric mucosa. Ibuprofen inhibits renal blood flow, glomerular filtration rate, tubular ion transport, renin release and water homeostasis. Ibuprofen may also affect platelet aggregation and possibly hepatic function. Serious hepatotoxicosis is not a common problem with ibuprofen.

Absorption of ibuprofen is rapid (0.1 to 1.5 h). Plasma half life in the dog has been reported to be 2-2.5 hours, but the elimination half life is considerably longer. Ibuprofen is metabolized in the liver and undergoes significant enterohepatic recirculation before being excreted in the urine. Geriatric animals and neonates, as well as animals with acute renal insufficiency, liver disease, and hypoalbuminemia are at higher risk of toxicosis. Administration of ibuprofen in combination with glucocorticoids, salicylates, or other NSAIDS could potentiate the adverse effects of these drugs.

Ibuprofen has a narrow margin of safety. Even at the therapeutic dog dosage of 5 mg/kg, ibuprofen may cause gastric ulcers and perforations with chronic use. In dogs, an acute exposure of 50-100 mg/kg can result in gastrointestinal signs (vomiting, diarrhea,
abdominal pain, anorexia), > 125 mg/kg can result in more severe GI signs (hematemesis, melena) plus renal damage (PU/PD, oliguria, uremia). Doses of > 400 mg/kg in the dog result in GI, renal, and CNS signs (seizure, ataxia, coma). Cats are thought to be twice as sensitive to ibuprofen’s toxic effects as dogs due to their limited glucuronoyl-conjugating capacity. Ferrets that ingest ibuprofen are at high risk for CNS depression and coma, with or without GI upset.

The onset of GI upset is generally within the first 2-6 hours after ingestion, with GI hemorrhage and ulceration occurring 12 hours to 4 days post ingestion. Renal failure often occurs within the first 12 hours after massive exposure to an NSAID but may be delayed for 3-5 days.

Emesis can be performed in the asymptomatic animal. Activated charcoal adsorbs ibuprofen and may need to be repeated (enterohepatic recirculation). A cathartic should also be used, unless the animal is dehydrated or has diarrhea. GI protectants are very important. A combination of misoprostal, H2 blockers, sucralfate and omeprazole can be used to manage and/or prevent gastric ulcers. Animals should be started on IV fluids at twice maintenance for 48 hours if renal failure is expected. Monitor BUN, creatinine, and urine specific gravity (baseline level, 24, 48, and 72 h). Acid-base disturbances are rare and usually transient. Dialysis may be necessary if unresponsive oliguric or anuric renal failure develops.

Fluids, whole blood, inotropic agents, and electrolytes should be given to control hypotension and hemorrhage, maintain renal function, and correct electrolyte abnormalities. Assisted ventilation and supplemental oxygen may be required if animal is comatose. Seizures should be treated with diazepam.

Prognosis is good if the animal is treated promptly and appropriately. Gastrointestinal ulceration usually responds to therapy. Acute renal insufficiency resulting from ibuprofen administration has been considered reversible, but development of papillary necrosis is generally considered irreversible.

Other NSAIDs

Clinical signs and treatment are similar to ibuprofen. However, tolerance of NSAIDS varies considerably between species and for most NSAIDs the minimum toxic or lethal dose is not clearly established. Hepatotoxicity can be seen with any NSAID and is thought to be an idiosyncratic immune mediated reaction. Most cases are reversible with supportive care.

Naproxen (Naprosyn®, Aleve®): OTC formulations of naproxen include 220, 250, 275, 375, 500 and 550 mg pills and 125 mg/tsp suspension. Half life in the dog is 74 hours, as the drug undergoes extensive enterohepatic recirculation. Ulcerative gastritis is possible in dogs at 5 mg/kg and doses of > 25 mg/kg can cause acute renal failure. Due to the prolonged half life, fluids need to be continued for at least 72 hours and GI protectants for 10-14 days.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) all differ structurally, but have the same ability to inhibit presynaptic neuronal reuptake of serotonin. Drugs in this class include fluoxetine (Prozac®, Sarafem®), paroxetine (Paxil®), sertraline (Zoloft®), fluxovamine (Luvox®), citalopram (Celexa®) and escitalopram (Lexapro®). They have
little to no effect on non-serotonin neurotransmitters and thus have less anticholinergic, sedative and cardiovascular side effects than other types of antidepressants.

All SSRIs are well absorbed and are highly protein bound. The SSRIs are metabolized in the liver and eliminated in the urine and/or feces. The most common signs of overdose are depression, vomiting, anorexia, ataxia, muscle tremors, arrhythmia (tachycardia and bradycardia are possible), and hypertension. Serotonin syndrome may be seen in some cases, especially when SSRIs are ingested with MAO inhibitors. The term serotonin syndrome has been used to describe multiple signs associated with severe SSRI toxicosis, including agitation, tremors, tachycardia, and hyperthermia. Other less common signs include diarrhea, salivation, mydriasis, seizures, nystagmus, and coma. Hypotension and hyponatremia have been reported in humans.

Emesis should only be attempted with recent exposures, assuming that the patient is asymptomatic. Gastric lavage may be considered if large numbers of pills were ingested. Activated charcoal with a cathartic should be administered and may be effective several hours after exposure. It is thought that repeat doses of activated charcoal may be effective in SSRI elimination.

Treatment consists of monitoring vital signs closely, controlling clinical signs and providing appropriate supportive care. Diuresis does not enhance excretion because SSRIs are highly protein bound, but fluid therapy should be considered to help support blood pressure and maintain renal function. Diazepam can be used to control seizures and treatment of CNS signs may also help in the control of some of the other signs such as tachycardia, hypertension, and hyperthermia. Propranolol is a serotonergic receptor antagonist and may be used to counter tachycardia. Cyproheptadine, in addition to being an antihistamine and an appetite stimulant, is a non-selective serotonin reuptake inhibitor and has been useful in the treatment of serotonin syndrome (dog 1.1 mg/kg; cat 2 to 4 mg). Cyproheptadine may be crushed in saline and given rectally if vomiting is a problem. Chlorpromazine or acepromazine can be used in addition to cyproheptadine to treat agitation.

Overdoses of SSRIs have fewer cardiac effects and are much less likely to be fatal than overdoses of TCAs or MAO inhibitors. However, the outcome of antidepressant toxicosis depends on dose, treatment, and exposure to other highly protein bound medications. When dogs ingest more than one type of medication, the likelihood of serotonin syndrome increases. The syndrome most commonly occurs when two or more serotonergic agents with different mechanisms of action are administered either concurrently or in close succession, leading to excessive levels of serotonin in the CNS. The prognosis also depends on the overall health of the dog, especially if there is a history of liver and/or renal disease. Liver disease can inhibit metabolism of these drugs and renal disease can delay excretion. Prognosis is generally good with rapid and aggressive therapy. Serotonin syndrome is more difficult to treat, but is rarely fatal.

**Calcium Channel Blockers (CCB)**

Calcium channel blockers (verapamil, diltiazem, nifedipine, etc.) slow the activity of the SA pacemaker as well as conduction through the AV node. They also cause frequency-dependent channel blockade in the AV node so that it is effective in slowing supraventricular arrhythmias. Calcium channel blockers reduce total peripheral
resistance, blood pressure, and cardiac afterload. They can also cause negative inotropic effects, but this is rarely of clinical significance.

Calcium channel blockers have a low margin of safety, causing hypotension and dysrhythmias. Bradycardia is the most common arrhythmias although others are possible. Hyperglycemia, hyperkalemia, hypokalemia, and hypocalcemia are possible. Standard decontamination practices should be performed in cases of significant exposure. Any dose exceeding the therapeutic dose should be monitored for cardiovascular signs and electrolyte abnormalities. Geriatric or debilitated animals may develop signs at less than therapeutic doses. Fluid replacement and calcium administration may help correct blood pressure and conduction abnormalities. Atropine and isoproterenol may be used for bradyarrhythmias and may be more effective following calcium administration. If hypotension persists, insulin/dextrose, norepinephrine, neosynephrine, dopamine, dobutamine, or amrinone can be tried. The newest treatment is intralipids. Prognosis is dependent on dosage and response to therapy.

**Albuterol**

Albuterol (Proventil®, Ventolin®) is a synthetic sympathomimetic amine with primarily beta-2 receptor agonist properties. It is used most commonly for the treatment of asthma. Albuterol binds to beta-2 receptors on the surface of the smooth muscle cells in many different tissues as well as in skeletal muscle, liver and cardiac tissue. Binding to the receptor initiates the conversion of ATP to cyclic AMP, which mediates a variety of intercellular responses resulting in smooth muscle relaxation, increased skeletal muscle contractility and an intracellular shift of potassium. Overdoses of albuterol may lead to effects of beta-1 stimulation, including increased inotropic and chronotropic effects on the heart.

Dogs are usually exposed by chewing on inhalers but there are also solutions, syrups, powders, tablets, and extended release tablets available. When inhalers are punctured, dogs get an inhalation plus an oral exposure. This leads to a quick onset of signs and prolonged duration signs. When inhaled, signs can begin in five minutes. Ingestions usually have a lag time of 30 minutes before clinical signs start. In dogs, signs generally resolve within 12 hours except for certain individuals who may experience signs for up to 48 hours. The most common signs seen are tachycardia, vomiting, depression, tachypnea, hyperactivity, muscle tremors, hypokalemia, and weakness. Rarely, death has been reported.

Decontamination is not advised for inhaler, solution or syrup exposure due to rapid absorption and onset of actions. Emesis (if within minutes of ingestion) and activated charcoal advised with tablet ingestion only (especially extended relief tablets). Vital signs, heart rate and rhythm, and serum potassium levels should be monitored closely for at least the first 12 hours post-exposure and longer if clinical signs persist.

Propranolol or other non-selective beta blockers should be administered if heart rates greater than 160 to 180 bpm are observed. Propranolol slows the heart rate, has direct myocardial depressant effects and helps normalize serum potassium levels. Potassium may be supplemented as needed and should be considered if serum potassium levels fall below 2.5 mEq/l. Animals with known or underlying cardiac disease may be at risk for decompensation and sudden death. Agitation can be treated with diazepam or low dose acepromazine. Prognosis in most cases is very good.