Serotonin Toxicity

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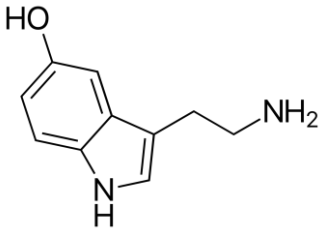

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Introduction

"With the increasing use of antidepressant medications in both humans and animals, it is not surprising that both the intentional and accidental ingestions of these medications is also on the rise."[1] Between 1998 and 2000, over 1,075 phone calls were made to the American Society for the Prevention of Cruelty to Animals (ASPCA) Poison Control Center concerning human anti-depressant medication ingestion by dogs.[7] In 2017, the Journal of the American Medical Association reported that 1 in 6 American adults are taking psychiatric medication, and therefore, the ASPCA Poison Control Center stipulates that prescription psychiatric medications are a common type of pet toxicant in households.

Serotonin toxicity, or "serotonin syndrome" is defined as a condition that manifests due to excess serotonergic agonism in the 5-HT receptors in both the central nervous system and periphery. This surplus of agonism can lead to autonomic imbalances that may become fatal. Serotonergic substances, also known as substances that increase the levels of serotonin in the body, that are reported to be associated with this syndrome include: human anti-depressant medications, human holistic supplements, behavior-altering veterinary medications, and recreational drugs.

Synthesis and Metabolism of Serotonin[10]

Serotonin is a neurotransmitter produced from the essential amino acid tryptophan. Two enzymatic reactions occur: the initial reaction converts tryptophan into 5-HTP, and the following reaction converts 5-HTP into serotonin (5-HT). The majority of these reactions take place in the

CNS, predominantly in serotonergic neurons in the brain stem, and enterochromaffin cells of the gastrointestinal tract; a smaller portion is synthesized within circulating platelets. 90-95% of serotonin is stored outside of the CNS within these circulating platelets and enterochromaffin cells, while the remaining amounts are stored within the CNS. Platelets absorb the majority of serotonin within the plasma, therefore resulting in low circulating active amounts.

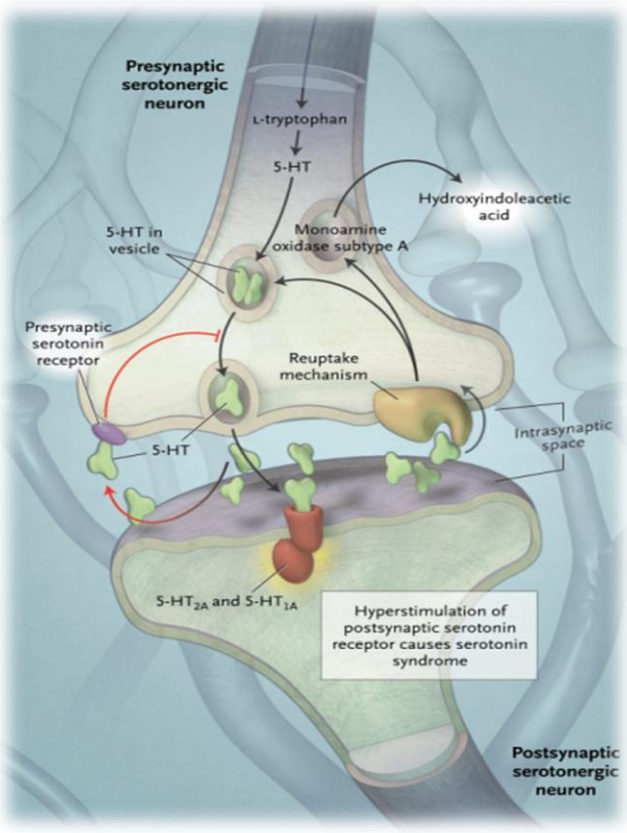

Figure 1: Synthesis and metabolism of serotonin.[12]

Serotonin is stored in presynaptic vesicles of serotonergic neurons. Serotonin is released from the presynaptic membrane and binds to serotonin-specific receptors, known as 5-HT receptors, on the postsynaptic membrane, or to auto-receptors on the presynaptic membrane which will act as a negative feedback mechanism to serotonin release. If it binds to auto-

receptors, it will enter the presynaptic cytosol and be metabolized and inactivated by monoamine oxidase (MAO). Alternatively, the serotonin can be re-packaged into vesicles to be recycled. The mechanism of having the serotonin within the synaptic cleft be taken up into the presynaptic cytosol for degradation is known as the re-uptake mechanism. The effect that serotonin has on the postsynaptic membrane is determined by how much serotonin is available in the synaptic cleft and can thus bind to the receptors.

After MAO has metabolized serotonin within the presynaptic membrane, it will then be further degraded in the liver and then excreted via the kidneys, with a very small amount being excreted in feces.

Function of Serotonin[1]

Within the CNS, serotonin plays a role in regulating the circadian rhythm, emesis centers in the hypothalamus, pain perception, mood, appetite, and thermoregulation. In the periphery, serotonin takes part in vasoconstriction, platelet aggregation, uterine contraction, intestinal peristalsis, and bronchoconstriction.

Pathophysiology of Serotonin Toxicity

Increase in Serotonin Precursors	Inhibition of Serotonin Metabolism	Increased Serotonin Release	Serotonin Reuptake Inhibitors	Stimulation of Serotonin Receptors (agonists)
L-Tryptophan *1-5-Hydroxytryptophan*	*MAO inhibitors*	*Amphetamines* *MDMA* *Cocaine*	*SSRIs* *TCAs* *Tramadol* *Fentanyl* *Methadone* *Meperidine*	*LSD* *Lithium* *Sumatriptan* *Buspirone*

Table 1: Examples of serotonergic substances and their mechanism of increasing serotonin levels.

As previously mentioned, serotonin toxicity occurs when there is an excess of serotonergic agonism in the 5-HT receptors, be it in the CNS, periphery, or both. This can occur through various mechanisms as stated in table 1: via increasing the precursors to serotonin, inhibiting the metabolism of serotonin, increasing the release of serotonin in the presynaptic cleft, increasing the inhibition of serotonin reuptake mechanisms, and agonizing serotonin receptors.

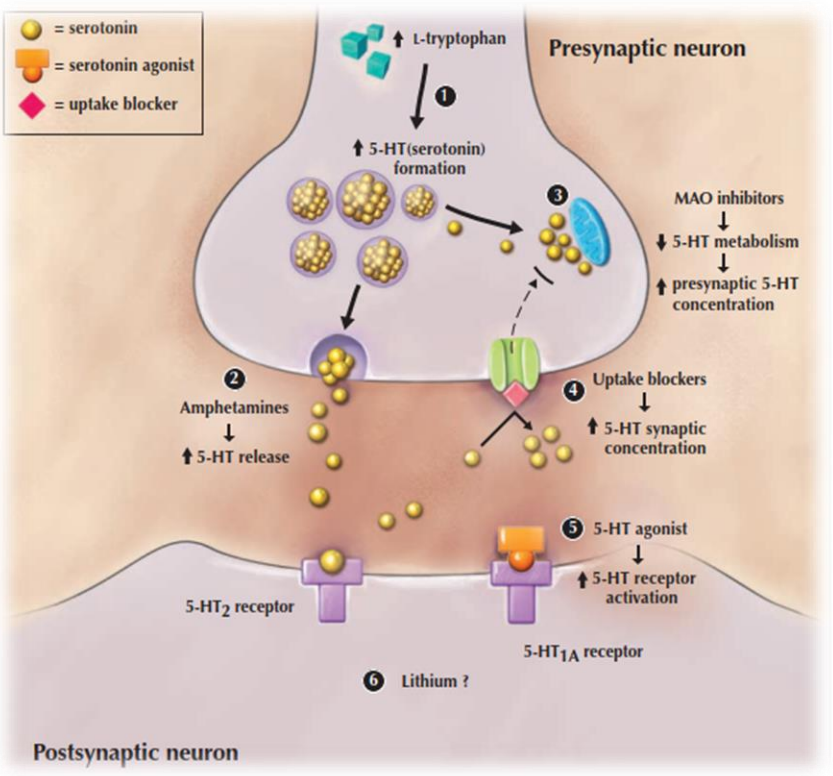

Figure 2: Mechanisms of serotonin syndrome. [12]

Figure 2 demonstrates the most common substances and their mechanism of serotonergic activity. Increased doses of L-tryptophan will increase 5-HT (serotonin) formation (1). Amphetamines, MDMA, and cocaine increase the release of stored serotonin, subsequently increasing levels within the presynaptic cleft resulting in more available to

bind to 5-HT receptors on the postsynaptic membrane (2). MAO inhibitors will increase the concentration of serotonin within the presynaptic membrane by inhibiting the degradation of 5-HT (3). Serotonin re-uptake inhibitors (SSRIs) and tri-cyclic anti-depressants (TCAs) will inhibit the transport of serotonin into the presynaptic membrane therefore increasing levels within the synaptic cleft (4). LSD, lithium, sumatriptan, and buspirone directly agonize receptors on the postsynaptic membrane thus increasing receptor response (5).

It is important to note that this syndrome is not an idiopathic reaction.[12] In humans, this syndrome generally occurs due to administration of multiple serotonergic drugs at once, or overdose of a single serotonergic agent (such as MDMA), while in pets, it predominantly arises due to accidental ingestion.[10] Due to TCA's and SSRI's being highly protein-bound, the concurrent administration of a second highly-protein bound drug may displace TCA's and SSRI's thus rendering them more active and resulting in serotonin toxicity.[6,7] A decrease in renal and hepatic function has been associated with serotonin syndrome, due to 5-HT being metabolized in these organs.[1]

Clinical Signs

Clinical signs can occur within 10 minutes to 6 hours after ingestion, making this syndrome a rapidly progressing one.[7] These signs can range from mild to life-threatening and fall into 3 categories: mental status changes, autonomic instability, and neuromuscular abnormalities.

In an article published in the Journal of the American Veterinary Medical Association in 2019 titled *Duloxetine Ingestion in 364 dogs,* the most common signs

observed were: lethargy, mydriasis, vomiting, trembling, and vocalization. The more severe and uncommon clinical signs consisted of hyperthermia ranging from 103 to 108 degrees Fahrenheit, absent pupillary light reflexes, bradypnea, bradycardia, and death.[3] In a study of 456 pets ingesting TCAs, hyperexcitability and vomiting were the most common clinical signs, with lethargy, ataxia, and muscle tremors being the next most common. Bradycardia was seen in the late stages of the syndrome. In this study, 7% of the pets died.

Severe sequelae that have been observed include: cardiac arrhythmias, disseminated intravascular coagulation, respiratory compromise, and rhabdomyolysis with subsequent myoglobinuria and renal failure.[2]

Diagnosis

There is not a specific diagnostic test for serotonin syndrome; gastric contents, urine, or blood can be submitted to a toxicology laboratory for screening of drugs associated with the syndrome.[1] In human medicine, this syndrome is diagnosed using the Hunter Serotonin Toxicity Criteria; this comprises a list of clinical signs along with a history of serotonergic substance ingestion in order to diagnose the syndrome.[11] This has been adapted by veterinary medicine due to it being consistent with what is seen in companion animals, with the exception of certain clinical signs such as diaphoresis and animals developing temperatures higher than 102.5 degrees Fahrenheit.

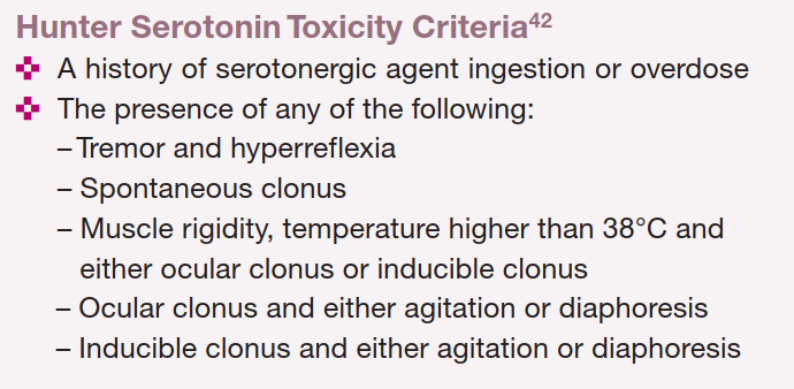

Figure 3: The Hunter Serotonin Toxicity Criteria as used in human medicine and adapted by veterinary medicine.[11]

Treatment and Monitoring Parameters[1,5,8]

Any serotonergic drugs should be immediately discontinued, and medical management should be initiated, which is the most crucial part of managing the syndrome.

Medical management includes both symptomatic treatment as well as serotonin-receptor antagonists. Activated charcoal, gastric lavage, or emesis are indicated if it is known that the animal ingested these substances less than 4 hours ago; however if severe neurological signs are present, these are to be avoided so as to decrease the risk for aspiration pneumonia; a cathartic can be used if that is the case. Because most serotonergic agent metabolites are excreted in the urine, fluid therapy is mandatory. Intravenous fluids along with wetting the feet with cold water, or cold baths, and providing a fan can help with cooling of the patient. Intravenous diazepam or phenobarbital can be administered for neurologic signs.

Serotonin receptor antagonists have been found to be extremely effective in the treatment of serotonin toxicity in humans and animals. Cyproheptadine, a 5-$HT2_A$ receptor antagonist, has shown to prevent or decrease muscle rigidity and thus the hyperthermia associated it. It is dosed at 1.1mg/kg in canines, and 2-4mg total dose in felines; this can be administered orally or rectally every 4-6 hours. Chlorpromazine, a phenothiazine derivative, blocks multiple 5-HT receptors; it has anti-emetic and hypotensive properties, and is therefore indicated in patients with emesis or hypertension. It is dosed intravenously, intramuscularly, or subcutaneously at 0.5mg/kg every 6 hours. Propranolol is a beta blocker that has 5-$HT1_A$ antagonism, it has been associated with the treatment of tachycardia and supraventricular arrhythmias in relation to serotonin toxicity.

Intravenous lipid emulsion as part of treatment of lipophilic serotonergic agent overdose, such as tramadol, has shown to reduce tachycardia, normalize arterial and diastolic blood pressures, and prevent seizures. Adverse effects should be monitored such as: fluid overload, pancreatitis, transient increases in liver enzymes, and inhibition of other lipophilic drugs administered.[4]

Doxapram has been used in humans to stimulate respiration in patients that underwent neuromuscular paralysis due to this syndrome, but its use in animals has not been studied. Instead, mechanical ventilation should be considered.

Dexmedetomidine has had promising results on the agitation and tremoring caused by this syndrome.

Caution should be taken when administering medications that are highly protein bound, such as non-steroidal anti-inflammatory drugs (NSAIDs) or thyroid medications,

as these can worsen toxicosis.[7] Attentiveness should be given to possible serotonergic activity that other drugs may have; these include but are not limited to mirtazapine, fentanyl, and tramadol. As this can lead to "polypharmacy toxicosis", resulting in exacerbation of the clinical picture.[10]

Magnesium containing cathartics should be avoided; TCA's and other serotonergic drugs have been reported to delay gastric motility and cause increased absorption of magnesium, leading to hypermagnesemia and resultant cardiac and respiratory arrest.[4]

Important parameters to serially monitor include: blood pressure, heart rate and rhythm, respiration rate, liver values, kidney values, and rectal temperatures. Patients should be placed on seizure watch and should be properly hydrated during hospitalization.

Prognosis

Prognosis is dependent on the amount of serotonergic agent ingested; severity of clinical signs are positively correlated with increased dosage ingestion.[10] For every 1-unit increase in the mg/kg dose ingested for fluoxetine, the probability of becoming symptomatic and having worsening clinical signs increased by 6%.[10]

Prognosis is also dependent on the secondary complications resulting from the toxicosis. These may include aspiration pneumonia, neuromuscular paralysis, infarcts, or myoglobinuria. Patients with mild clinical signs had a good prognosis, and patients with severe clinical signs or impaired liver or renal function had a more guarded prognosis.[5,6] Most patients recovered within 12-36 hours with prompt, aggressive, supportive care.[8]

Differential Diagnosis for Serotonin Toxicity

The following is a list of differential diagnosis that have been reported, these act similarly to serotonin syndrome in regards to the neurologic and gastrointestinal signs seen.[14] The main differentiation between these differentials and serotonin syndrome is a history of serotonergic substance ingestion as stated in the Hunter Serotonin Toxicity Criteria.

- Sleep medications (zolpidem, zopiclone, zaleplon)
- Wild mushrooms
- Tremorgenic mycotoxins (compost or moldy foods)
- Opioids/opiates
- Chocolate or caffeine toxicity
- Illicit drugs
- Sympathomimetics
- Anticholinergics
- Insecticides (carbamates, organophosphates)
- Rodenticides (zinc phosphide, bromethalin, strychnine)
- Infectious causes
- Metabolic causes
- Molluscicides (metaldehyde)
- Brain neoplasias
- Ammonia toxicity/liver failure/portosystemic shunts
- Heat stroke
- Salt toxicity
- Water toxicity
- Toad toxicity

Conclusion

Initial clinical signs can be subtle, and usually consist of head tremors, ataxia, vocalization, nausea and diarrhea. Improvement is seen about 24 hours after discontinuing the serotonergic agent and initiating treatment.[11] Nonetheless, clinical signs involving SSRI-associated serotonin syndrome, such as fluoxetine, have been reported to improve in about one week.[7]

The majority of patients will recover in about 36 hours with prompt and aggressive supportive care, and no long-term effects have been reported.[8] Death is not common but has been reported. And finally, as with any mystery poisoning patient, history is key!

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