

Serotonin Syndrome

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Serotonin, or 5-hydroxytryptamine, is a neurotransmitter that acts throughout the body. Medications that affect serotonin level or activity are increasingly being used in humans for various conditions and in animals for separation anxiety, pain control, cognitive dysfunction syndrome, and compulsive disorders. In many cases, increasing the level or activity of serotonin can be beneficial. However, an excessive increase in serotonin can lead to an iatrogenic toxidrome known as *serotonin syndrome* (SS), which can be fatal. Clinical reports of SS are becoming more common in the human medical literature. Although such reports are still rare in the veterinary literature, as veterinarians use more medications that affect serotonin metabolism, it is critical that they be aware of the potential hazards.

MECHANISM OF ACTION OF SEROTONIN

Serotonin is derived from L-tryptophan, which is available in food. In the central nervous system, it is produced in the raphe nuclei and stored in vesicles in presynaptic membranes. When released from these vesicles, serotonin activates both pre- and postsynaptic receptors. The action of serotonin within the synapse is terminated by its reuptake into the presynaptic terminal.¹ Serotonin in the central nervous system affects behavior, attention, cardiorespiratory function, pain perception, aggression, motor control, temperature control, sleep, appetite, and sexual function. Serotonin is also produced in intestinal enterochromaffin cells and stored in platelets and acts on the peripheral nervous system to affect vasoconstriction, platelet aggregation, uterine contractions, intestinal peristalsis, and bronchoconstriction. Serotonin is degraded by monoamine oxidase and, ultimately, metabolized into 5-hydroxyindoleacetic acid, which is excreted in urine.

CAUSES

Exactly how excess serotonin causes SS is not understood. However, SS can result with any combination of the following: foods that facilitate the synthesis of serotonin, medications that facilitate the synthesis of serotonin, medications that increase the presynaptic release of serotonin, medications that inhibit the reuptake of serotonin back into the presynaptic neuron, medications that inhibit the metabolism of serotonin, and medications that facilitate the action of serotonin at the presynaptic neuron. An overdose of a single medication that affects serotonin activity can also cause SS. Some illegal drugs can contribute to SS if an animal finds and consumes them.

The cytochrome P450 enzymes are a superfamily of heme proteins that catalyze the oxidative metabolism of a wide range of endogenous compounds and xenobiotics, including many of the medications that affect serotonin. In humans, substantial individual variation has been identified in the ability to metabolize certain medications affecting serotonin activity, specifically because of different levels of activity of specific P450 enzymes. This variation is probably present within veterinary patients as well. For exam-

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About This Column

Behavior problems are a significant cause of death (euthanasia) in companion animals. While most veterinary practices are necessarily geared toward the medical aspect of care, there are many opportunities to bring behavior awareness into the clinic for the benefit of the pet, the owner, and ourselves. This column acknowledges the importance of behavior as part of veterinary medicine and speaks practically about using it effectively in daily practice.

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ple, we have treated two Black Russian terriers with fluoxetine (Reconcile, Eli Lilly). After administering a typical starting dose, we found that to avoid excessive sedation, both required a much lower dose than we usually prescribe for dogs. Typical clinical doses of fluoxetine and paroxetine are 1 to 2 mg/kg in dogs and 0.5 to 1.5 mg/kg in cats. Doses of selegiline range higher (up to 4 mg/kg in dogs). Patients that are sensitive to these medications may exhibit lethargy or excessive salivation within the normal dose range. Doses greater than 8 mg/kg can cause tremors, while doses greater than 25 mg/kg are likely to cause seizures.² Thus, typical clinical doses should not cause serious problems but may cause minor problems in a small population of patients that are particularly sensitive, probably due to deficiencies in their P450 enzyme system.

PREVENTION

The primary way to prevent SS is to avoid using combinations of medications that facilitate serotonin activity. Some of these medications or their metabolites have long half-lives; therefore, it is important to allow a sufficient washout period when switching patients from one medication that increases serotonin activity to another. For example, fluoxetine should be discontinued for a minimum of 5 weeks before starting a patient on a monoamine oxidase inhibitor (MAOI) such as selegiline. Selegiline must be discontinued for a minimum of 2 weeks before starting a patient on fluoxetine or any other selective serotonin reuptake inhibitor or tricyclic antidepressant.

Specific drug combinations that are likely to occur in veterinary practice may be particularly problematic. For example, fluoxetine inhibits the 2D6, 3A4, 2C9, and 2C19 isoforms of the P450 enzymes. Tramadol is metabolized by the 2D6 isoform and, therefore, will be metabolized much more slowly than usual in a patient receiving fluoxetine. Therefore, tramadol should be avoided in patients already on fluoxetine.

CLINICAL SIGNS AND DIAGNOSIS

SS should be suspected when the history indicates that the animal may have or has consumed multiple or excessive quantities of medications with the effects listed in Box 1. Dogs with SS typically begin exhibiting signs rapidly; the time to onset of signs after ingestion of substances associated with SS has been reported as ranging from 10 minutes to 4 hours.³ If treated, most recover within 12 to 36 hours. We have been unable to identify any reports of SS in cats, but because many of the med-

Box 1. Substances That Can Contribute to Serotonin Syndrome

Serotonin syndrome may result when one of the following substances is ingested in excess or when multiple substances that affect serotonin levels simultaneously are ingested, either through deliberate dosing or accidentally. This list is not comprehensive and includes illicit drugs and drugs not approved for veterinary use.

- **Food or medication that facilitates synthesis of serotonin**
 - L-Tryptophan
 - Cheese
- **Medications that increase presynaptic release of serotonin**
 - Amphetamine
 - Methylphenidate
 - 3,4 methylenedioxymethamphetamine (MDMA, Ecstasy)
- **Medications that inhibit the reuptake of serotonin into the presynaptic neuron (including all selective serotonin reuptake inhibitors and tricyclic antidepressants)**
 - Amitriptyline
 - Bupropion
 - Chlorpheniramine
 - Clomipramine (Clomicalm)
 - Duloxetine
 - Fentanyl
 - Fluoxetine (Reconcile)
 - Paroxetine
 - Pethidine
 - Sertraline
 - Tramadol
 - Trazodone
 - Venlafaxine
- **Medications that inhibit the metabolism of serotonin (including all monoamine oxidase inhibitors)**
 - Amitraz (Mitaban, Preventic collar)
 - Linezolid
 - Selegiline (Anipryl)
- **Medications that act as serotonin agonists at the postsynaptic membrane**
 - Buspirone
 - Lithium
 - Lysergic acid diethylamide (LSD)

ications that are reported to cause SS in humans and dogs are also used in cats, this possibility should always be considered when a cat presents with suggestive clinical signs, especially when it has a history of consumption of the relevant medications.

Box 2. Clinical Signs of Serotonin Syndrome

- **Autonomic hyperactivity:** diarrhea, mydriasis, tachycardia, tachypnea, hypertension, diaphoresis, fever
- **Neuromuscular signs:** hyperreflexia, myoclonus and secondary hyperthermia, tremors, rigidity, seizures, hyperreflexia; pyramidal rigidity (in the advanced stage)
- **Altered mental status:** confusion, agitation, excitement

Unfortunately, no diagnostic test or specific clinical sign is pathognomonic for SS. Because serotonin affects multiple systems, signs of toxicity are multiple and varied. Affected animals present with a cluster of signs consistent with a mixture of autonomic and neuromuscular hyperactivity and altered mental status, such as myoclonus, tremors, and seizures (Box 2). The differential diagnosis includes neuroleptic malignant syndrome, nonconvulsive seizures (toxic ictal delirium), central nervous system infection (encephalitis, meningitis), and toxicity caused by several different agents.

The limited amount of information in the veterinary literature provides some information on how SS manifests in dogs. Gwaltney-Brant et al³ reviewed 21 cases of dogs that had consumed various doses of 5-hydroxytryptophan, the precursor to serotonin that is available as a dietary supplement, that were reported to the ASPCA Animal Poison Control Center (APCC) from 1989 to 1999. The doses consumed ranged from 2.5 mg/kg, which did not cause any clinical signs, to 573 mg/kg. The minimum toxic dose in this study was 23.6 mg/kg. Three dogs consumed fatal doses of 128 mg/kg or greater. The clinical signs observed in all the dogs closely paralleled those reported in the literature on humans with SS. Neurologic signs included seizures, depression, tremors, hyperesthesia, ataxia or paresis, disorientation, coma, hyperreflexia, mydriasis, and blindness (transient and apparent). Gastrointestinal signs included vomiting, diarrhea, abdominal pain, hypersalivation, flatulence, and bloat. Other signs included hyperthermia (>103.6°F [39.8°C]), vocalization, weakness, tachycardia, cyanosis, recumbency, dyspnea, and hypothermia.

Mohammad-Zadeh et al² have recently reported on 197 cases that were reported to the ASPCA APCC between 2002 and 2004. Of these, 189 cases involved overdoses of sertraline, fluoxetine, or paroxetine; four involved overdoses of an MAOI; and four involved overdoses of Saint-John's-wort. The most common clinical

Box 3. Summary of Treatment for Suspected Serotonin Syndrome

1. Decontamination (i.e., induce emesis or give adsorbents)

This step may be considered *only* within the first 30 minutes after consumption of the substance(s) believed to be causing SS. Otherwise, induction of emesis or administration of adsorbents is contraindicated and may exacerbate clinical signs or cause aspiration.

2. Discontinue any medication or food that ...

- Facilitates the synthesis of serotonin
- Increases the release of presynaptic serotonin
- Inhibits the reuptake of serotonin into the presynaptic neuron
- Inhibits the metabolism of serotonin
- Acts as a serotonin agonist at the postsynaptic membrane

3. Give serotonin antagonists.

- Cyproheptadine (5-HT_{2A} antagonist) at 1.1 mg/kg PO or rectally q1–4h^a
- Chlorpromazine (5-HT_{2A} antagonist)
- Methysergide (5HT_{2C} and tHT_{1A} antagonist)

4. Give supportive care.

- Benzodiazepines (diazepam or lorazepam; clonazepam is not effective)
- Propranolol, a nonspecific β-blocker
- Cooling techniques if the patient is hyperthermic
- Fluids
- Tracheal intubation if neuromuscular paralysis occurs

^aWisner T. Antidepressant drug overdoses in dogs. *Vet Med* 2000;95:520-525.

signs exhibited by animals that had ingested excessive amounts of sertraline, fluoxetine, or paroxetine were lethargy, vomiting, mydriasis, agitation, hyperactivity, and ataxia. MAOI overdose was most commonly associated with restlessness, ataxia, disorientation, seizure, tachypnea, and tremors. In the dogs that consumed overdoses of Saint-John's-wort, the most common clinical signs were depression, vomiting, tachycardia, and polydipsia.

TREATMENT

Treatment of SS requires a multipronged approach that is summarized in Box 3. It includes discontinuing all medications that facilitate serotonin activity, giving serotonin antagonists, and providing supportive care. Because of the rapid onset of signs, inducing vomiting or administering adsorbents should only be considered within the first 30 minutes after consumption of impli-

cated substances. Otherwise, these treatments may result in exacerbation of clinical signs or in aspiration.

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