Iron Intoxication in a Dog Consequent to the Ingestion of Oxygen Absorber Sachets in Pet Treat Packaging

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Abstract Oxygen absorbers are commonly used in packages of dried or dehydrated foods (e.g., beef jerky, dried fruit) to prolong shelf life and protect food from discoloration and decomposition. They usually contain reduced iron as the active ingredient although this is rarely stated on the external packaging. Although reduced iron typically has minimal oral bioavailability, such products are potential sources of iron poisoning in companion animals and children. We present a case of canine ingestion of an oxygen absorber from a bag of dog treats that resulted in iron intoxication necessitating chelation therapy. A 7-month-old female Jack Russell terrier presented for evaluation of vomiting and melena 8–12 h after ingesting 1–2 oxygen absorber sachets from a package of dog treats. Serum iron concentration and ALT were elevated. The dog was treated with deferoxamine and supportive care. Clinical signs resolved 14 h following treatment, but the ALT remained elevated at the 3-month recheck. The ingestion of reduced iron in humans has been reported to cause mild elevation of serum iron concentration with minimal clinical effects. To our knowledge, no cases of iron intoxication following the ingestion of oxygen absorbers have been reported. The lack

of ingredient information on the packaging prompted analysis of contents of oxygen absorber sachets. Results indicate the contents contained 50–70% total iron. This case demonstrates that iron intoxication can occur following the ingestion of such products. Human and veterinary medical personnel need to be aware of this effect and monitor serum iron concentrations as chelation may be necessary.

Keywords Heavy metal poisoning · Food preservatives · Chelation therapy · Deferoxamine · Reduced iron · Oxygen scavenger

Introduction

Packages of dried foods, nuts, and processed meats often contain oxygen absorber sachets (2–30 g net weight) that are added to prolong the shelf life and protect food from the discoloration and decomposition caused by oxidation or aerobic microorganisms (Fig. 1). The most common active ingredient in food-grade oxygen scavenging systems is reduced iron, used for its ability to consume oxygen via conversion to iron oxide [1]. Reduced iron is a term generally used to refer to the end product of iron oxide that has been reduced with hydrogen or carbon monoxide. This form of elemental iron is a common iron fortificant of foods.

With respect to oxygen absorbers, the ingredient information is not typically included on the exterior packaging making it challenging for physicians and veterinarians to determine the proper course of treatment when faced with patient exposures. Even in cases where the outer packaging lists iron as an ingredient, the label does not state the specific salt formulation or total amount of elemental iron. Determining this information is difficult even for experienced clinical toxicologists, and therefore creates difficulty

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Fig. 1 A collection of oxygen absorber sachets from human-grade and pet food packaging purchased in the USA by the authors. Only one of the five sachets mentions iron on the packaging. (Courtesy of Dr. Ahna G. Brutlag, Pet Poison Helpline, Minneapolis, MN)

calculating the risk of toxic exposure following ingestion. Adding to the confusion, such sachets may easily be mistaken for desiccants containing silica gel, a relatively inert and non-toxic ingredient.

Case summary

A 7-month-old female intact Jack Russell terrier weighing 5.18 kg presented to a veterinary clinic for evaluation of vomiting of 3 h duration. In the 8–12 h preceding examination, the dog had chewed into an unopened package of rawhide pet treats as well as the two oxygen absorber sachets that were included in the rawhide packaging. One of the oxygen absorber packets was completely emptied, and the other was punctured and spilled. There was no known exposure to other toxins or foreign material, and the dog had no known health problems.

The physical exam revealed lethargy, melena, and a tense abdomen with the remainder being unremarkable. Abdominal radiographs revealed granular, radiopaque material within the distal colon consistent with granular iron. The serum iron concentration was 436 $\mu\text{g/dl}$ (reference 94–220 $\mu\text{g/dl}$). Complete blood count (CBC) and activated clotting time (ACT) results were within reference ranges. The fecal flotation exam was normal except for the presence of black stool with mucous. Results of a limited serum biochemical analysis were within reference ranges with the exceptions of mildly elevated ALT (ALT=175 U/l; reference 10–100 U/l) and mildly elevated BUN (BUN=31 mg/dl; reference 7–27 mg/dl).

Treatment for iron intoxication commenced with milk of magnesia (5 ml PO once), sucralfate (100 mg/kg slurry PO q 8 h), and famotidine (1 mg/kg IM or IV q

12 h). Two hours after admission one 60-ml warm water enema was administered, and the dog defecated dark tarry feces, black granular material believed to be the contents of the oxygen absorber sachets, and white liquid resembling milk of magnesia. Chelation therapy was instituted with a constant rate infusion of deferoxamine (15 mg/kg/h IV for 21 h) and supportive care including IV fluids (Normosol-R at 3.86 ml/kg/h) and oral metronidazole (10 mg/kg PO q 12 h). The dog's urine was a gold color 3 h after instituting deferoxamine and a dark amber color 6 h later.

Three hours following presentation the dog vomited again; maropitant (1.5 mg/kg, SQ, 104 once) was administered maropitant (1.5 mg/kg, SQ, once) and the vomiting resolved. The dog's lethargy resolved approximately 8 h following the initial exam, and melena was last noted 14 h following the initial exam. Twenty hours after the initial presentation ALT was reduced to 136 U/l and all other values were within reference ranges. Twenty-six hours after the initial exam, the dog was discharged on oral sucralfate, oral metronidazole, and a bland diet. During a follow-up telephone call the week after ingestion, the pet owner reported that the dog remained asymptomatic following discharge. Three months later a recheck examination and labs revealed a normal physical examination, an elevated ALT (217 U/l), mildly elevated BUN (31 mg/dl), and normal CBC and urinalysis. The owner did not return the dog for recheck of liver enzymes.

Discussion

To the best of our knowledge, this is the first documented case of iron intoxication following ingestion of iron-containing oxygen scavengers. Reported sources of unintentional iron intoxication in humans and animals include prenatal vitamins, multi-vitamins with iron, iron supplements (prescription or OTC), or, less commonly ferric chloride, parenteral iron, iron-based slug bait and fertilizers, and reduced-iron containing products such as instant hand/foot warmers [2–4]. Reduced iron, the active ingredient believed to be in iron-based oxygen scavengers, is reported to have poor solubility in water and weak acids, which likely results in low oral bioavailability. Until recently, the reduced iron contained in products such as oxygen absorbers or instant hand/foot warmers was not deemed to be of toxicological significance [3, 5]. However, the particle size of reduced iron is critically important to determine the bioavailability; the smaller the iron particle, the greater its bioavailability [6].

The mechanisms of iron absorption in mammals are extremely complex and continue to be the subject of intense investigation. The chemical form of iron influences absorption and transport mechanisms, but many other factors

including pH, binding components, transporter proteins, and reducing enzymes affect iron uptake [7]. Although ferrous (2+) and ferric (3+) salts have similar solubility, ferric (3+) salts have generally lower bioavailability. The rate at which reduced (elemental) iron dissolves in the stomach and duodenum is largely unknown but is greatly influenced by particle size. Thus, knowledge of the chemical form of iron and the particle size of reduced iron is critical in order to estimate the bioavailability and risk of toxicity. Iron oxide, the end product of iron-based oxygen scavengers, has very poor oral bioavailability and is not thought to be problematic following ingestion [4]. Thus, it is likely that oxidized or “spent” oxygen scavengers pose minimal toxicological threat to humans or animals following ingestion. However, because the degree of oxidation cannot be determined by the outward appearance of the packet, medical professionals cannot easily determine the bioavailability and health hazard. Complicating the calculation of risk in these exposures is the lack of readily available information regarding the scavenger’s ingredients or amount of elemental iron. In this case, such information was not easily accessible.

Following ingestion, the absorption of iron is also regulated by the body’s current iron stores. At therapeutic concentrations, iron is primarily absorbed in the duodenal enterocytes by divalent metal transporter 1 (DMT1) from where it is either transported to the systemic circulation via transferrin or stored as ferritin and discarded as the cell is sloughed. However, in cases of oral overdose, iron asserts its toxic effect via the creation of iron-induced reactive oxygen species (ROS) that directly damage the gastrointestinal (GI) epithelium, resulting in the dysfunction and bypass of the intestinal regulatory system which allows for increased passive absorption of iron down its concentration gradient. Once the reserve of transferrin has been saturated, “free” or unbound reactive iron results in the formation of additional ROS.

The generation of ROS as a result of iron intoxication is due to the fact that, as a transition metal, iron is a key participant in both the Fenton and Haber–Weiss reactions, resulting in the creation of hydroxyl radicals. As physiologic defenses for the detoxification of ROS become overwhelmed, ROS result in direct cellular damage such as lipid membrane destruction (via hydroxyl radical initiated lipid peroxidation), along with damage to mitochondria and macromolecules [4, 8]. The organ systems most affected include the GI tract, liver, and vasculature. Early signs of iron intoxication include vomiting, diarrhea, abdominal pain, lethargy, and GI hemorrhage with possible hemodynamic compromise. Progressive cellular damage results in metabolic acidosis, hepatic damage and coagulopathy, capillary leak syndrome, shock, and death [2, 4, 8]. In

rare cases, gastric outflow obstruction due to stricture formation occurs 2–8 weeks following ingestion [2].

The range of toxicity for humans and dogs following oral iron exposure is similar. Ingestions of less than 5–20 mg/kg of elemental iron typically result in mild clinical signs but are not likely to result in significant toxicosis [4, 9, 10]. Ingestions between 20 and 60 mg/kg of elemental iron can develop mild to moderate clinical signs, necessitating treatment or monitoring [2, 4, 11]. Ingestions greater than 60 mg/kg can result in serious poisoning or death. In animals and humans, oral doses between 100 and 250 mg/kg are potentially lethal [4, 8, 9, 12].

Ingestions of more than 20–40 mg/kg elemental iron or, in cases such as this where the amount of elemental iron is not known and clinical signs are visible, obtaining serum iron concentrations is warranted [2, 4]. In oral overdose, peak concentrations of iron occur 2–6 h following ingestion, depending on the formulation. As absorption rates vary with product dissolution (surface area) and serum concentrations may change rapidly, obtaining a serum iron concentration 4–6 h after the ingestion of most intact products is recommended. In the case of liquid or chewable iron formulations, serum concentrations should be collected 2–3 h after ingestion. Additionally, monitoring the iron concentration every 6–8 h during chelation therapy can help to guide the duration of treatment. In humans and dogs, peak serum iron concentrations greater than 500 µg/dl are associated with significant toxicosis including metabolic acidosis and shock, and chelation with deferoxamine is often necessary. Regardless of the serum iron concentration, if the amount of ingested iron is believed to be greater than 20 mg/kg and the patient is displaying signs consistent with intoxication (beyond mild vomiting), decontamination, abdominal radiographs, deferoxamine, and supportive care including GI protectants and IV fluids are recommended. In this case, the patient presented too late for effective oral decontamination; however, due to the presence of radiopaque material in the distal colon, decontamination was performed via an enema (versus emesis or whole bowel irrigation). The dog was also treated with oral milk of magnesia in hopes of precipitating iron in the GI tract as insoluble iron hydroxide. Famotidine and sucralfate were administered to decrease gastric and intestinal acidity and thereby decrease the solubilization and absorption of iron as well as aid in the reduction of gastric damage and reduce the risk of stricture formation. Metronidazole was administered to aid in the management of acute colitis. Additional supportive therapies such as maropitant (antiemetic) were administered due to the dog’s persistent vomiting, and IV fluids were utilized at a twice maintenance rate in order to maintain adequate organ perfusion and correct for ongoing losses.

The oxygen absorber sachets ingested by this dog contained no ingredient information on the packaging, nor

was the salt formulation or amount of elemental iron available from customary sources (MSDS, medical databases such as Micromedex, the manufacturer). Thus, in effort to estimate the amount of iron, chemical analysis of three randomly chosen brands of oxygen absorbers found in packages of human-grade food products was performed. Unfortunately, analysis of the oxygen absorber ingested by the dog in this case was not possible as the sample was not saved. The samples were digested in a combination of nitric and hydrochloric acid at 180°C and quantitatively analyzed by inductively coupled argon plasma atomic emission spectrometry (ICP-AES; FISIONS, Accuris Model, Thermo Optek Corporation, Franklin, MA). The oxygen absorbers contained 42%, 69% and 71% iron with low concentrations of chloride (less than 0.5%), sulfate (less than 0.004%), and phosphorus (less than 0.03%). Based on these findings, the oxygen absorbers most likely contained metallic iron powder, which would be consistent with the term reduced iron.

Assuming iron-based oxygen absorbers contain a 50% concentration of elemental iron in a bioavailable form, a 5-kg dog would only need to ingest 0.1–0.3 g of the contents to exceed a toxic dose (20–60 mg/kg elemental iron). Likewise, a 15-kg child or dog need only ingest 0.3–0.9 g of contents to exceed the same dose. As the typical sizes of oxygen scavenger sachets range from 2–30 g (net weight), the ingestion of such an amount is easily conceivable.

As evidenced by the patient's clinical signs, serum iron concentrations, radiographic evidence, and exposure history, the dog was diagnosed with iron intoxication secondary to the ingestion of iron-based oxygen absorbers. This case demonstrates that the reduced iron contained in oxygen absorbers, when ingested, can result in iron intoxication. Human and veterinary medical personnel need to be aware

of this effect and monitor serum iron concentrations as chelation may be necessary.

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Conflict of interest None.

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