5-Hydroxytryptophan toxicosis in dogs:
21 cases (1989–1999)

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Objective—To determine epidemiologic characteristics, clinical findings, and treatment outcome of 5-hydroxytryptophan (5-HTP) toxicosis in dogs.

Design—Retrospective study.

Animals—21 dogs with evidence of accidental 5-HTP ingestion.

Procedure—Information was retrieved from the National Animal Poison Control Center database. Records of dogs ingesting 5-HTP between January 1989 and February 1999 were reviewed for information on signalment, dose ingested, clinical signs (onset, severity, duration), treatments administered, and outcome.

Results—Clinical signs of toxicosis developed in 19 of 21 (90%) dogs. Neurologic signs included seizures (9 dogs), depression (6), tremors (5), hyperesthesia (5), and ataxia (4). Gastrointestinal tract signs included vomiting or diarrhea (12 dogs), signs of abdominal pain (3), and hypersalivation (2). Other clinical signs were hyperthermia (7 dogs) and transient blindness (3). Three dogs died. No important clinical laboratory or necropsy findings were reported. The doses of 5-HTP ingested ranged from 2.5 to 573 mg/kg (1.1 to 260 mg/lb) of body weight; the minimum toxic dose reported in our study was 23.6 mg/kg (10.7 mg/lb), and the minimum lethal dose was 128 mg/kg (58.1 mg/lb). Onset of signs ranged from 10 minutes to 4 hours after ingestion, and signs lasted up to 36 hours. Of 17 dogs with clinical signs of toxicosis that received treatment, 16 recovered; treatment consisted of decontamination, seizure control, thermoregulation, fluid therapy, and supportive care.

Conclusions and Clinical Relevance—Ingestion of 5-HTP in dogs can result in a potentially life-threatening syndrome resembling serotonin syndrome in humans; which requires prompt and aggressive care. (J Am Vet Med Assoc 2000;216:1937–1940)

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pected toxicosis, possible toxicosis, doubtful toxicosis, or exposure only (ie, when no signs were present at the time of the call and none were reported on follow-up).

Incidents are categorized as toxicosis if all temporal, clinical, and historic data are consistent with the expected syndrome; as suspected toxicosis if clinical signs are characteristic of the expected syndrome, but some data are not available; as possible toxicosis if only a few signs are consistent with the expected syndrome; and as doubtful if clinical signs and exposure history are not consistent with the expected syndrome. The NAPCC database was searched for records of dogs ingesting 5-HTP between January 1989 and February 1999.

Results

Twenty-one incidences of dog exposures to 5-HTP were retrieved from the NAPCC database; 1 additional dog was not included in this survey because the product involved was a dietary supplement containing more than 10 other natural ingredients besides 5-HTP, making it difficult to determine whether the reaction seen was attributable solely to the 5-HTP. No incidences of 5-HTP exposures were found in the database until late 1995, and most affected dogs (17/21; 81%) were identified from 1998 and 1999. Two (10%) incidents were categorized as exposures with no signs developing, 12 (57%) were assessed as suspected toxicosis, and 7 (33%) were toxicoses.

Breeds most commonly involved in accidental 5-HTP ingestion were Labrador Retrievers (5/21; 24%), mixed breeds (3/21; 14%), and Boxers (2/21; 10%). Fourteen of 21 (67%) dogs were male. Ages of the dogs ranged from 2 months to 10 years; 13 of 19 (68%) dogs were ≤ 1 year of age (ages were not available for 2 dogs).

The amount of drug ingested (dose) could be estimated in 19 of 21 (90%) dogs and ranged between 2.5 to 573 mg/kg (1.1 to 260 mg/lb) of body weight. Of the dogs assessed as exposure only, 1 dog ingested 2.5 mg/kg (1.1 mg/lb) and was not treated; the other clinically normal dog ingested 222 mg/kg (100.9 mg/lb) but was decontaminated (emesis) within 30 minutes of exposure. The lowest dose at which signs developed was 23.6 mg/kg (10.7 mg/lb); death was reported for 3 dogs at 128, 131.9, and 287 mg/kg (58.2, 60, and 157.7 mg/lb), respectively.

Clinical signs developed in 19 of 21 (90%) dogs. Onset of clinical signs ranged from 10 minutes to 4 hours following ingestion. Neurologic signs developed in all 19 dogs with clinical signs of toxicosis and included seizures (9 dogs), depression (6), tremors (5), hyperesthesia (5), ataxia or paresis (4), disorientation (2), coma (1), and hyperreflexia (1). Four of 19 dogs had mydriasis, and 3 developed transient, apparent blindness (eg, bumping into objects, decreased pupillary light responses, lack of menace response). Vomiting or diarrhea was observed in 12 of 19 dogs; other gastrointestinal tract signs included abdominal pain (3 dogs), hypersalivation (2), flatulence (1), and bloat (1). Other reported signs included hyperthermia (range of rectal temperature was 39.8 to 42.2 C [103.7 to 108 F]; 7 dogs), vocalization (4), weakness (1), tachycardia (1), cyanosis (1), recumbency (1), dyspnea (1), and hypothermia (1). Three of 19 dogs with clinical signs of toxicosis died.

Of the treated dogs, all but 1 recovered following treatment by the attending veterinarians (16/17 dogs receiving treatment). Dogs that recovered responded well to anticonvulsants, thermoregulation, fluid therapy, and decontamination. Most treated dogs (14/17) were clinically normal within 12 hours of initiation of treatment, and all dogs were clinically normal within 36 hours of initiation of treatment. Clinical blindness, when it developed, was usually the last sign to resolve.

Clinical laboratory tests (serum biochemical analysis and CBC) were performed in 5 of 19 dogs with clinical signs of toxicosis, and there were no important clinical laboratory alterations reported. Necropsy results on 2 of the dead dogs were unremarkable other than congestion of multiple organs and postmortem hyperthermia. Histologic evaluation revealed pulmonary edema, diffuse congestion of liver and lung, and acute renal tubular necrosis and hemorrhage.

Discussion

5-Hydroxytryptophan is a precursor to serotonin, a CNS neurotransmitter that is also a potent promoter of platelet aggregation and has stimulatory effects on smooth muscle of the respiratory and gastrointestinal tracts and cardiovascular system. The usual metabolic pathway to the formation of serotonin involves the conversion of tryptophan, an essential amino acid, to 5-HTP via tryptophan hydroxylase in a rate-limiting fashion. Once formed, 5-HTP is constitutively converted to serotonin by aromatic L-amino acid decarboxylase (Fig 1). In laboratory animals, experimental serotonin excesses have been induced through oral and parenteral administration of 5-HTP. Symptoms consistent with excesses of serotonin in humans have been documented in people on drugs that inhibit serotonin breakdown such as monoamine oxidase inhibitors often in combination with drugs that enhance serotonin formation or release such as amphetamines or 5-HTP. The syndrome of serotonin excess in humans and laboratory animals has been termed serotonin syndrome. Patients with serotonin syndrome had abnormalities in cognitive and behavioral functions, autonomic nervous system function, and neuromuscular function.

Virtually all dogs with clinical signs of toxicosis in our study had neurologic and gastrointestinal tract signs that were consistent with those seen in human patients with serotonin syndrome. Neurologic signs were seen in all 19 dogs with clinical signs of toxicosis. Overstimulation of serotonin receptors within the CNS may have been the cause of seizures, hyperesthesia, disorientation, and other neurologic signs that were seen in affected dogs. Likewise, gastrointestinal tract signs in clinically affected dogs most likely resulted from excessive stimulation of serotonin receptors within the gastrointestinal tract causing diarrhea, vomiting, signs of abdominal pain, and bloat.

Neuromuscular effects (eg, tremors, hyperreflexia, ataxia), also seen in a number of dogs ingesting 5-HTP,
are the most commonly described signs for humans with serotonin syndrome.\(^5\) Hyperreflexia, a commonly described sign for human serotonin syndrome, was described for only 1 dog; however, it is possible that ataxia and tremors seen in dogs with 5-HTP intoxication were also associated with rigidity that was not specifically reported as a separate sign.

Signs of autonomic dysfunction including hyperthermia, diarrhea, mydriasis, abdominal pain, hyper-salivation, tachycardia, and tachypnea were present in many of the dogs ingesting 5-HTP. Hyperthermia may be caused by a direct effect of serotonin on the brain’s thermoregulatory center, an indirect effect caused by prolonged muscle activity, or a combination of these 2 effects.\(^5\) The cause of the apparent blindness seen in 3 dogs is not certain. In humans with serotonin syndrome, dilated and unresponsive pupils have been reported as autonomic events, but blindness has not. It is possible that the dogs were still visual, but ataxia and alterations of pupillary light responses gave the clinical appearance of blindness.

Histologic evaluation of tissues from 2 of the dead dogs revealed pulmonary edema, renal tubular necrosis, and multiple tissue congestion. These lesions are consistent with cardiorespiratory tract compromise, which is possibly brought on by hyperthermia, hypoxia, or prolonged seizure activity. Additionally, over-stimulation of serotonin receptors in the heart, blood vessels, and bronchi may have contributed to the effects on the cardiovascular and respiratory system, further enhancing the adverse effects on these systems. Because serotonin has potent platelet aggregating activity, alterations in coagulation variables might be expected with 5-HTP excess. No clinical coagulation abnormalities were identified in any of the dogs in our study; this was consistent with serotonin syndrome in humans in which coagulation abnormalities are rare and, if present, are usually related to disseminated intravascular coagulation secondary to hyperthermia or rhabdomyolysis.\(^7\)

The minimum toxic dose in this report was 23.6 mg/kg (10.7 mg/lb). It is possible that the minimum toxic dose for some dogs may be lower than this, as we had no instances of dogs ingesting doses between 2.5 mg/kg (1.1 mg/lb) and 23.6 mg/kg (10.7 mg/lb). The minimum lethal dose in dogs in this report was 128 mg/kg (58.2 mg/lb). There did not appear to be a good correlation between dose ingested and severity of clinical signs; however, several factors (eg, differences in the amount of 5-HTP absorbed prior to decontamination, time between ingestion and treatment, and individual variation in sensitivity to 5-HTP) could have been responsible for this poor correlation.

5-Hydroxytryptophan is available as an over-the-counter dietary supplement in capsule form ranging from 25 to 500 mg/capsule in strength. On the basis of the doses calculated in our report, a 500-mg capsule could potentially cause clinical signs in a 20-kg (44-lb) dog and could be potentially fatal to a 4-kg (8.8-lb) dog. Additionally, several formulations are available that contain 5-HTP along with other products including extracts of St. John’s wort (Hypericum perforatum), an herbal supplement that purportedly has monoamine oxidase inhibitory activity and has been associated with serotonin syndrome in humans.\(^8\) In instances of exposure to any herbal or nutritional supplement products, examination of the entire list of ingredients listed on the container is important, as the presence of 5-HTP in the product may not be apparent on the basis of the product name or the first several ingredients listed on the label.

Although some dogs did not develop clinical signs until 2 to 4 hours after ingestion of 5-HTP, approximately half of the dogs did develop signs within 1 hour of exposure. Following institution of veterinary medical care, all surviving dogs were clinically normal within 36 hours.

Early decontamination of clinically normal dogs may prevent the development of signs or lessen the severity of any signs that may develop. Because of the potential for rapid onset of clinical signs, if more than 30 minutes has elapsed from the time of ingestion of 5-HTP, decontamination should be done only under veterinary supervision. Emesis or gastric lavage should be followed by activated charcoal administration; activated charcoal should be used with caution in animals with clinical signs of toxicosis because of the risk of aspiration.

In dogs with clinical signs of toxicosis, treatment goals consist of managing severe signs (eg, seizures, hyperthermia), supporting vital functions, decontamination to minimize further drug absorption, and mon-
itoring for the development of complicating factors. Diazepam (0.2 to 1 mg/kg [0.09 to 0.45 mg/lb], IV, to effect) or barbiturates (pentobarbital, 3 to 13 mg/kg [1.4 to 6.8 mg/lb], slow IV, to effect) may be used to manage seizures or tremors. Fluid therapy is important to stabilize the dog and maintain cardiovascular function. Thermoregulation (eg, fans, cool water baths) is essential in hyperthermic dogs to prevent organ damage or disseminated intravascular coagulation. Close monitoring of the patient is necessary for the prompt detection and treatment of complications or exacerbation of signs; 1 dog that died had initially responded well to supportive therapy but was found dead the next morning when the veterinary staff returned to the clinic, underscoring the importance of continuous monitoring of affected dogs until they return to clinically normal.

Although no important clinical laboratory abnormalities were found in dogs in our study, serum biochemical analysis and CBC determination would provide a baseline and may aid in detecting previously existing conditions that could complicate recovery. Repeat evaluation of clinical laboratory values 48 to 72 hours following recovery would enable the clinician to ascertain whether substantial organ damage may have taken place during the acute toxicosis.

Cyproheptadine, a serotonin antagonist, has been used clinically to reduce the duration of signs in humans experiencing serotonin syndrome; experimentally, cyproheptadine has been shown to block the development of serotonin syndrome in laboratory animals. In 3 recent instances of suspected serotonin syndrome in dogs, we have suggested the use of cyproheptadine, and the results have been promising. Although further investigation is needed to fully determine the utility of cyproheptadine in dogs with serotonin syndrome, we feel that it may be a useful adjunct in the treatment of dogs ingesting 5-HTP. The recommended dosage would be 1.1 mg/kg (0.5 mg/lb), PO or rectally, every 1 to 4 hours until signs resolve; rectal administration may be preferred when severe vomiting or recent administration of activated charcoal render the oral route unfeasible.

In summary, 5-HTP ingestion in dogs can result in a potentially lethal condition resembling serotonin syndrome in humans. Although the signs can develop quickly after ingestion and be quite severe, most dogs will recover if given prompt and aggressive veterinary care.

References