WHY PETS INGEST HUMAN MEDICATIONS: ANTI-DEPRESSANTS AND ADD/ADHD MEDICATIONS **TOXICOLOGY**

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INTRODUCTION

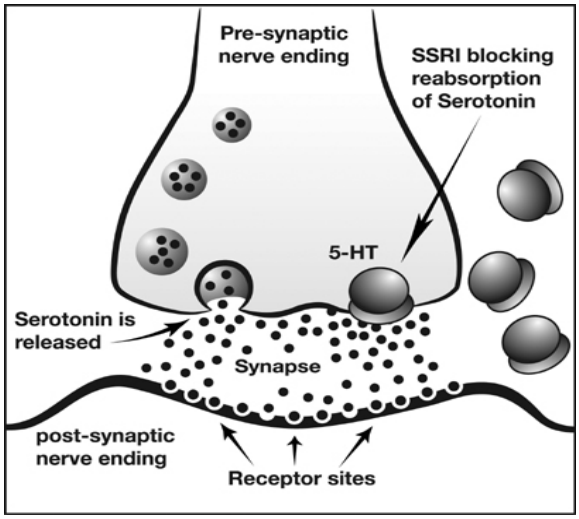
Over 50% of the calls made to Pet Poison Helpline, a 24/7 animal poison control helpline based out of Minneapolis, MN, USA, involve human medications. Of these, antidepressants and amphetamines comprise the top 2 of 3 human medication poisoning calls received. According to the US Centers for Disease Control and Prevention (CDC), the use of antidepressants and other psychotropic drugs in adults has tripled between the periods 1988-1994 and 1999-2000. Approximately 10% of Americans – or 27 million people – were taking antidepressants in 2005. The most common antidepressants include a class of drugs called selective serotonin reuptake inhibitors (SSRIs). Likewise, the prevalence of amphetamine toxicosis has increased in veterinary medicine due to the prevalence of amphetamine use in the USA. Amphetamines, which are the primary drug used to treat Attention Deficit Disorder (ADD)/Attention Deficit Hyperactivity Disorder (ADHD), are prevalent in the home setting due to the increased diagnosis of this disease among children in America. According to the National Institute of Health, an estimated 3-5% of children in the United States have ADD/ADHD. As a result, both of these prescription drugs are readily accessibility to pets. Pets seem to ingest human medications for a myriad of reasons: inappropriate pet-proofing; ingestion of palatable, chewable pills in unsecured containers (if veterinary flavored); and accidental therapeutic dosing (e.g., pet owner accidentally pills the human pill to the dog).

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

SSRIs are a class of medications used in human medicine (for depression) and in veterinary medicine (for separation anxiety, lick granulomas, feline urine spraying, etc.). SSRIs include drugs like fluoxetine (Prozac® in human beings; Reconcile® in veterinary medicine), citalopram (Celexa®), fluvoxamine (Luvox®), escitalopram (Lexapro®), paroxetine (Paxil®), and sertraline (Zoloft®). In veterinary medicine, common clinical signs from SSRIs include sedation or central nervous system (CNS) stimulation, anorexia, and lethargy, even at therapeutic doses. Other similar drugs include selective norepinephrine re-uptake inhibitors (SNRIs), which include common drugs like duloxetine (Cymbalta®), nefazodone (Serzone®), and venlafaxine (Effexor®). SNRI and SSRI drugs result in similar clinical signs of toxicosis, and therefore are treated similarly.

Mechanism of Action

SSRIs work by blocking the reuptake of serotonin in the pre-synapse, thus increasing levels of serotonin within the presynaptic membrane. Increases in levels of serotonin, even in small doses, may lead to serotonin syndrome.



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Levels of toxicity
While each SSRI has a different range of toxicity, limited animal studies evaluating pharmacokinetics and toxic ranges are available. Some drugs (such as citalopram, escitalopram) have limited to no established toxic dose based on prospective animal studies in veterinary medicine. With fluoxetine, animal studies have revealed that the median lethal dose (LD_{50}) is >100 mg/kg. Single, acute, oral doses at 100 mg/kg (in research beagles) resulted in drooling, mydriasis, tremors, anorexia, and vomiting, while more chronic, oral dosing studies revealed the following:

- 1 mg/kg/day, PO x 1 year resulted in tremors, mydriasis, and a slow pupillary light reflex (PLR).
- 4.5 mg/kg/day, PO x 1 year resulted in tremors, a slow PLR and ataxia.
- 20 mg/kg/day, PO X 6 months, and then decreased to 10 mg/kg/day, PO X 6 months resulted in tremors, anorexia, a slow PLR, mydriasis, aggressive behavior, nystagmus, emesis, lethargy and ataxia.

Drug interactions
With SSRI toxicosis, the level or severity of toxicosis may be enhanced with concurrent drug use or exposure, including the following drugs: serotonergic agents (such as serzone, dextromethorphan, buproprion, duloxetine, etc.), monoamine oxidase (MAO) inhibitors (e.g., selegiline), tricyclic antidepressants (e.g., clomipramine), and drugs that lower the seizure threshold.

Clinical signs
With SSRI toxicosis, toxicity is dose-dependent. The higher the dose, the greater the risk for serotonin syndrome (see "Serotonin syndrome" below). Lower doses typically result in clinical signs of lethargy, anorexia, vomiting, hypersalivation, nausea, agitation, or CNS signs such as tremors. Higher doses may result in more severe neurologic impairment (including ataxia, nystagmus, aggressive behavior, tremors, head tilt, seizures, lethargy, and weakness), diarrhea, and cardiovascular effects (bradycardia, tachycardia, hypertension).

Serotonin syndrome
As more serotonin is made available in the presynaptic membrane, signs of serotonin syndrome may develop in a dose-dependent manner. Signs of serotonin syndrome include autonomic instability, including CNS stimulation (mydriasis, tremors, seizures), secondary hyperthermia from tremoring (with temperatures commonly exceeding 105ºF [40.5ºC]), gastrointestinal signs (vomiting, diarrhea, abdominal pain), and cardiovascular effects (severe tachycardia or bradycardia, hypertension, etc.).

Treatment
The mainstay therapy for treatment of toxicosis in veterinary medicine is typically decontamination (including emesis induction, administration of activated charcoal, etc.). However, with SSRI ingestions, clinical signs can be seen within 30 minutes to an hour, and judicious use of emesis induction at home by the pet owner must be carefully evaluated. Emesis induction should only be recommended with very recent ingestion in asymptomatic patients (< 10-15 minutes). Veterinarians should only perform emesis induction if physical examination parameters are normal, as the development of seizures during emesis induction can result in severe complications (e.g., aspiration pneumonia, death). Special attention to the temperature, pulse rate, respiratory rate (TPR), and neurologic status should be evaluated prior to emesis induction. Emesis is contraindicated in symptomatic patients, as it may lower the seizure threshold and result in the acute onset of seizures. The administration of one dose of activated charcoal with a cathartic should be administered once the patient has been adequately decontaminated (e.g., emesis induction or gastric lavage with an inflated endotracheal tube), and provided the patient has an intact gag reflex and is not at increased risk for aspiration pneumonia. With extended-release SSRI products, multiple doses of activated charcoal (without a cathartic) should be administered every 4-6 hours X 2-3 more doses. For further review on decontamination and specific treatment, attendees are referred to a veterinary toxicology book for more detailed information.

Patients should be hospitalized for monitoring and symptomatic supportive care until clinical signs resolve (typically 12-24 hours, but up to 72 hours for extended release products). Agitated patients should be sedated (e.g., acepromazine or chlorpromazine), provided they are stable (e.g., normotensive or hypertension). Thermoregulation and appropriate cooling measures may be necessary if severe hyperthermia is present. Hyperthermic patients should only be cooled to 103.5ºF (39.7ºC), as profound hypothermia may develop due to resetting of the hypothalamus. Frequent TPR (temperature, pulse rate, respiratory rate), electrocardiogram (ECG) monitoring, and blood pressure monitoring should be performed, and hyperthermic or dehydrated patients should be treated with IV fluid therapy to

aid in cooling, rehydration, and improving perfusion. It should be noted that fluid therapy does not enhance excretion of SSRIs, however.

For patients showing severe agitation, hypertension, and tachycardiac, the use of sedatives may be necessary.

- Chlorpromazine: 0.5 mg/kg slow IV or IM slow to effect PRN
- Acepromazine: 0.05-0.1 mg/kg IV, IM, or SQ PRN

For patients showing tremors or seizures, the use of muscle relaxants and anti-convulsant therapy may be required.

- Methocarbamol: 55-220 mg/kg IV or PO q. 6-8 hours as needed (not to exceed 330 mg/kg/day, ideally)
- Phenobarbital: 4-16 mg/kg IV to effect
- Diazepam is not routinely used, based on extrapolation from human medicine, as it is thought to potentially exacerbate serotonin syndrome.

For patients demonstrating signs of serotonin syndrome, the use of additional sedatives, beta-blockers, and anti-hypertensives may be necessary. The use of serotonin antagonists such as cyproheptadine can also be used.

- Cyproheptadine:
    - Cats: 2-4 mg total dose PO or rectal q. 4-6 hours as needed until resolution of signs
    - Dogs: 1.1 mg/kg PO or rectal q. 4-6 hours as needed until resolution of signs

Prognosis

Overall, the outcome for SSRI toxicosis is good with appropriate decontamination and treatment. Patients with severe hyperthermia secondary to tremors or seizures are at higher risk for disseminated intravascular coagulation (DIC), and may have a poorer prognosis. Patients with severe neurologic signs may also require prolonged treatment and care.

AMPHETAMINES

Aside from the treatment for ADD/ADHD, amphetamines are also used for a variety of other medical causes, including obesity (for weight loss), narcolepsy, or as illegal drugs (e.g., ecstasy, methamphetamines). Examples include dextroamphetamine and amphetamine (Adderall®), D-amphetamine (Dexedrine®), methamphetamine (Desoxyn®), and lisdexamfetamine (Vyvanse®).

Mechanism of action

Amphetamines are sympathomimetic amines and stimulate the sympathetic system. Amphetamines stimulate α and β receptors to release norepinephrine and serotonin; this results in increased levels of catecholamines at the synapse. Amphetamines also increase release of serotonin from the presynaptic membrane. As a result, secondary stimulation of the CNS, the cardiovascular system, and the respiratory system (specifically at the reticular activation system and medullary respiratory center) result.

Level of Toxicity

As there are several different types of amphetamines available, the range of toxicity is highly variable and depends on the specific drug itself. Typically, clinical signs have been reported at 1-2 mg/kg, and the median lethal dose (LD_{50}) in dogs for most amphetamines is reported to range from approximately 9-30 mg/kg. Fatalities have been reported as low as 1.5 mg/kg (human) and 3.1 mg/kg (dog). The half-life of amphetamines varies from 7-34 hours.

Drug Interactions

Certain drugs interact with the metabolism or underlying pharmacokinetics of amphetamines. Tricyclic antidepressants (TCA) and monoamine oxidase (MOA) inhibitors result in more norepinephrine being made available, increasing sympathetic activity and worsening clinical signs. As amphetamines are excreted in the urine and urine elimination is pH dependent (e.g., elimination of amphetamines is faster with acidic urine), drugs that alkalinize the urine (e.g., sodium bicarbonate, acetazolamide) result in increased renal tubular absorption of amphetamines.

Clinical signs

As amphetamines are quickly absorbed orally, are highly lipid soluble, and can cross the blood brain barrier, they can result in high tissue levels (particularly to the liver, lungs, and kidneys and CNS). Amphetamine toxicosis

results in sympathetic stimulation and secondary clinical signs including agitation, nervousness, tail twitching, cardiopulmonary signs (tachypnea, hypertension, tachycardia), CNS signs (mydriasis, head bobbing, tremors, seizures), hyperthermia secondary to agitation or tremors, gastrointestinal signs (nausea, vomiting, diarrhea), and potentially myoglobinuria (secondary to severe hyperthermia or tremors). Clinical signs are seen almost immediately, or may be delayed for several hours (particularly with extended release formulas). Clinical signs of serotonin syndrome can also seen with amphetamine toxicosis.

Treatment

The mainstay therapy for treatment of toxicosis in veterinary medicine is typically decontamination (including emesis induction, administration of activated charcoal, etc.). However, with amphetamine ingestions, clinical signs can be seen within 20 minutes to an hour, depending on the formulation (e.g., immediate release tablets vs. sustained release capsules, long acting tablets, etc.). As discussed above (See SSRI Treatment), the judicious use of emesis induction at home by the pet owner or at the clinic by the veterinarian must be carefully evaluated. Emesis induction should only be recommended with very recent ingestion in asymptomatic patients (typically < 20 minutes). Please see the SSRI treatment section for further information on decontamination and administration of activated charcoal.

Treatment for amphetamine toxicosis is similar to SSRI toxicosis. Patients should be hospitalized for monitoring and symptomatic supportive care until clinical signs resolve (typically 12-24 hours, but up to 72 hours for extended release products). Agitated patients should be sedated (e.g., acepromazine or chlorpromazine), provided they are stable (e.g., normotensive or hypertension). Thermoregulation and appropriate cooling measures may be necessary if severe hyperthermia is present. Hyperthermic patients should only be cooled to 103.5ºF (39.7ºC), as profound hypothermia may develop due to resetting of the hypothalamus. Frequent TPR (temperature, pulse rate, respiratory rate), ECG monitoring, and blood pressure monitoring should be performed. Patients should be treated with IV fluid therapy to aid in increased excretion of the amphetamine, promote cooling (in hyperthermic patients), prevent myoglobinuria, aid in rehydration, and improve perfusion. For patients showing severe agitation, hypertension, tachycardiac, tremors, seizures, or serotonin syndrome, please see treatment recommendations for SSRI above.

CONCLUSION

Overall, the outcome for SSRI and amphetamine toxicosis is good with appropriate decontamination and treatment. Patients with severe hyperthermia secondary to tremors or seizures are at higher risk for DIC, and may have a poorer prognosis. Patients with severe neurologic signs (e.g., head bobbing, refractory seizures, etc.) may require prolonged treatment and care, and carry a poorer prognosis.

Pet owners should be appropriately educated on how to pet-proof the house, and be trained on what common prescription medications are poisonous. Pet owners should also be appropriately educated on crate training to help minimize toxin exposure. Once a pet is exposed to a toxicant, it is imperative to determine if emesis is appropriate and to understand when it may be contraindicated (e.g., symptomatic patient, rapid onset of clinical signs, delayed time since exposure, etc.). Knowledge of the underlying mechanism of action, the pharmacokinetics (including absorption, distribution, metabolism, and excretion), and the toxic dose of the toxicant are imperative in determining appropriate decontamination and therapy for the patient.

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