J. Med. Toxicol. (2017) 13:183–186
DOI 10.1007/s13181-017-0600-1

CASE REPORT

Serotonin Syndrome from 5-Hydroxytryptophan Supplement Ingestion in a 9-Month-Old Labrador Retriever

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Received: 13 May 2016 / Revised: 14 January 2017 / Accepted: 24 January 2017 / Published online: 16 February 2017

Abstract
Introduction 5-Hydroxytryptophan (5-HTP) supplements are available over the counter and labeled as sleeping aids and anxiolytics for human use. 5-HTP is a serotonin precursor and overdose can lead to serotonin syndrome.
Case Report A 9-month-old female Labrador retriever was evaluated after ingestion of a 5-HTP supplement. Signs of agitation developed within 1 h of ingestion, and emesis was attempted by the owner with 3% hydrogen peroxide (H_2O_2) orally. On presentation, the dog was obtunded, bilaterally mydriatic and salivating. Physical exam revealed tachypnea, tachycardia, hyperthermia, and hypertension. Eighteen hours post presentation, the dog developed melena, hematemesis, and pigmenturia. A hemogram revealed mild anemia with evidence of oxidative erythrocyte damage (eccentrocytes, Heinz bodies, and siderocytes). A chemistry panel revealed markedly elevated creatine kinase and hyperbilirubinemia, supporting hemolytic anemia. A urinalysis revealed pigmenturia. Hemolytic anemia was presumed to be caused by oxidative damage secondary to gastrointestinal ulceration and circulatory embolism of H_2O_2. Treatment included fluid therapy, a mannitol constant rate infusion, antiemetics, gastroprotectants, and cyproheptadine as a serotonin antagonist. The patient responded well to treatment and was discharged within 48 h of presentation.
Discussion Serotonin syndrome is an increasingly common toxic syndrome in veterinary medicine with the availability of over-the-counter medications that alter serotonin metabolism. The importance of appropriate client education regarding emesis with H_2O_2 is highlighted.

Keywords Serotonin syndrome · 5-HTP · Hydrogen peroxide · Cyproheptadine · Dog

Introduction

Serotonin syndrome is classified as a range of clinical signs associated with elevations in the body's serotonin level through a variety of mechanisms, including intoxication with serotonin precursors, or through ingestion of drugs that alter serotonin regulation, resulting in persistence of serotonin at nerve terminal sites [1]. The syndrome is well recognized in the medical literature, and the prevalence of serotonin syndrome in both humans and non-human animals has increased over the past 15 years with increasing use of pharmaceuticals as antidepressants [1]. In normal metabolism, serotonin is produced in two steps, through hydroxylation of tryptophan into 5-hydroxytryptophan (5-HTP) and then decarboxylation into serotonin [1]. Serotonin is synthesized and stored in serotonergic and catecholaminergic neurons as well as the pineal gland in the central nervous system (CNS). Outside of the CNS, serotonin synthesis mostly occurs in enterochromaffin cells and, to a lesser extent, platelets [2]. The resulting clinical signs involve many systems and include tachycardia, hypertension, hypersalivation, nausea, vomiting, hyperthermia, tachypnea, and a range of CNS signs including sedation, recumbency, hyperexcitability, agitation, tremors, mydriasis, and seizures [1]. While serotonin intoxication is life-threatening, it responds well to prompt medical therapy and a majority of dogs recover within 12 h of initiation of treatment [3].

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Case Report

A 25-kg, 9-month-old female intact Labrador retriever was presented to the emergency room after ingestion of an over-the-counter 5-HTP supplement. The dog ingested approximately 30 tablets containing 100 mg 5-HTP each as the active ingredient, giving an estimated dose of 120 mg/kg. The dog's owner noted the ingestion and attempted to induce emesis unsuccessfully at home by administering approximately 9.5 mL/kg of 3% H_2O_2 per os. Within an hour post ingestion of the supplement, the dog started showing the first signs of agitation and was taken to the primary care veterinarian for evaluation. On presentation, the dog was tachycardic at 150 beats per minute (bpm, reference range 80–118 bpm [4]), hyperthermic at 40.0 °C (reference range 37.9–39.9 °C [5]), and hypertensive with a systolic blood pressure of 174 mmHg (reference range 111–145 mmHg [4]). The ASPCA Animal Poison Control Center was consulted at that time. The patient was administered 20 mL/kg of Lactated Ringer's solution, maropitant, acepromazine, methocarbamol, and rectal butorphanol before referral to a veterinary teaching hospital.

On presentation to the veterinary teaching hospital, approximately 4 h post ingestion, the patient was laterally recumbent and obtunded, showing periodic response to noxious and noise stimulation and occasional thrashing behavior. Mydriasis was present bilaterally with an intact pupillary light response and decreased gag response. Temperature was 40.3 °C, heart rate was 160 bpm and systolic blood pressure was elevated at 231 mmHg. Respiratory rate and effort were increased at 72 breaths per minute (reference range 18–34 breaths per minute [5]) and profuse salivation was noted.

Initial diagnostics were performed including a venous blood gas panel revealing a severe respiratory acidosis and metabolic acidosis, with a lactate of 1.8 (reference range 0–2 mmol/L). A mildly elevated potassium of 5.33 mmol/L (reference range 3.9–5.1 mmol/L) was noted, and blood glucose (106 mg/dL; reference range 60–120 mg/dL) and packed cell volume (43%; reference range 42–57%) results were within normal limits. Urine was noted to be port-wine colored and was consistent with pigmenturia upon centrifuging the sample. Three-view thoracic radiographs revealed a mild-to-moderate, asymmetric interstitial lung pattern worse in the right caudal lung lobe. Differentials for this finding included aspiration pneumonia and non-cardiogenic pulmonary edema secondary to intoxication [6].

Initial treatments included intravenous fluid therapy rate of 120 ml/kg/day with isotonic buffered fluids. Oxygen therapy via nasal cannula was instituted due to the concern for respiratory depression, and continuous ECG and blood pressure monitoring were performed overnight. A urinary catheter was placed to continue monitoring urinary output due to the concern of pigment induced acute kidney injury (AKI).

The following morning, the patient remained obtunded and tachypneic (60 breaths per minute) with a sustained systolic hypertension (140–200 mmHg). Mydriasis, salivation, and pigmenturia did not improve. A urinalysis obtained through cystotomy showed a specific gravity of 1.030, proteinuria, bilirubinuria, and 20–100 rbc/HPF, centrifugation again confirmed pigmenturia in addition to the hematuria. Bloodwork was performed 18 h post intoxication and a complete blood count (Table 1) revealed a non-regenerative anemia. Few nucleated red blood cells, large numbers of eccentrocytes, and few Heinz bodies and siderocytes were indicative of intravascular hemolytic anemia from oxidative damage to red blood cells. A mixed stress and inflammatory leukogram was present with mild toxic changes observed in neutrophils. The chemistry profile (Table 2) revealed mild elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), mild hypoalbuminemia, moderate hyperbilirubinemia, and markedly elevated creatine kinase. Inflammatory changes were consistent with gastroenteritis from oral hydrogen peroxide administration. Indirect and total hyperbilirubinemia was consistent with hemolytic anemia, and elevated creatine kinase was consistent with the episodic muscle tremors.

Cyproheptadine was administered at a dose of 1.1 mg/kg orally every 2–4 h. Cyproheptadine is a serotonin antagonist and has been used to reduce the duration of clinical signs associated with serotonin syndrome in some human patients and has shown promise for treating canine patients [3]. To increase diuresis, fluids were maintained at 120 mL/kg/day and a mannitol continuous rate infusion was instituted at 100 mg/kg/h. Diuresis does not enhance renal excretion of serotonin [3]; however, fluid diuresis and mannitol therapy are used to protect against pigmenturia induced AKI. Antiemetic therapy was instituted with maropitant at 1 mg/kg intravenously every 24 h. Gastroprotectant therapy was initiated due to the history of high-dose hydrogen peroxide administration, pantoprazole was administered at 1 mg/kg intravenously every 12 h, and sucralfate at 1 g orally every 4 h.

The patient showed a rapid response to therapy and became markedly more alert and ambulatory throughout the day. Pigmenturia markedly improved and the urinary catheter was removed. Mydriasis and salivation were resolved; however, the patient developed hematochezia in the evening and metronidazole was started at a dose of 10 mg/kg orally every 12 h. Improvement continued overnight and a complete blood count and renal panel were submitted the following morning, which showed improvement (Tables 1 and 2). The patient was discharged with oral medications including sucralfate, omeprazole, and metronidazole. Labwork at the primary veterinarian one week after discharge demonstrated improvement in regenerative anemia and chemistry values within references ranges.

Table 1 Complete blood count during hospitalization

Result name	18 h post presentation	42 h post presentation	Range
Hematocrit (%)	34 (L)	34.4 (L)	41–58
Hemoglobin (g/dL)	11.7 (L)	12.1 (L)	14.1–20.1
Nucleated red blood cells (/100 WBC)	2 (H)	3 (H)	0–1
WBC (thou/uL)	13.2	16.8 (H)	5.7–14.2
Segmented neutrophils (thou/uL)	11.5 (H)	11.4 (H)	2.7–9.4
Band neutrophils (thou/uL)	0.7 (H)	0.3 (H)	0.0–0.1
Lymphocytes (thou/uL)	0.3 (L)	3.7	0.9–4.7
Monocytes (thou/uL)	0.8	1.2	0.1–1.3
Eosinophils (thou/uL)	0.0 (L)	0.2	0.1–2.1
Basophils (thou/uL)	0.0	0.0	0.0–0.1
Platelet count (thou/uL)	167 (L)	195	186–545
Total protein (g/dL)	5.2 (L)	6.4	5.9–7.8
Plasma appearance	Hemolysis	Normal	
WBC exam	Toxic changes in neutrophils—mild	Toxic change in neutrophils—mild	
RBC morphology	Eccentrocytes—moderate, echinocytes—few	Eccentrocytes—moderate, Heinz bodies—few, siderocytes—few	
Hematology comments	Platelet clumps noted		

Table 2 Chemistry profile during hospitalization

Result name	18 h post presentation	42 h post presentation	Range
Sodium (mEq/L)	155 (H)	150	145–153
Potassium (mEq/L)	3.9 (L)	4.4	4.1–5.6
Chloride (mEq/L)	117 (H)	112	105–116
Urea nitrogen (mg/dL)	20	14	10–32
Creatinine (mg/dL)	1.0	0.9	0.6–1.4
Calcium (mg/dL)	9.8	10.0	9.3–11.4
Phosphate (mg/dL)	4.9	4.7	2.9–5.2
Total protein (g/dL)	4.9 (L)	5	5.3–7.0
Albumin (g/dL)	2.9 (L)	3.1	3.1–4.2
ALT (U/L)	143 (H)		20–98
AST (U/L)	505 (H)		14–51
Alkaline phosphatase (U/L)	107		17–111
GGT (U/L)	<3		0–6
Total bilirubin (mg/dL)	0.4 (H)		0.0–0.2
Direct bilirubin (mg/dL)	0.1		0.0–0.1
Indirect bilirubin (mg/dL)	0.3 (H)		0.0–0.2
Creatine kinase (U/L)	6559 (H)		48–261

Discussion

Serotonin syndrome can be life-threatening due to the widespread effects of serotonin on multiple organ systems. The minimum toxic dose for dogs is reported to be 23.6 mg/kg, with a reported minimum lethal dose of 128 mg/kg [3]. This dog's ingestion of 5-HTP was estimated to be 120 mg/kg, near the given minimum lethal dose of the serotonin precursor. While the consequences of untreated serotonin toxicosis can be dire, prompt and aggressive intervention has a good prognosis and affected dogs can fully recover within 36 h [3]. Supportive treatment is aimed at ameliorating clinical signs and includes antiemetic therapy, fluid therapy, sedation or neurological support, and monitoring cardiac and renal function. Additionally, cyproheptadine has shown variable success as a serotonin antagonist [3]. In this case, mannitol therapy was used in conjunction with fluid diuresis to decrease the risk of renal injury due to pigmenturia. The effects of mannitol include expansion of intravascular blood volume, renal vasodilation, and osmotic effects, which increases intratubular pressure to overcome tubular obstruction, and the use of mannitol in cases of human myoglobinuria secondary to rhabdomyolysis is supported in clinical studies [7]. Although the origin of pigmenturia in this case was not confirmed to be myoglobinuria versus hemoglobinuria, this therapy can be considered as an adjunct for serotonin syndrome if pigmenturia is present. Prognosis is worse in dogs when severe signs occur, including arrhythmias, seizures, and other complications of serotonin syndrome such as rhabdomyolysis resulting in myoglobinuria and AKI, disseminated intravascular coagulation, and respiratory depression.

An important aspect to highlight in this case is the additional finding of intravascular hemolytic anemia

(IHA) during the patient's clinical course. IHA is not a finding associated with serotonin syndrome; however, the hallmark findings of eccentrocytes and Heinz bodies raised the presumptive diagnosis of oxidative damage, which was considered secondary to the high oral dose of H_2O_2. Five times the maximum recommended dose (2.2 mL/kg with a maximum of 45 mL per dog [8]) of 3% H_2O_2 was used to induce emesis in this patient. H_2O_2 causes adverse effects via three main mechanisms: corrosive damage, gas production, and oxidative damage [9], which can produce gastrointestinal ulceration, possibly resulting in perforation, gastric dilatation due to oxygen production, and gas embolization [8, 9]. Normally, each milliliter of 3% H_2O_2 produces 10 mL of oxygen (O_2) [10]. This dog was administered 240 mL, expected to produce 2.4 L of O_2, causing increased pressure within the gastrointestinal tract, which already had compromised mucosa due to peroxidation of membrane lipids. We speculate that pressure and mucosal damage increased absorption of H_2O_2 into the circulation [11]. All cells can produce and consume H_2O_2, and estimates of normal H_2O_2 plasma concentrations have ranged up to 5 μM [12]. Oversaturation of endogenous H_2O_2 regulation is expected to lead to oxidative damage to lipid membranes. In blood, this would result in hemolysis. Further investigation is needed, but hemolysis should be considered by the clinician in future cases when H_2O_2 overdosing is suspected in dogs.

Conclusion

Serontonin syndrome may occur in animals after ingestion of human supplements. Recognition of this syndrome by caregivers is important, and caution is needed when using hydrogen peroxide as an emetic agent.

Compliance with Ethical Standards

Conflicts of Interest None.

Sources of Funding None.

References

1. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med. 2005;352(11):1112–20.
2. Mohammad-Zadeh LF, Moses L, Gwaltney-Brant SM. Serotonin: a review. J Vet Pharmacol Ther. 2008;31(3):187–99.
3. Gwaltney-Brant SM, Albretsen JC, Khan SA. 5-Hydroxytryptophan toxicosis in dogs: 21 cases (1989–1999). J Am Vet Med Assoc. 2000;216(12):1937–40.
4. Egner B, Carr A, Brown S. Essential facts of blood pressure in dogs and cats: a reference guide. Egner Vet-Verlag; 2003.
5. Aiello SE. Reference guides. Merck & Co, Inc: The Merck Veterinary Manual website; 2015. http://www.merckvetmanual.com/mvm/appendixes/reference_guides/normal_rectal_temperature_ranges.html. Accessed 9 May 2016
6. Özkan ME, Dweik R, Ahmad MD. Drug induced lung disease. Cleve Clin J Med. 2001;68:782–95.
7. Khan FY. Rhabdomyolysis: a review of the literature. Neth J Med. 2009;67(9):272–83.
8. Khan SA, Mclean MK, Slater M, Hansen S, Zawistowski S. Effectiveness and adverse effects of the use of apomorphine and 3% hydrogen peroxide solution to induce emesis in dogs. J Am Vet Med Assoc. 2012;241(9):1179–84.
9. Watt BE, Proudfoot AT, Vale JA. Hydrogen peroxide poisoning. Toxicol Rev. 2004;23(1):51–7.
10. Byrne B, Sherwin R, Courage C, Baylor A, Dolcourt B, Brudzewski JR, Mosteller J, Wilson RF. Hyperbaric oxygen therapy for systemic gas embolism after hydrogen peroxide ingestion. The Journal of emergency medicine. 2014;46(2):171–5.
11. Burns RA, Schmidt SM. Portal venous gas emboli after accidental ingestion of concentrated hydrogen peroxide. The Journal of emergency medicine. 2013;45(3):345–7.
12. Forman HJ, Bernardo A, Davies KJ. What is the concentration of hydrogen peroxide in blood and plasma? Arch Biochem Biophys. 2016;603:48–53.