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Topical Review

Selective Serotonin Reuptake Inhibitor Exposure

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A B S T R A C T

Many antidepressants inhibit serotonin or norepinephrine reuptake or both to achieve their clinical effect. The selective serotonin reuptake inhibitor class of antidepressants (SSRIs) includes citalopram, escitalopram (active enantiomer of citalopram), fluoxetine, fluvoxamine, paroxetine, and sertraline. The SSRIs are as effective as tricyclic antidepressants in treatment of major depression with less significant side effects. As a result, they have become the largest class of medications prescribed to humans for depression. They are also used to treat obsessive-compulsive disorder, panic disorders, alcoholism, obesity, migraines, and chronic pain. An SSRI (fluoxetine) has been approved for veterinary use in treatment of canine separation anxiety. SSRIs act specifically on synaptic serotonin concentrations by blocking its reuptake in the presynapse and increasing levels in the presynaptic membrane. Clinical signs of SSRI overdose result from excessive amounts of serotonin in the central nervous system. These signs include nausea, vomiting, mydriasis, hypersalivation, and hyperthermia. Clinical signs are dose dependent and higher dosages may result in the serotonin syndrome that manifests itself as ataxia, tremors, muscle rigidity, hyperthermia, diarrhea, and seizures. Current studies reveal no increase in appearance of any specific clinical signs of serotonin toxicity with regard to any SSRI medication. In people, citalopram has been reported to have an increased risk of electrocardiographic abnormalities. Diagnosis of SSRI poisoning is based on history, clinical signs, and response to therapy. No single clinical test is currently available to confirm SSRI toxicosis. The goals of treatment in this intoxication are to support the animal, prevent further absorption of the drug, support the central nervous system, control hyperthermia, and halt any seizure activity. The relative safety of the SSRIs in overdose despite the occurrence of serotonin syndrome makes them more desirable than other antidepressants. The prognosis in animals that receive treatment is excellent. In one retrospective study, there were no deaths in 313 SSRI-poisoned dogs. No characteristic or classic histopathologic lesions result from SSRI toxicosis. Differential diagnoses for SSRI overdose must include ingestions of other serotonergic medications such as phenylpiperidine opioids (fentanyl and tramadol), mirtazapine, buspirone, amitraz, and chlorpheniramine.

Introduction

Beginning in the last half of the twentieth century, depression became recognized as a pervasive and widespread problem in Western societies. According to a study by the Centers for Disease Control and Prevention, antidepressant use in the United States increased 5 times between 1988 and 2008.[1] In addition, a remarkable 11% of American adults admitted to having taken prescription antidepressants between 2005 and 2008.[1,2] A variety of medications have been utilized in the treatment of depression including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and a number of atypical antidepressants. Most antidepressants work through the inhibition of serotonin or norepinephrine reuptake or both as a means through which they achieve their therapeutic effects.[3] In addition, in the past 50 years, the neurotransmitter serotonin has become recognized as central in the development and treatment of clinical depression. As a result, along with the tricyclic antidepressants, a number of medications have been developed to manipulate the amount of serotonin available in the central nervous system (CNS). These include the serotonin reuptake inhibitors (SSRIs), serotonin agonists, and serotonin antagonists, which all have been utilized and prescribed for a wide number of human psychiatric illnesses.[2] At present, SSRIs are still considered a first-line therapy treatment of depression.[4] Additionally, SSRIs are used to treat obsessive-compulsive disorders, panic disorder, alcoholism, obesity, anxiety, and various psychological disorders such as migraine headache syndromes and chronic pain.[5] SSRIs are just as effective as the tricyclic antidepressants for treatment of major clinical depression and have less significant side effects.[6,7] The relative safety of the SSRIs when ingested in overdose, compared with the monoamine oxidase inhibitors (MAOIs) and cyclic antidepressants, also makes them a more optimal and desirable choice for therapy.

As a result, SSRIs have become the largest class of prescribed medication in the treatment of clinical depression.[3] The class of SSRIs includes fluvoxamine (Luvox), citalopram (Celexa), escitalopram (Lexapro—the active enantiomer of citalopram), fluoxetine (Prozac in humans; Reconcile in veterinary medicine), paroxetine (Paxil), and sertraline (Zoloft). In veterinary medicine, SSRIs are used (frequently in off-label use) for a wide variety of behavioral issues, which has included feline spraying, lick granuloma control, and especially for treatment of canine separation anxiety.[8] In 2007, the first specific veterinary SSRI (Reconcile) was approved by the Food and Drug Administration for treatment of canine behavioral problems, specifically separation anxiety.[9] In this discussion, we examine the state of our understanding of the SSRIs, and investigate their mechanism of action, pathophysiology, toxic dose, clinical signs, treatment, and prognosis for affected animals.

Toxic Dose

Despite their widespread use and easy availability, there is surprisingly little information in previous reports to accurately define a minimum acute dosage of any SSRI. A number of studies and review articles have included data concluding that SSRIs, as a class, have a wide margin of safety, particularly when compared

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with tricyclic antidepressants and monoamine oxidase inhibitors.[10,11] One study in humans conducted by a panel from the American Association of Poison Control Centers concluded that doses greater than 5 times the single therapeutic dose warranted referral to an emergency room.[11] Thus, doses greater than 5 times the lowest adult therapeutic dose of a particular SSRI (ie for citalopram, 100 mg; fluoxetine, 100 mg; fluvoxamine, 250 mg; paroxetine, 100 mg; and sertraline, 250 mg) should receive treatment. Citalopram is regarded as the SSRI possessing the greatest potential for toxicity (adverse electrocardiographic effects), although there are little specific toxic dose data concerning this drug.[12] For animals, limited data are available, although toxic doses for some of the drugs have been established.[8] For fluoxetine, in dogs, the median lethal dose is greater than 100 mg/kg.[8] Beagles treated with a single acute dose of 100 mg developed clinical signs. One study in dogs reported the appearance of minor signs, like salivation and lethargy, at 1-3 mg/kg of paroxetine and sertraline, with more severe signs such as hyperthermia and tremors not seen until the dose was 8-10 mg/kg of fluoxetine and sertraline.[2] Seizure activity was not seen until dose exceeded 25 mg/kg of fluoxetine and sertraline, but was observed when doses exceeded 3 mg/kg of paroxetine.[2] Animals treated with long-term drug administration for 1 year showed increased severity of clinical signs with increasing dosage. In cats, fluoxetine caused clinical signs following a single dosage of 50 mg/kg.[8] Cats also showed a worsening in the severity of clinical signs with increased SSRI dosage. For citalopram and its enantiomer escitalopram, dosages greater than 0.3 mg/kg in dogs have been shown to cause clinical signs. For human beings, dosages greater than 600 mg resulted in moderate effects and dosages greater than 1700 mg caused severe toxicity. In children, doses greater than 200 mg caused prolongation of the QT interval on the electrocardiogram. For paroxetine in dogs, 1 mg caused sedation and 10 mg/kg or higher resulted in changes in their electrocardiograph. In humans, 100-800 mg ingestions at a single time caused no clinical signs. Similarly, in children 5 years old and younger, a single ingestion of up to 120 mg resulted in no clinical signs. Adults could tolerate a single ingestion of up to 1000 mg with no or very minimal effects. In adult humans, single ingestion of greater than 3600 mg resulted in the serotonin syndrome. For the SSRI sertraline, the median lethal dosage for dogs following a single ingestion is 80 mg/kg of body weight. In dogs, 10-200 mg/kg cause recognized clinical signs. For human beings, 700-2100 mg shows no clinical signs. Four grams in an adolescent has been reported to cause seizures. In children, ingestions of 400-500 mg total have been shown to lead to the serotonin syndrome. For children, there was 1 reported death with a single ingestion of 2.5 g, but another child who ingested 13.5 g and developed clinical signs recovered uneventfully after treatment. Table 1 shows therapeutic human dosages for SSRIs. Table 2 shows lowest dosage of SSRIs to cause moderate to severe toxicity in humans. Table 3 shows median dose ingested to cause symptomatic SSRI poisoning in animals (dogs).

Toxicokinetics and Mechanism of Action

The SSRIs are a chemically diverse group of agents that share the ability to inhibit the presynaptic uptake of serotonin within the CNS. These drugs are commonly prescribed for treatment of mild to moderate depression, anxiety disorders, obsessive-compulsive behaviors, migraines, and other neuropathic pain.[12,13,14] Manipulation of serotonin and norepinephrine has a central role in the treatment of depression. However, the exact etiology of depression and the mechanism by which increased serotonergic and norepinephrine neurotransmission modulates mood and temperament remains unclear. Depression has been theorized to be caused by decreased neuronal serotonin storage, decreased synaptic serotonin, increased serotonin receptor sensitivity, and serotonin overactivity resulting in depressed dopamine neurotransmission.[15,16,17] Serotonin is a biogenic amine produced from the essential amino acid tryptophan. The majority of the body's serotonin is synthesized within the CNS and enterochromaffin cells. Serotonin within the CNS is stored in the presynaptic vesicles of the serotonergic neurons, pineal gland, and catecholaminergic neurons. The presynaptic membrane releases serotonin and binds to serotonin-specific receptors on the postsynaptic membrane. In addition, serotonin may bind to autoreceptors on the presynaptic membrane, which acts as a negative feedback to further serotonin release. Serotonin is removed from the synaptic cleft by binding to a selective serotonin transporter. This molecule transports the serotonin into the presynaptic cytosol.[17] Once there, the serotonin is metabolized by monoamine oxidase (MAO) or repackaged in vesicles.[18] The effect at the postsynaptic membrane is determined by the amount of serotonin available to bind 5-hydroxytryptamine (5-HT) receptors.[19] Antidepressant agents specifically targeted at altering CNS concentrations of serotonin are from 1 of 4 groups.[3] Firstly, there are antidepressant

Table 1
Therapeutic Doses of SSRIs in Humans

Drug	Daily Therapeutic Dose	Maximum Daily Dose	Dosage Forms
(1) Citalopram	adult: 20 mg	60 mg	10, 20, 40 mg tablets 10 mg/5mL oral solution
(2) Escitalopram	adult: 10 mg	20 mg	5, 10, 20 mg tablets 5 mg/5mL oral solution
(3) Fluoxetine	adult: 20 mg child (6-18 y): 10 mg	80 mg 20 mg	10, 20, 40 mg capsules 10 mg tablets 90 mg weekly capsule 20 mg/5mL oral solution
(4) Fluvoxamine	adult 50 mg child (8-17 y): 25 mg	300 mg 200 mg	25, 50, 100 mg tablets
(5) Paroxetine	adult: 20 mg child: 10 mg	60 mg 60 mg	10, 20, 30, 40 mg tablets 10 mg/5mL oral solution Paxil CR (controlled-release) tablets 12.5, 25. 37.5 mg tablets
(6) Sertraline	adult: 50 mg once daily child (6-12 y): 25 mg once daily	200 mg 200 mg	25, 50, 100 mg tablets 20 mg/mL oral concentrate

Table 2
Lowest Dosage of SSRIs to Cause Mild to Severe Toxicity in Humans

Drug	Time to Peak Serum Concentration	Lowest Reported Dose to Cause More Than Mild Toxicity
(1) Citalopram	4 h	adult: 400 mg
(2) Escitalopram	5 h	adult: 100 mg child: 100 mg
(3) Fluoxetine	6-8 h	adult: NA child: 100 mg
(4) Fluvoxamine	3.8 h	adult: 750 mg child: 400 mg
(5) Paroxetine	4.9-6.4 h	adult: 360 mg
(6) Sertraline	4.5-8.4 h	adult: 500 mg child: 400 mg

medications that inhibit serotonin metabolism such as monoamine oxidase inhibitors (MAOI). Second, are drugs that inhibit reuptake of serotonin from the synaptic cleft across the presynaptic membrane by selective serotonin transporter (such as SSRIs and tricyclic antidepressants). Third, are drugs that augment serotonin release (amphetamines and their analogs). Finally, serotonin levels can be altered by drugs acting as serotonin precursurs.[2] The MAOI inhibitors and the tricyclic antidepressants were the first prescribed serotonergic agents utilized to treat depression and anxiety.[20] These medications are responsible for a variety of adverse effects because of their antihistaminergic and antimuscarinic actions.[20] The tricyclic antidepressants in particular can cause quinidinelike proarrhythmic myocardial effects and cause alpha-adrenergic blockades that may lead to hypotension.[3] SSRIs act more specifically on synaptic serotonin concentrations with minimal effects on catecholamine, acetylcholine, and histamine.[2] This specificity of SSRIs minimizes the adverse effects seen with MAOIs and tricyclic antidepressants.[20] Subsequently, the SSRIs have largely replaced the once widely prescribed tricyclic antidepressants because of their comparative safety and less frequent adverse effects. Thus, as a result of their high safety profile and fewer troublesome side effects, SSRIs are currently the first-line therapy prescribed for depression.[11] SSRIs are available only through prescription of a licensed veterinarian or physician. All of the SSRIs are well-absorbed after oral ingestion. Fluoxetine, paroxetine, and sertraline are the most protein bound. All SSRIs are metabolized in the liver.[8] The SSRIs have numerous active metabolites. Fluoxetine's active metabolite, norfluoxetine, has very similar pharmacologic effects to the parent molecule. The SSRIs have diverse elimination patterns, however, most are excreted in the urine with sertraline excreted in the bile in dogs.[8]

Clinical Signs

Most effects following severe overdose with SSRIs are direct extensions of their pharmacologic activity in therapeutic doses.[3] Excess serotonergic stimulation is a prominent feature and is generally nonselective. Short-term clinical signs with an overdose in humans are dizziness, nausea, vomiting, and blurred vision, and it may cause CNS depression and sinus tachycardia.[3] Seizures and QS complex prolongation have been reported.[12] In dogs, at lower dosages, hypersalivation, anorexia, agitation, vomiting, and tremors are typically observed.[8] Vomiting, diarrhea, weakness, ataxia, nystagmus, head tilt, bradycardia, aggressive behavior, tremors, and seizures have all been described in dogs upon significant SSRI overdose.[8] The signs are dose dependent and usually appear within 1 hour.[11] In addition, the higher the dose ingested, the greater the chances for development of the serotonin syndrome.[11] It may be better termed "serotonin toxicity". This is a potentially life-threatening complication of antidepressant drug therapy.[3] It often goes unidentified due to its nonspecific symptoms. This is a clinical syndrome that manifests itself as autonomic instability, altered mental status, seizures, and extrapyramidal syndrome including muscle rigidity and hyperthermia.[11] Dogs with serotonin syndrome display multiple signs including mental status changes, agitation, myoclonus, hyperreflexia, shivering, tremors, vomiting, diarrhea, and hyperthermia.[2] The syndrome is produced most often by the concurrent use of 2 or more xenobiotics that increase serotonin activity in the CNS. Simultaneous use of SSRIs and cocaine, methadone, tramadol, and even the herbal medication St. Johns Wort have all been implicated in causing serotonin syndrome.[3] A partial list of drugs with potential for serotonin syndrome is included in Table 4. In humans and dogs, it has been reported that most patients recover from serotonin syndrome after 24 hours of discontinuing the SSRI and initiating supportive care.[21,22] For all SSRIs, hyperthermia and gastrointestinal and neurologic signs are the most common clinical manifestations of overdose.[2,8] In a recent retrospective study in dogs, there was no statistical difference between different SSRI medications and the type of clinical signs that developed.[2] Thus, there was no statistical difference between the medications with regard to the frequency of the appearance of a particular clinical sign. For SSRIs, the clinical signs that develop appear stereotyped. Citalopram and its enantiomer escitalopram have been reported to be more likely to cause QT interval widening–related cardiac issues and the development of seizures in people.[12] These effects are directly dose related. In humans, SSRI overdose rarely results in life-threatening effects but fatalities have been recorded. In 1 human fatality, the patient ingested 75 times[3] the recommended maximum daily dose of fluoxetine. One recent study of SSRIs in dogs reported no fatalities[2] recorded in more than 300 animals poisoned in a 5-year period. In some dogs, GI upset and CNS signs have been noted when fluoxetine was used at therapeutic doses for separation anxiety treatment. These effects in dogs may represent mild serotonin toxicity.[9] In most cases, the initial onset of clinical signs following SSRI ingestion is within a few hours.[2,11,23] Onset of the serotonin syndrome is usually within 6 hours of ingestion, with an escalating severity of clinical signs.[11] Recently, considerable evidence has accumulated that the SSRI escitalopram causes fewer seizures in cases of human overdose than the SSRI citalopram.[12] This may make escitalopram a safer drug in cases of overdose but this finding has not been confirmed in animal studies.[2] Table 5 summarizes the clinical signs seen in dogs following SSRI toxicity. For both humans and animals, the clinical signs observed after SSRI overdose are the result of excessive serotonin in the CNS.

Table 3
Median Dose Necessary to Cause Symptomatic SSRI Toxicity in Dogs[2]

Drug	Symptomatic Median Dose Range (mg/kg)
(1) Citalopram	4.2 mg/kg (n = 10 dogs)
(2) Escitalopram	4.4 mg/kg (n = 7 dogs)
(3) Fluoxetine	15.9 mg/kg (n = 12 dogs)
(4) Fluvoxamine	1.5 mg/kg (n = 1 dog)
(5) Paroxetine	7.7 mg/kg (n = 5 dogs)
(6) Sertraline	11.6 mg/kg (n = 22 dogs)

Minimum Database and Confirmatory Tests

Currently, no diagnostic test capable of determining if an animal is suffering from SSRI overdose is available. Although tremoring and seizuring animals in life-threatening cases can be

Table 4
Drugs with Potential to Cause Serotonin Syndrome

SSRIs	**Miscellaneous**
Citalo pram	Buspi rone
Fluoxetine	Carbamazepine
Fluvoxamine	Cocaine
Paroxetine	Cyclobenzaprine
	Dextromethorphan
SNRIs	Ergot Alkaloids
	Fentanyl
Duloxetine	5 Hydroxytryptophan
Sibutramine	Linezolid
Venlaxafine	Lithium
	L-Tryptophan
TRIPTANs	Meperidine
	Methamphetamine
Almotriptan	Methylene blue
Eletriptan	Metoclopramide
Frovatriptan	Mirtazapine
Naratriptan	Ondansetron
Rizatriptan	Phenelzine
Sumatriptan	Selegiline
Zolmitriptan	St. John's Wort
	Tramadol
	Tranyloypromine
	Trazodone
	Tricyclic antidepressants
	Valproic acid

easy to recognize, subclinical and mild cases are more difficult to separate from other causes. A complete blood count (CBC), biochemical panel with electrolytes, and urinalysis can be helpful in establishing both the state of the animal and the presence of other etiologies. With overdose or suspected ingestion of citalopram or escitalopram, an electrocardiogram and cardiac monitoring are recommended to identify the development of ventricular dysrhythmias and QT elongation.[12] A history including the availability of an SSRI to the dog, witnessing the ingestion, or the presence of tablets or capsules in the vomitus can all aid in obtaining a correct diagnosis. In dogs, the most common clinical effects in symptomatic animals were GI and CNS signs.[2,23] Likewise, the clinical signs manifested by this toxidrome (lethargy, salivation, hyperthermia, mydriasis, vomiting, diarrhea, cardiovascular signs, rigidity, tremors, and seizures) must be noted and identified for the early recognition of SSRI overdose. Although definitive diagnostic tests are lacking, the time-tested triad of history, clinical signs, and laboratory results should never be underestimated in helping confirm the diagnosis of a particular toxicosis.

Treatment

Just as in any poisoning, initiation of treatment must not supersede the essentials of emergency medicine. Temperature, respiration, heart rate and rhythm must all be strictly monitored and never overlooked. The treatment of patients with SSRI intoxication is largely supportive. Although there is no known specific antidote and the vast majority of SSRI poisonings recover uneventfully, initiation of supportive therapy is essential, particularly if other causes may be at work. Asymptomatic animals may be induced to vomit if ingestion has occurred within the last hour (apomorphine 0.04 mg/kg IV). The goals of therapy in SSRI overdose are to prevent further absorption of the drug, counter the GI signs, support the CNS, and provide further support. Activated charcoal (1 mg/kg) may be useful to help absorb any drug remaining in the GI tract.[8,11] Although intravenous fluids do not hasten the elimination or excretion of SSRIs, they are necessary to replace GI losses, support the cardiovascular system, bring down the body temperature, and maintain adequate tissue perfusion.[8] Patients should be monitored regularly to check for hyperthermia. Basic blood work (CBC and biochemical panel) and urinalysis should be performed to rule out other concurrent problems. Regular electrocardiograms should be performed to identify any cardiac arrhythmias.[12] The animal should be observed closely for development of serotonin syndrome—agitation, hyperthermia, vomiting, diarrhea, hypertension, hyperreflexia, muscle rigidity, tachycardia, tremors, and seizures. Animals experiencing SSRI overdose should be placed on a regular seizure watch. Tremors may be managed with methocarbamol (55-220 mg/kg IV) given slowly to effect.[8] Seizures stemming from this intoxication can be controlled with phenobarbitol (3-5 mg/kg IV) or diazepam (0.25 to 0.5 mg/kg IV). Intractable seizures can be stopped using either propofol, 2-6 mg.kg IV, or continuous rate infusion at 0.6 mg/kg/min IV. Propofol dosage can be decreased by 25% if phenothiazines (acepromazine or chlorpromazine) have previously been given. If seizures continue with IV phenobarbitol and propofol, they should be halted using inhalant isoflurane. Benzodiazapines have been reported in one study to actually exacerbate the serotonin syndrome and associated agitation.[8] We have not witnessed this effect and find benzodiazepines useful in treatment of SSRI toxicosis. Agitation itself should be regulated through the use of phenothiazines such as acepromazine (0.05-0.1 mg/kg given SQ, IM, or IV) or chlorpromazine (0.5-1.0 mg/kg IV or IM given slowly and starting at the lower end of the range). Phenothiazines must be utilized keeping in mind that they may lower the animal's seizure threshold and that benzodiazepines may be safer. If serotonin syndrome develops, cyproheptadine can be given to animals with severe clinical signs at the following dosages: for dogs, 1.1 mg/kg (given orally) and for cats, 2.0-4.0 mg total dose (given every 6 hours until clinical signs resolve).[8] Amitraz collars (and in other forms) should not be employed for several weeks following SSRI toxicity. In humans, many features overlap between the serotonin syndrome and the neuroleptic malignant syndrome.[3] Altered mental status, ataxia, incoordination, and tremors resulting in hyperthermia are common clinical signs in both syndromes. However, neuroleptic malignant syndrome involves rapid blockage of dopaminergic neurons in the CNS, whereas serotonin syndrome is thought to follow severe overstimulation of serotonin receptors. Neuroleptic malignant syndrome can last for as long as 2 weeks whereas serotonin syndrome generally resolves quickly. Currently, it is not known whether the neuroleptic malignant syndrome actually occurs in animals.[8] Table 6 summarizes SSRI-overdose therapy.

Table 5
Clincial Signs Reported In Dogs Following SSRI Overdose

- Anorexia
- Hypersalivation
- Agitation
- Vomiting
- Diarrhea
- Tremors
- Weakness
- Ataxia
- Nystagmus
- Head tilt
- Bradycardia
- Seizures
- Aggressive behavior
- Hyperthermia
- Mydriasis
- Rigidity

Prevention and Prognosis

Despite the appearance of serotonin syndrome in some cases, the SSRIs as a group are relatively safe in overdose situations.[21] In one retrospective study, no dogs (sample size = 313) were

Table 6
Therapy For SSRI Overdose

- Induction of **emesis** if animal is asymptomatic and ingestion was in last hour.
- **Activated charcoal** can be administered/one dosage (1g/kg).
- **Intravenous fluids** recommended for temperature control, to replace losses, protect the kidneys, support the cardiovascular system, and maintain tissue perfusion.
- Animal should be placed on **seizure watch** in addition to regularly monitoring the temperature.
- **Agitation:** Phenothiazines – Acepromazine at 0.05 – 0.1 mg/kg IV,IM, SQ, Chlorpromazine at 0.5 – 1.0 mg/kg IM, IV
- **Tremors:** Methocarbamol at 55 – 220 mg/kg IV slowly to effect (not to exceed 330 mg/kg/day – monitor for CNS and respiratory effects)
- **Seizures:** Phenobarbitol at 3 – 5 mg/kg IV
  Diazepam at 0.25 – 0.5 mg/kg IV
  Propofol at 2 – 6 mg/kg IV or 0.6mg/kg/min CRI (decrease 25% if phenothiazines already used)
  - Non-responsive seizures managed by masking with isoflurane
- **Serotonin syndrome:** Cyproheptadine (for animals with severe signs)
  For dogs: 1.1 mg/kg every 6 hours (orally)
  For cats: 2 – 4 mg total every 6 hours until signs subside
- Goals of treatment: prevent absorption, support the kidneys, support the CNS, manage body temperature and seizures, support.

reported either to have died or to have been euthanized following ingestion of SSRIs.[2] Prevention of accidental ingestion and subsequent toxicosis involves responsible storage of all human medications; locked or latched cabinets, cabinets off the ground, proper disposal of outdated medications (never in household trash cans, waste baskets, or other waste receptacles). Medications should never be kept in kitchens where pets may "counter surf" on countertops or placed on nightstands within easy reach of the bed. Animals presented close to the time of toxin ingestion and receiving treatment early have the best prognosis.[2] Owners should be encouraged to bring in the original containers for any human medications. There may be a 1-800 number or manufacturer information with regard to poisoning.

Gross and Histologic Lesions

There are no specific, pathognomic histologic lesions seen in SSRI overdose.[8] A vast majority of animals survive and show no long-term effects.

Differential Diagnoses

The tricyclic antidepressant clomipramine used in veterinary medicine for behavioral problems has also been implicated in causing the serotonin syndrome and should not be used in conjunction with the SSRIs.[8] Other serotonergic medications causing similar clinical signs to SSRIs include phenylpiperidine opioids (fentanyl, tramadol, etc.), buspirone, duloxetine, mirtazapine, buspirone, amitraz, and chlorpheniramine. These other serotonergic agents should not be used in conjunction with the SSRIs. However, generally these other agents work through receptors other than just serotonin and as a result have very different clinical signs. A high index of suspicion is required to confirm a diagnosis of SSRI intoxication, particularly when other drugs may be the culprit or when the avenue of ingestion or exposure is not immediately evident. Laboratory tests can be critical but the strength of a thorough physical examination must not be underestimated! Animals ingesting toxic compounds rank among the most challenging cases small animal clinicians face. Nevertheless, through the prudent utilization of available resources (local toxicology laboratories, local hospitals, local toxicologists, regional veterinary colleges, the national poison hotline (800-222-1222), the animal poisoning hotline (888-426-4435), and an awareness of current literature and treatment protocols) many potentially life-threatening exposures can have successful outcomes.

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