“ESCAPE HATCH”

Clinicopathologic Conference

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“Hatch” is a 2-year-old neutered male Australian Shepherd who presented to MSU-CVM on emergency on 7/24/19 for tremors and suspected seizures after his owners returned from a one and a half week trip. Hatch had an episode last year after being fed a high protein diet (24%), during which he became inappetant and lethargic. He has been apparently healthy otherwise and is vaccinated regularly. He is currently due for his annual vaccinations. He has not been given flea, tick or heartworm prevention in the last 2 months. He lives primarily indoors, with access to a backyard and lives near a school with dumpsters where he has been known to eat trash. His owners report that he has not gotten into anything recently to their knowledge, but he has been staying with a pet sitter. Hatch was apparently normal when his owners arrived home. The tremors started around 9 pm. Hatch was given 50 mg of carprofen and a tablet of Zyrtec at 10pm. Hatch fell asleep and the tremors stopped. When he was stimulated, the tremors returned, and the owners called to bring him to MSU at 4 AM. His owners later determined that he consumed a bucket full of moldy vegetables from their neighbors’ yard.

On physical exam, Hatch was bright, alert and responsive. Hatch was experiencing severe generalized tremors at presentation. He weighed 19.8 kg with a body condition score of 5/9. His temperature was 104.8 F, his pulse was 132 beats per minute, and he was panting. His mucous membranes were pink and moist, with a CRT of less than 2 seconds, indicating an adequate hydration status. Hatch's pupils were severely mydriatic. No abnormalities were found on examination of his ears, nose and throat. Normal bronchovesicular sounds were heard bilaterally in all lung fields on thoracic auscultation. No crackles, wheezes, murmurs, or arrhythmias were appreciated. Hatch's abdomen was tense but non-painful on palpation. Based on clinical signs, a tentative diagnosis of tremorgenic mycotoxicosis was made.

The term mycotoxin was first published in 1962 after contaminated peanut meal was linked to the deaths of approximately 100,000 turkey poults in England (Bennett). Mycotoxins are derived from toxic fungal metabolites and are commonly acquired through accidental ingestion of contaminated foods, or potential dermal exposure or inhalation. Mycotoxicosis differs from mycoses, fungal infections, as it is not an opportunistic infection rather, a toxicity or poisoning. Mycotoxins can be classified as hepatotoxins, nephrotoxins, neurotoxins, and immune toxins. There are numerous mycotoxins reported in veterinary and human medicine. Some examples include aflatoxins, which are hepatotoxic metabolites of aspergillus species, citrinin, a nephrotoxic penicillium derivative, ergot alkaloids, fumonisons, tricothecenes, zearalenone etc (Bennett). The most common tremor inducing mycotoxins are the penicillium species derivatives penitrem A and roquefortine (Barker et al). These are considered neurotoxic and their mechanism of action is not fully understood. These mycotoxins can access the blood-brain barrier because their lipophilic nature. Proposed causes of the characteristics tremoring related to the toxicity include neurotransmission interference and potential increase in smooth muscle activity (Barker et al).

Similar to Hatch, named after his aptitude for escaping, dogs typically present on emergency for tremors or suspected seizures after ingestion of tremorgenic mycotoxins (Barker et al). The onset of tremors after ingestion can vary from 30 minutes to several hours. Dogs can also present with hypersalivation, pyrexia of greater than 104*F, or nystagmus and can be very sensitive to sounds and touch. They may also present with nonspecific signs such as vomiting, diarrhea, lethargy and unwillingness to rise. Acute onset of tremors or seizure-like episodes can, however, be attributed to other differential diagnoses. Consideration should be given to other causes of acute tremoring when dogs present on emergency. These include eclampsia,

hypocalcemia, hypoglycemia, and hepatic encephalopathy such as with portosystemic shunts. Ingestion of other toxic substances such as marijuana or cocaine, macadamia nuts, bromethalin based rodenticides, ethylene glycol, acetaminophen, ivermectin or even paintballs have been reported causes of tremors in dogs (Barker et al). Other causes can include blood transfusion reactions or infectious diseases such as distemper or rabies. The primary cause can be determined based on owner history, such as previously reported dietary indiscretion, known ingestion of substances or recent purchase of certain items (Barker et al).

Treatment of tremorgenic toxin ingestion is typically symptomatic, revolving around the resolution of tremors, and or seizures, and correcting any pyrexia (Barker et al). The primary toxin is usually not identified and anti-toxins are not typically available. Elimination of the toxin from the body can be achieved through induction of emesis, if the patient presents quickly after ingestion. It is typically an accepted method of treatment within 1 hour of ingestion. Apomorphine is routinely used to induce emesis, along with activated charcoal for oral decontamination. Anticonvulsants such as diazepam, midazolam, or propofol can be used as constant rate infusions to control tremoring. It has been reported that seizures induced by mycotoxins respond poorly to diazepam. The muscle relaxant methocarbamol can also be used as a constant rate infusion used to alleviate tremoring (Barker et al).

Intralipid emulsion (ILE) therapy has been reported in humans with acute barbiturate overdoses (Lee). It is commonly used in veterinary medicine for treatment of ivermectin toxicity in dogs and cats. For example, when dogs ingest horse ivermectin products, and cats are given dog ivermectin products, resulting in overdosage toxicity. Other uses include the overdose of medications such as local anesthetics (e.g. bupivacaine, lidocaine), tricyclic antidepressants, propranolol, muscle relaxants, and other macrocyclic lactones such as moxidectin (Barker et

al)ILE should be considered for patients not responding well to standard therapy for severe neurotoxic or cardiotoxic poisoning, especially with strongly lipophilic substances.

The exact mechanism of lipid emulsion therapy remains unknown. The most commonly accepted mechanism is the lipid acting as a “lipid sink” by sequestration of lipophilic compounds into intralipid compartment within the intravascular space. This entails compartmentalization of the drug into the lipid resulting in less toxin in the vasculature available for absorption into the tissues. This allows for the transfer of the intralipid and lipophilic substances from target organs, such as the brain and heart, into tissues where lipid can be stored, metabolized or excreted (Gwaltney and Meadows) Other reported hypotheses include: providing cardiac myocytes energy to increase cardiac performance, possible restoration of myocardial function by increasing intracellular calcium concentration, and increasing the overall fatty acid pool, which can then overcome potential inhibition of mitochondrial fatty acid metabolism (Lee).

Intralipid emulsions are labeled for use in parenteral nutrition and are not formulated specifically for anecdotal use. Intralipid emulsion therapy for treatment of toxicosis is considered extra label usage in veterinary medicine. Because of this, no administration limits have technically been established (Robben et al). There are a variety of reported dosage ranges for constant rate infusions. Dosing of a 20% solution intralipid emulsion is recommended for intoxications, as 10% solutions do not typically produce effective results. A common dosage modality reported involves the administration of “1.5 ml/kg IV bloused over 1 minute, followed by 0.25 ml/kg/min for 30-60 minutes. The initial bolus could be repeated 1-2 times if no response to the initial bolus is obtained, with a goal to not exceed 8 ml/kg/day (Lee)”. Side effects of lipid emulsion therapy potentially include hyperlipidemia, hepatomegaly, icterus, splenomegaly, fat embolism, thrombocytopenia, hemolysis, and prolonged clotting times.

Patients should be monitored closely, especially over the first 20 minutes to 1 hour during ILE therapy for any signs of allergic reactions, similar to transfusion reactions, or volume overload. Blood work should be obtained prior to ILE administration, as increased lipid content can falsely change values (Robben et al). Hyperlipidemia can be monitored with serial PCV/ TP testing to determine the degree of lipidemia (Lee). Triglycerides can be monitored after administration to determine the patient's lipid clearance (Robben et al). Adverse effects have been rarely reported. Two primary effects include microbial contamination, if handled improperly, and direct reaction to the lipid product or its components, rarely occur. Neurologic complications and detrimental changes to respiratory function has been reported in ILE use in human patients with severe sepsis or acute respiratory distress syndrome. Pancreatitis has also been anecdotally reported in human medicine as a potential complication of chronic hyperlipidemia, along with hemolysis. Corneal lipidosis has been reported in one cat treated for permethrin toxicosis (Robben et al).

Due to the reported responsiveness to treatment and initial suspicion of tremorgenic mycotoxicosis, Hatch was administered lipid emulsion therapy upon presentation to help bind any potential toxin. He was then given methocarbamol and midazolam, muscle relaxants, intravenously to help control his muscle tremors. Hatch responded better to methocarbamol, and his tremors were best controlled on a methocarbamol CRI after the completion of ILE therapy Initial blood work (NOVA) performed revealed no significant abnormalities. An ECG was also performed and revealed normal sinus rhythm.

On July 25th, 2019 , Hatch's tremors were markedly improved. He was able to walk unassisted and only demonstrated mild ataxia. At this point, he was eating normally and therefore switched to oral methocarbamol. Hatch continued to show improvement throughout the day. A serum chemistry revealed a mildly elevated creatinine kinase but otherwise did not reveal

any other significant abnormalities. Hatch was discharged the same day and sent home with oral methocarbamol until symptoms resolved or for the next 2 days. Intralipid emulsion therapy offers an affordable option for treatment of suspected tremorgenic toxicosis. It can provide rapid clinical improvement in some cases of toxicity as well as with adjunctive treatments.

ILE containers typically have a shelf life of 2 years if unopened, and last about 24 hours after opening. The reported side effects should not be intimidating with careful patient monitoring and appropriate use. It is, however, typically not used as a first line therapy for responsive toxicities and reserved as an adjunctive treatment for severe cases not responding to initial treatment. More research and ILE formulated for use in toxicities would be beneficial and offer more insight into tremorgenic mycotoxicosis treatment modalities. Cases such as Hatch's provide evidence for a very successful response to treatment and can serve as an example of appropriate ILE usage as a first line therapy alongside standard treatment modalities.

Sources:

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