Title

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Journal

Veterinary Medicine and Science, 9(6)

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Publication Date

2023-11-01

DOI

10.1002/vms3.1253

Peer reviewed

DOI: 10.1002/vms3.1253

CASE REPORT

WILEY

5-Hydroxytryptophan toxicity successfully treated by haemodialysis in a dog

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Partial results of this manuscript have been presented at a scientific meeting as a resident abstract—The International Veterinary Emergency and Critical Care Symposium 2022.

Abstract

Objective: To describe a case of 5-hydroxytryptophan (5-HTP) toxicity successfully treated with haemodialysis in a dog.

Case Summary: A 3-year-old, male neutered Labrador Retriever, weighing 28.2 kg, presented to the emergency department approximately 4–5 h after ingesting a human supplement containing 200 mg of 5-HTP. The amount of 5-HTP ingested was estimated between 980 and 1988 mg (35–71 mg/kg). At presentation, the dog demonstrated progressive neurologic abnormalities consistent with serotonin syndrome, including altered mentation and ataxia. Due to the magnitude of the ingested dose and progression of clinical signs, extracorporeal blood purification with intermittent haemodialysis was chosen to expedite clearance of 5-HTP. High-efficiency haemodialysis was initiated, and the dog showed continued clinical improvement throughout the 5-h treatment. Clinical signs resolved completely within 12 h. Sequential blood and urine samples were obtained to document levels of both 5-HTP and serotonin. The dog was discharged 24 h after presentation with complete resolution of clinical signs.

New or Unique Information: This is the first report documenting the serial changes in 5-HTP concentrations during treatment with haemodialysis.

KEYWORDS
5-hydroxytryptophan, haemodialysis, extracorporeal, serotonin syndrome

1 | INTRODUCTION

Serotonin syndrome is a drug-induced toxicosis that results from excess concentrations of serotonergic drugs stimulating peripheral and central serotonin receptors (Gwaltney-Brant et al., 2000). Examples of medications that can cause serotonin syndrome when ingested in excess include antidepressants (selective serotonin reuptake inhibitors [SSRIs], monoamine oxidase inhibitors, tricyclic antidepressants), serotonin releasing drugs (amphetamines, lithium), and serotonin precursors (such as 5-hydroxytryptophan [5-HTP]). Serotonin has multiple physiologic actions centrally and peripherally. Central nervous system effects include regulation of mood, circadian rhythm, and thermoregulation. Peripheral effects include platelet aggregation, vasoconstriction, intestinal peristalsis, and bronchoconstriction (Mohammad-Zadeh et al., 2008).

Serotonin syndrome is a pathological expression of excessive serotonin stimulation, and in companion animals, it often occurs as a result of accidental ingestion of medications promoting serotonin responses. In humans, 5-HTP, a serotonin precursor, is used to treat conditions such as depression, obesity, and sleep disorders (Gwaltney-

Brant et al., 2000). 5-HTP is widely available as an over-the-counter dietary supplement promoting serotonergic effects. Once ingested, 5-HTP is readily absorbed and converted to 5-hydroxytryptamine (5-HT, serotonin). 5-HT then binds to serotonin receptors in the central and peripheral nervous systems. Clinical signs of serotonin syndrome induced by 5-HTP intoxication in dogs range from mild to life threatening. These include altered mentation, agitation, hyperexcitability, vision impairment, seizures, neuromuscular signs (tremors, myoclonus, rigidity, ataxia), gastrointestinal (vomiting, diarrhoea), cardiovascular effects (tachyarrhythmias, bradyarrhythmias), and hyperthermia (Gwaltney-Brant et al., 2000; Mohammad-Zadeh et al., 2008). A previous study reported the minimum toxic and lethal doses of ingested 5-HTP promoting clinical signs in dogs as 23.6 and 128 mg/kg, respectively (Gwaltney-Brant et al., 2000).

To date, treatment for 5-HTP intoxication has been largely supportive including intravenous (IV) fluids, sedation, anticonvulsants, and thermoregulation. Reported antidotes may include 5-HT2 receptor antagonists (cyproheptadine or chlorpromazine) (Graudins et al., 1998). Recovery has been documented to take anywhere from 12 to 48 h and depends largely on patient signalment, dose ingested, and initial decontamination (Graudins et al., 1998; Gwaltney-Brant et al., 2000). However, death has been reported at ingested doses of 128, 131.9, and 287 mg/kg (Gwaltney-Brant et al., 2000). Intravenous lipid emulsion (ILE) has been described as successful treatment in humans for serotonin syndrome secondary to overdoses with tricyclic antidepressants and SSRIs (Dagtekin et al., 2011). In veterinary medicine, there are no known reports documenting treatment for serotonin syndrome or 5-HTP toxicosis with ILE, and it is only recommended in severe cases not responding to other therapies. Extracorporeal therapies such as haemodialysis have been described for the treatment of toxicosis from a variety of drugs and poisons in human and veterinary medicine (Culler &Vigani, 2019; King et al., 2019). This report describes the indication and application of haemodialysis for the effective treatment of severe 5-HTP intoxication in a dog.

2 | CASE SUMMARY

A 3-year-old, male neutered Labrador Retriever, weighing 28 kg, was presented to the emergency room for hypersalivation, vocalisation, agitation, and inability to ambulate. Between 1 and 3 h prior to presentation, the dog ingested between 5 and 10 diet pills,[1] each containing 2.0 mg of vitamin B6, 75 mg magnesium, and 200 mg 5-HTP (equating to 35.4–70.9 mg/kg of potential exposure to 5-HTP). This dog had a benign medical history, other than previous episodes of dietary indiscretion. At presentation, vital parameters were within normal limits with exception of episodic heavy panting and mild hypertension (rectal temperature: 38.9°C [102.1°F]; heart rate: 115 bpm; mucous membranes: pink; capillary refill time: 1–2 s; oscillometric blood pressure[2]: 184/129 [136] mmHg). The dog was hypersalivating, vocalising, disoriented, severely agitated, and unwilling to ambulate. Thoracic auscultation revealed increased sounds in all quadrants with intervals of normal respiratory rate and effort between panting. Neurologic assessment revealed dysphoric mentation, bilateral mydriasis, and absent menace response. Proprioception could not be assessed due to the dog's unwillingness to ambulate.

Consultation with a veterinary poison control centre[3] supported a presumptive diagnosis of 5-HTP toxicosis based on estimated ingestion of 1000–2000 mg (35.4–70.9 mg/kg). The magnesium (minimum 750 mg) and vitamin B6 (minimum 20 mg) ingested were considered unlikely to result in any of the observed clinical signs. Venous blood gas[4] values revealed mild respiratory alkalosis: pH 7.530 (reference interval [RI] 7.35–7.44), $PvCO_2$ 18.8 mmHg (RI 33.6–41.2 mmHg), PvO_2 81 mmHg (RI 25.5–70.2 mmHg), sodium 145.2 mmol/L (RI 146–156 mmol/L), base excess −7.1 mmol/L (RI 0–4 mmol/L), and bicarbonate 15.8 mmol/L (RI 18.8–25.8 mmol/L). CBC and serum chemistries were within normal limits with the exception of serum creatinine, 1.6 mg/dL (RI 0.5–1.1 mg/dL). Radiographs of the thorax and abdomen were unremarkable.

Midazolam[5] (0.2 mg/kg IV) was administered upon presentation to attempt to relieve neurologic clinical signs. Vocalisation and agitation worsened shortly after midazolam administration, which was reversed with flumazenil[6] (0.01 mg/kg IV). Subsequently, a single dose of mannitol[7] (0.5 g/kg IV) was administered for potential cerebral oedema followed by lactated Ringer's solution[8] as a supportive measure to prevent dehydration after giving an osmotic diuretic. This was initiated at 140 mL/h. Cyproheptadine[9] (1 mg/kg) was given rectally once as a serotonin antagonist. No improvement in clinical signs was appreciated. Emesis was not induced due to the altered mentation of the dog and length of time since ingestion.

Due to the severity of clinical signs and lack of response to initial therapies, intermittent haemodialysis was suggested as an extracorporeal blood decontamination therapy to hasten recovery compared to continued medical management. The procedure was started within 3 h of admission to the hospital. Although the metabolic properties of 5-HTP are not thoroughly described in the literature for canines, 5-HTP has a smaller molecular mass (220.2 Da) and low protein binding (19%), making intermittent haemodialysis (IHD) the most suitable blood purification modality (Magnussen & Van Woert, 1982). The right cervical region of the dog was surgically prepared and a topical lidocaine and prilocaine cream analgesic[10] was applied. Vascular access was established by an 11.5 Fr × 24 cm, dual lumen catheter[11] placed in the right jugular vein using a modified Seldinger technique. Due to the degree of obtundation, general anaesthesia was not required

[1] One Life (re)Solv 5-HTP Plus Magnesium Plus Vitamin B6 Capsules.
[2] Cardell Insight Veterinary Monitor, Midmark Corp., Zoe Medical Inc., Topsfield, MA.
[3] American Society for the Prevention of Cruelty to Animals Animal Poison Control Center.
[4] Stat Profile pHOx Ultra - Nova Biomedical, Waltham, MA.
[5] Midazolam, West-ward, Eatontown, NJ.
[6] Flumazenil, Hikma Farmaceutica; Eatontown, NJ.
[7] Mannitol, Nova-Tech, Inc., Grand Island, NE.
[8] Lactated Ringers solution, ICU Medical Inc., Lake Forest, IL.
[9] Cyproheptadine, Cadila Healthcare Ltd., Matoda, Ahmedabad, India.
[10] Lidocaine 2.5%, prilocaine 2.5% cream, USP, Teligent Pharma, Inc., Buena, NJ.
[11] Dual lumen catheter, AngioDynamics Inc, Queensbury, NY.

for catheter placement. Adequate sedation was obtained with a single dose (0.02 mg/kg IV) of acepromazine.[12]

Intermittent haemodialysis was performed on a Baxter Phoenix intermittent haemodialysis platform[13] using a 75-mL paediatric blood circuit[14] and a Fresenius F160 NR hemodialyser.[15] Dialysis was prescribed based on delivery of >2.0 L/kg of blood to the hemodialyser projected to promote a 5-HTP reduction ratio approaching a prescribed urea reduction ratio (URR) of >90% for maximum clearance of the toxin. Systemic anticoagulation was provided by a 1400-IU priming dose of unfractionated heparin, followed by an IV constant rate infusion (CRI) titrated to maintain an activated clotting time between 160 and 180 s. The average compensated blood flow rate throughout the procedure was 300 mL/min. A total of 80.9 L of blood was treated over the 300-min duration of treatment. A CRI of 0.9% sodium chloride[16] IV was initiated 60 min after the start of treatment to match the observed urine output. A total of 600 mL was provided during the treatment including the 'rinse back' volume of the extracorporeal circuit. The haemodialysis procedure was uneventful, and the measured URR was 80% for the treatment as determined from the pre-blood urea nitrogen (BUN) of 15 mg/dL and post-BUN of 3 mg/dL.

During the IHD procedure, serum samples for 5-HTP concentrations were drawn from the inlet-line sampling port before initiating treatment and every 30 min throughout treatment. Paired urine samples were obtained similarly from the indwelling urinary catheter at 30-min intervals. Following the IHD procedure, blood was collected every 6 h while the dog was hospitalised post-procedure and then every 24 h after discharge from the hospital.

Within the first 3 h of the procedure, respiratory rate and effort improved. The dog gradually became more appropriately responsive and ate a meal. By the end of the 5-h procedure, there was complete resolution of clinical signs. He was monitored in the critical care unit overnight and supported with lactated Ringers' solution at 70 mL/h. He was discharged the following afternoon, and no oral medications were prescribed. The dog returned the following 2 days for subsequent blood draws to assess the potential of toxin 'rebound' and remained clinically normal. Quantitative analysis using mass spectrometry and liquid chromatography[17,18] for serial serum and urine concentrations of 5-HTP was performed.

Figure 1 shows the change in serum 5-HTP concentrations during IHD. There is a first-order exponential drop in the serum concentration of 5-HTP during the initial 2.5 h of the IHD procedure (from 1364.7 to 701.0 ng/mL) followed by a plateau over the subsequent 2 h with values varying between 259.9 and 348.8 ng/mL. At the fifth hour of IHD, the serum concentration of 5-HTP was not detectable. The estimated blood volumes were also calculated and are represented in Figure 1. The blood volume was estimated as 8.5% of the patient's body weight. Blood volumes processed represent the compensated blood flow rate × the interval treatment time divided by the patient's estimated blood volume. Figure 2 depicts serial changes in the urinary concentration of 5-HTP during the IHD treatment, which is correspondent to the reduction in plasma 5-HTP. The 5-HTP reduction ratio in the urine during the initial 4.5 h of haemodialysis was 82.7%, which also was correspondent to the serum reduction ratio of 77.5% determined at 4.5 h. There is a steady decline in urine concentration of 5-HTP over the course of treatment and in the 12 h post-treatment. Figure 3 illustrates the changes in serum 5-HTP concentration collected over an additional 67 h following IHD. There was a continued decline in concentration of 5-HTP over the 48 h following IHD. There was no detectable 5-HTP at the 48 and 72 h time points.

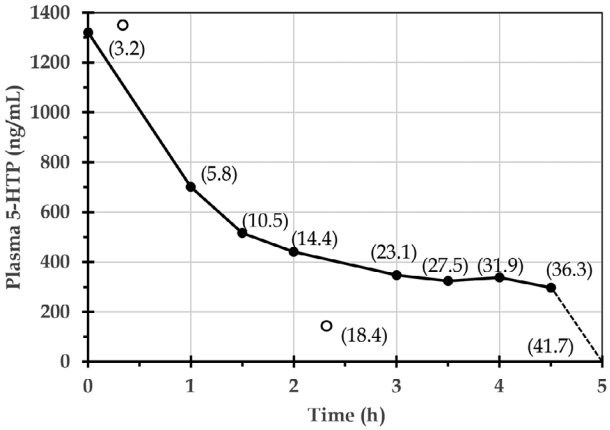

FIGURE 1 Serial plasma concentration of 5-hydroxytryptophan (5-HTP) during intermittent haemodialysis treatment in a dog with 5-HTP toxicity. The values represented in parentheses within the figure indicate the estimated blood volumes processed at the time of each 5-HTP measurement.

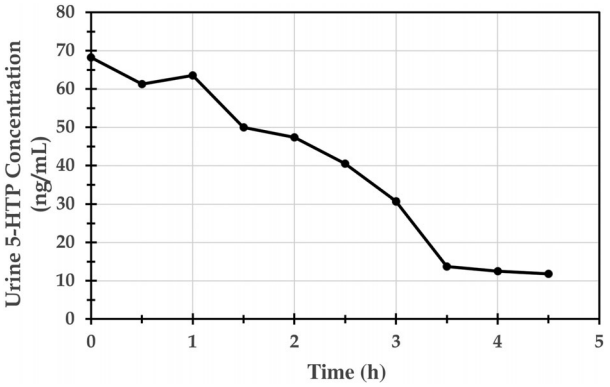

FIGURE 2 Serial urine concentration of 5-hydroxytryptophan (5-HTP) during the intermittent haemodialysis treatment in a dog with 5-HTP toxicity.

3 | DISCUSSION

This dog was estimated to have ingested a toxic amount (30–70 mg/kg) of 5-HTP in a supplement containing 5-HTP. When ingested, 5-HTP is

[12] Acepromazine maleate injection, VetOne, Boise, ID.
[13] Baxter Phoenix Dialysis Platform, Gambro Dasco, Model 66 41036, Medolla, Italy.
[14] Gambro Cartridge Blood Set (75mL), Parque Industrial Pacifico, Tijuana, Mexico.
[15] Optiflux Capillary dialyzer, Fresenius Medical Care, Waltham, MA.
[16] 0.9% sodium chloride, B. Braun Medical Inc, Bethlehem, PA.
[17] TSQ Altis triple quadrupole mass spectrometer, ThermoFischer Scientific, Waltham, MA.
[18] Vanquish liquid chromatography system, ThermoFischer Scientific, Waltham, MA.

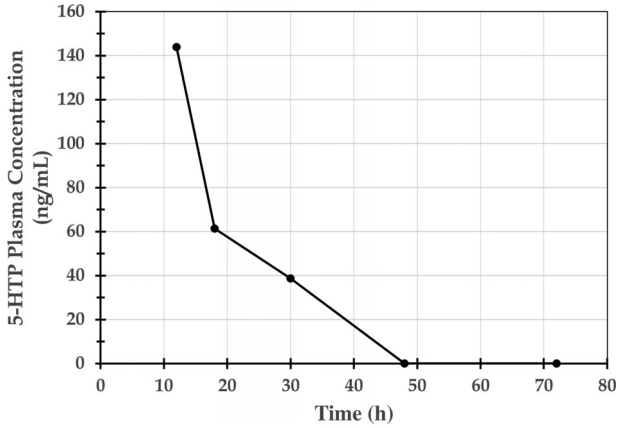

FIGURE 3 Serial plasma concentration of 5-hydroxytryptophan (5-HTP) during the 72 h following haemodialysis treatment in a dog with 5-HTP toxicity.

rapidly absorbed in the gastrointestinal tract and subsequently converted to serotonin (5-HT) with potential to promote a serotonin syndrome if ingested in toxic amounts (Magnussen & Nielsen-Kudsk, 1980). Prompt, aggressive medical management with IV fluids, cyproheptadine, and gastroprotectants has been utilised successfully to manage intoxications in dogs with accidental ingestions approximating 120 mg/kg (Gwaltney-Brant et al., 2000; Jennifer et al., 2017).

Many dogs are presented on an emergent basis following ingestion of various toxins in amounts causing significant morbidity or mortality. Extracorporeal therapies have emerged to effectively decontaminate dogs with excessive drug or toxin exposures with potential to dramatically improve outcomes for these patients. Intermittent haemodialysis, hemoperfusion, and therapeutic plasma exchange are the extracorporeal modalities most indicated to manage severe intoxication. The molecular size of the target toxicant as well as its volume of distribution and the degree of plasma protein or lipid binding, are important considerations when selecting which extracorporeal therapy would be most effective (Monaghan & Acierno, 2011).

Haemodialysis is a diffusive modality most effective for clearance of solutes whose molecular mass is less than 2000 Da. As the molecular mass of the toxicant increases, its clearance will decrease until the molecule size exceeds the size of the diffusion channels of the dialysis membrane at which diffusion ceases. The degree of protein binding of the toxin must be considered also. Small-molecular-weight toxins that are highly bound to plasma proteins are not effectively cleared by haemodialysis, relegating hemoperfusion or therapeutic plasma exchange as alternatives. Distribution volume of the toxicant also must be considered in selecting treatment modality. If the distribution volume is high (>0.6–2 L/kg), the bulk of the toxin within the vascular compartment is small and modalities like hemoperfusion and plasma exchange are relatively ineffective for total body clearance or decontamination. In general, as the volume of distribution increases to greater than 0.3 L/kg, high-efficiency haemodialysis becomes the most effective extracorporeal therapy for removal of toxins of an appropriate molecular weight.

The small molecular mass (220.2 Da), limited protein binding (19%), and distribution volume (<0.6 L/kg) of 5-HTP predicted high-efficiency haemodialysis would be the most effective extracorporeal modality for treating the clinical intoxication. The results of the reported treatment indicated a reduction ratio of at least 77% over the course of the 5-h treatment. This degree of clearance is consistent with reduction ratios for urea of approximately 90% for dogs of similar size with similar volumes of processed blood. The relative differences between 5-HTP and urea are likely due to the greater molecular mass for 5-HTP compared to that for urea. The relativity of 5-HTP reduction ratio to that of urea indicates haemodialysis is an effective extracorporeal therapy for this intoxication and provides a useful comparator to prescribe high-efficiency haemodialysis for future intoxications. These comparative reduction ratios between urea and 5-HTP further suggest 5-HTP has a distribution volume similar to that of urea.

With exception of potentially analytical aberrations between pre-treatment and 30, 150, and 300 min, there is a typical first-order exponential drop in the serum concentration of 5-HTP during the initial 4.5 h of the IHD procedure (from 1364.7 to 297.0 ng/mL). The predicted clearance in the final 30 min of treatment appears anomalous compared to the proceeding curve projection and likely represents an analytical or sampling error. Alternatively, the apparent anonymous 5-HTP concentrations at 30 min and the plateau between 180 and 270 min may represent intermittent appearance of 5-HTP into the vascular compartment from extravascular compartments at appearance rates approximating the dialytic clearance between pre-treatment and 30 min and between 180 and 270 min. The assay methodology for 5-HTP was optimised for a limit of quantitation of 50 ng/mL, so it is tenable the final measurement could exist below the detection limits at existing dialytic clearance rates in the absence of net 5-HTP appearance. The urine concentration of 5-HTP mirrors the changes in serum concentration, which may also be expected as 5-HTP is eliminated by urinary excretion. Presuming the validity of the post-treatment 5-HTP concentration, there is an increase in serum 5-HTP concentration from the end of the IHD session to the 12 h post-treatment assessment, suggesting 'rebound' of the drug into the vascular compartment from extravascular pools that were below the thresholds for clinical manifestations. From the available results, the dialytic and plasma half-time elimination rates for this formulation of 5-HTP can be estimated. The dialytic clearance produced an apparent plasma half-time elimination for 5-HTP of less than 2 h compared to the post-treatment metabolic clearance predicting a plasma half-time elimination of 9–10 h at plasma concentrations less than 150 ng/mL. These results demonstrate the extracorporeal clearance was superior to endogenous clearance and dramatically accelerated the resolution of clinical signs.

Extracorporeal therapy was chosen to expedite resolution of 5-HTP intoxication in this case where the milligrammes per kilogramme dose ingested was not at the previously reported lethal threshold, but clinical signs were very severe. While the authors do not know if the dog would have shown improvement with only medical management, his clinical signs were resolved within the first 12 h of hospitalisation, and he was discharged approximately 24 h after admission. Haemodialysis represents a significant therapeutic advance compared to reported

36 h for resolution of clinical signs in some cases managed supportively (Gwaltney-Brant et al., 2000) and offered an improved option for a potentially life-threatening intoxication in this patient.

4 | CONCLUSION

This is the first report documenting resolution of clinical signs of 5-HTP toxicity with corresponding assessment of dialytic and metabolic changes in toxin elimination in a dog treated by extracorporeal therapy. High-efficiency haemodialysis appears to be an effective extracorporeal modality to treat suspected 5-HTP intoxication. It should be considered as a first-line therapy in patients presenting with severe and uncontrolled clinical signs or potentially lethal exposures.

AUTHOR CONTRIBUTIONS

Diana Victoria Arbona: Conceptualisation; investigation; writing—original draft; writing—review and editing. **Larry Cowgill**: Conceptualisation; investigation; supervision; writing—original draft; writing—review and editing. **Saya Press**: Conceptualisation; investigation; supervision; writing—original draft; writing—review and editing. **Stephanie Istvan**: Conceptualisation; investigation; supervision; writing—review and editing. **Cedric Dufayet**: Investigation; writing—review and editing.

ACKNOWLEDGEMENTS

The authors would like to thank the K.L. Maddy Analytical Pharmacology Lab of the University of California School of Veterinary Medicine and Heather Knych for her laboratory contribution to the findings in this report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

FUNDING INFORMATION

This case report received no external funding.

DATA AVAILABILITY STATEMENT

No.

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How to cite this article: Arbona, D. V., Cowgill, L. D., Press, S., Dufayet, C., & Istvan, S. (2023). 5-Hydroxytryptophan toxicity successfully treated by haemodialysis in a dog. *Veterinary Medicine and Science*, *9*, 2438–2442. https://doi.org/10.1002/vms3.1253