Malignant hyperthermia-like reaction secondary to ingestion of hops in five dogs

Karen L. Duncan, DVM; William R. Hare, DVM, PhD; William B. Buck, DVM, MS

- Malignant hyperthermia is a life-threatening disorder of skeletal muscles reported in human beings, pigs, dogs, cats, and horses.
- The condition can be triggered by stress or excitement in susceptible pigs and dogs, but the most common triggers of malignant hyperthermia are anesthetic agents.
- Ingestion of hops may trigger a malignant hyperthermia-like episode in susceptible dogs.

A 21-month-old 35-kg castrated male Greyhound (dog 1) and a 5-year-old 36-kg spayed female Greyhound (dog 2), belonging to the same owner, were examined at an emergency clinic because of an acute onset of panting, restlessness, and signs of pain. Dog 1 was the first dog to be affected and appeared to the owner to be tense and in pain. Although bright and alert on admission to the emergency clinic, the dog was anxious and tachypneic. Heart rate was 110 beats/min, rectal temperature was 38.9 C, and capillary refill time was < 1 second. Mucous membranes were bright red. The dog's abdomen was tense, but signs of pain were not evident during palpation. Radiographic evaluation of the abdomen revealed gaseous distention of the proximal part of the small intestine and colon. Results of a CBC were within reference limits. The PCV was 48%, and the total protein concentration was 6.5 mg/dl.

Within 20 minutes after admission to the emergency clinic, the dog's rectal temperature had increased to 40 C, and 10 minutes later, it had increased to 41.1 C. Flatulence developed, and the dog subjectively appeared to be in increasingly more pain. The dog was whimpering intensely and pacing constantly and was unwilling to lie down or be still. The high respiratory rate was unchanged.

Treatment was started with rapid IV infusion of isotonic saline (0.9% NaCl) solution. Butorphanol tartrate (10.5 mg, SC) was administered for pain relief, and diazepam (10 mg, IV) was administered for sedation, but there was not any apparent response. Prednisolone sodium succinate (200 mg) was given IV. Rectal temperature was decreased to 39.4 C with the use of cool water baths.

Permission was granted by the owner for an exploratory laparotomy. Anesthesia was induced with ketamine hydrochloride (200 mg, IV) and diazepam (10 mg, IV) and maintained with isoflurane, but the dog's rectal temperature increased to 42.2 C within 5 minutes. There was no response to cold water baths and IV administration of fluids, and the dog died before euthanasia could be performed. The onset of rigor mortis was evident in < 15 minutes. Because dog 2 had begun to have clinical signs by this time, a rapid necropsy was performed on dog 1. Approximately 600 ml of plant material was found in the stomach of dog 1. The owner identified the plant material as hops.

In the process of making beer that evening, the owner had boiled a 28-g hops plug in approximately 5.5 L of water containing malt extract, roasted barley, dry malt extract, gypsum, and yeast. A 28-g hops plug will expand to an approximate volume of 900 ml of rehydrated plant material. After boiling, the hops were strained from the mixture and discarded onto a compost pile. Both dogs briefly had access to the compost pile prior to bedtime; dog 1 had become clinically affected within 3 hours of exposure and had died within another 3 hours.

Dog 2 began panting rapidly and had signs of abdominal discomfort within 6 hours after exposure to the discarded hops and was admitted to the emergency clinic at that time. Initially, the dog's rectal temperature was 38.8 C, but it increased to 39.4 C within 30 minutes. The dog's heart rate was 190 beats/min, and signs of tenderness were evident during abdominal palpation. Abdominal radiography revealed gaseous distention of the proximal part of the colon. Apomorphine hydrochloride was given to induce emesis, and hops material was identified in the vomitus. Treatment consisted of 1 L of isotonic saline solution infused rapidly, IV, dexamethasone (40 mg, IV), and amoxicillin (400 mg, SC). To facilitate gastric lavage, the dog was sedated with diazepam (10 mg, IV) and ketamine (200 mg, IV) and anesthetized with isoflurane. The stomach was lavaged, and an enema was administered. Approximately 250 ml of hops was recovered in the washings. One hundred twenty milliliters of an activated charcoal slurry was administered via the gastric tube. During the anesthetic procedure, the dog's rectal temperature reached 39.7 C. While recovering from anesthesia, the dog became tachypneic. Suspecting a metabolic acidosis, the attending veterinarian administered 60 mEq of sodium bicarbonate in 1 L of isotonic saline solution to the dog. In addition, sodium penicillin (2,000,000 U, IV) was administered every 6 hours. Within 2.5 hours, the dog appeared to be in less pain and was discharged to the referring veterinarian. Rectal temperature at the time of discharge was 38.9 C. The dog was discharged to its owner's care the same day, and although the dog was lethargic for a couple of days, recovery was otherwise unremarkable.
Blood samples were collected from dog 2 three days after the ingestion of hops and submitted for a CBC and serum biochemical analyses. Results of the CBC were within reference limits for pet Greyhounds. Biochemical abnormalities included mild hypernatremia (155 mEq/L; reference range, 139 to 154 mEq/L), high CO₂ concentration (26 mEq/L; reference range, 17 to 24 mEq/L), and high creatine kinase activity (379 U/L; reference range, 10 to 150 U/L). The serum potassium concentration was normal (4.0 mEq/L; reference range, 3.5 to 5.5 mEq/L), and the high sodium and CO₂ concentrations were within ranges reported for conditioned Greyhounds maintained for research. Two weeks later, the dog's creatine kinase activity was only slightly high (159 U/L).

Since April 1994, the National Animal Poison Control Center (NAPCC) has been consulted on 3 other dogs (a 3-year-old female Greyhound, a 1-year-old spayed female Labrador Retriever, and a 2-year-old female Greyhound) that developed signs of toxicity after ingestion of hops. The length of time before clinical signs were first noticed following ingestion were 3, 2.5, and 8 hours, respectively. Clinical signs in 2 of the 3 dogs included panting and brown-colored urine; the third dog developed seizures and apnea. Rectal temperature in all 3 dogs was ≥41.7 C. Creatine kinase activity was elevated in only 1 Greyhound, and it was found to be high (884 U/L; reference range, 8 to 60 U/L). Serum potassium concentration was analyzed in the same Greyhound and in the Labrador Retriever and was high only in the Labrador Retriever (5.7 mEq/L; reference range, 4.1 to 5.3 mEq/L). All 3 dogs died despite supportive treatment. In the 2 dogs in which time to onset of rigor mortis was reported, the onset was rapid (<10 minutes). None of these 3 dogs was anesthetized; thus, malignant hyperthermia (MH)-like signs could not be attributed to anesthesia.

Hops are the common name for cultivated members of the genus *Humulus*, not to be confused with wild hops (*Bryonia dioica*), a member of the gourd (*Cucurbitaceae*) family. Hops are used to impart the characteristic bitter flavor and pungent aroma to beer. Hops originate from the flowers (or cones) of the plant (*Humulus lupulus*) and are used exclusively for brewing beer. Of particular interest to brewers are the resins and essential oils found in the lupulin glands (tiny yellow specks found on the petals). Hops contain a number of potentially biologically active components (ie, resins, essential oils, phenolic compounds, nitrogenous constituents) that, either singularly or in combination, could be associated with adverse effects in animals. The lupulin glands contain soft and hard resins, of which the soft resins are the most important commercially. The soft resins contain alpha acids that isomerize during boiling and give the bitter flavor to finished beer. The alpha acids are phenolic compounds, including humulone and its analogues. These alpha acids are unstable, and their content in hops decreases with age.

Hops contain 0.5 to 2.5% essential oils. The essential oils include hydrocarbons, oxygenated components, and sulfur-containing components and provide the hops aroma. The hydrocarbon component is primarily monoterpenes (C₉H₁₆) and sesquiterpenes (C₁₅H₂₄). Humulene (α-caryophyllene), myrcene (β-caryophyllene), and farnesene are the 3 primary essential oils in hops. The essential oils are particularly unstable, and most are lost to evaporation after 10 to 15 minutes of boiling. The remaining essential oils are oxidized to humulene epoxides, humulenol, humulol, and humuladienone. The sulfur-containing components of the essential oils in hops include various thiols, sulfides, thiosteres, thiophenes, and episulfides.

Hops contain numerous phenolic compounds (2 to 4%), including coumaric acid, gallic acid, and caffeic acid, collectively referred to as tannins. Approximately 20 different polyphenolic compounds have been identified. The polyphenol xanthohumol is found in freshly harvested hops in concentrations up to 1%. This compound disappears rapidly through oxidation, even in cold storage. Xanthohumol has been shown to have potent estrogenic properties.

Hops contain 2 to 3.5% nitrogenous constituents, of which 0.5% are soluble. The presence of an uncharacterized alkaloid in hops has been confirmed. Other nitrogenous constituents include betaine, adenosine, hypoxanthine, and choline, as well as most of the essential amino acids.

Because many of the biologically active compounds in hops are volatile, they would not be expected to be found in substantial amounts in hops that have been boiled during the brewing process. However, if hops are only steeped at temperatures below boiling, it is possible that some of these compounds could still be present in biologically significant concentrations in discarded plugs of hops. We believe that clinical signs in the 5 dogs in this report were a result of ingestion of hops containing substantial amounts of 1 or more of these constituents.

Causes of hyperthermia in dogs include infections, immune-mediated disorders, neoplasia, administration of drugs that uncouple oxidative phosphorylation, and endocrinopathies. Although hyperthermia in these dogs may have been a result of a component of the ingested hops that acted to uncouple oxidative phosphorylation, we suspect that these dogs had MH because of the 5 were Greyhounds, all of the dogs were hyperthermic and generally unresponsive to routine cooling measures, serum creatine kinase activity was high in the 2 dogs in which it was measured, and serum potassium concentration was high in 1 dog. The dogs had brown-colored urine suggestive of myoglobinuria, and the onset of rigor mortis was rapid in the 3 dogs in which it was recorded.

Malignant hyperthermia is a life-threatening disorder of skeletal muscles reported in human beings, pigs, dogs, cats, and horses. The condition can be triggered by stress or excitement in susceptible pigs and dogs, but the most common triggers of MH are anesthetic agents, including volatile inhalants, amide local anesthetics, and depolarizing skeletal muscle relaxants. Clinical signs of MH can develop within a few minutes to several hours after a triggering event. The most common signs are tachycardia, high end-expired CO₂ partial pressure, hyperthermia, severe metabolic acidosis, and marked increases in serum mag-
nesium, phosphorus, calcium, and potassium concentrations.

A presumptive diagnosis of MH can be made, in part, on the basis of a familial history of hyperthermic episodes triggered by anesthetic agents, and MH should be suspected when dogs of breed known to be predisposed to MH develop typical signs. Definitive diagnosis is based on results of various tests, including the muscle contracture test, determination of RBC fragility, and the halothane-succinylcholine challenge exposure test. The 1 surviving dog in this report was later euthanatized for unrelated reasons and was, therefore, unavailable for confirmatory diagnostic testing.

For any dog with a similar history of exposure to spent hops that has signs of tachypnea and hyperthermia, the NAPCC suggests the following treatment plan. Aggressive decontamination is initiated by inducing emesis with 3% hydrogen peroxide (1 to 2 ml/kg of body weight, up to a maximum of 45 ml) or apomorphine (0.04 mg/kg, IV, or conjunctivally). A gastric lavage, or preferably an enterogastric lavage, should be performed followed by instillation of activated charcoal (1 to 2 g/kg). A cathartic such as magnesium sulfate (Epsom salts, 250 mg/kg) should be added to the activated charcoal slurry, with the final slurry containing approximately 10 times as much water as magnesium sulfate. Fluids should be administered IV to lower the body temperature and to increase urine output and prevent myoglobin-induced renal failure. Additional cooling measures can include placement of ice packs around the large superficial blood vessels of the body and administration of cool water lavages and enemas. Metabolic and respiratory acidosis commonly develops with MH, but was not documented in these dogs. If the presence of serious metabolic acidosis is confirmed in association with the hyperthermia resulting from hops exposure, sodium bicarbonate (1 to 2 mEq/kg, IV) should be administered with the IV fluids. Cardiac arrhythmias should be treated with procainamide, rather than lidocaine, because of lidocaine's association with increased myosplenic calcium concentrations.

Administration of dantrolene sodium was recommended by the NAPCC, but the drug was not available for use in treating the dogs in this report. Although the efficacy of dantrolene in reversing hyperthermia associated with hops ingestion is currently unknown, dantrolene is a hydantoin derivative that is effective in preventing and treating MH associated with other stimuli. On the basis of a review of the literature, the NAPCC recommends dantrolene be given at a dosage of 2 to 3 mg/kg, IV, or 3.5 mg/kg, PO, as soon as possible after hops exposure in dogs with MH-like signs. To prevent recurrence of MH-like signs, repeated dantrolene administration is recommended at a dosage of 100 mg, PO, every 12 hours, for 3 days.

Dipyrone was used as an antipyretic in 3 of these dogs. Dipyrone decreases body temperature by inhibiting release of endogenous pyrogens and, thus, lowers the hypothalamic thermostatic setting. We believe that hyperthermia in these dogs was a result of MH and not release of endogenous pyrogens. Thus, the usefulness of dipyrone administration following ingestion of spent hops is questionable.

The NAPCC strongly encourages use of the erythrocyte osmotic fragility and caffeine muscle contracture tests to confirm MH susceptibility of any dogs that survive a hyperthermic episode associated with hops ingestion. Studies are needed to identify the components of hops that presumably gave rise to the adverse effects in these dogs. Until then, pet owners who are also home brewers should be cautioned to dispose of spent hops in a manner that prevents ingestion by any animals. Potentially hazardous exposure of dogs to hops would seem to be likely only when home brewers use hops plugs, which contain compressed whole leaf hops, and unlikely if they employ the more popular, highly processed hops pellets, which leave little particulate matter to be strained and discarded from the brew.

References


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**Indicators of postoperative pain in cats and correlation with clinical criteria—J. D. Smith, S. W. Allen, J. E. Quandt, et al**

**Objective**—To identify clinical indicators that may help identify postoperative pain in cats after ovariohysterectomy.

**Animals**—Healthy, laboratory animal source cats.

**Procedure**—Clinical indicators of pain were identified, and relief from pain in response to butorphanol was studied in 5 groups of cats. Ten cats had 1 hour of general anesthesia only, followed by recovery without additional medication. Ten cats had general anesthesia and ovariohysterectomy, followed by recovery without additional medication. Ten cats had general anesthesia, ovariohysterectomy, and postoperative administration of 0.1 mg of butorphanol/kg of body weight. Another 10 cats had general anesthesia, ovariohysterectomy, and postoperative administration of 0.3 mg of butorphanol/kg. Ten cats received 0.1 mg of butorphanol/kg, IM, only. Samples and recorded data were obtained before, during, and after the anesthesia period. Clinical variables measured included heart rate, blood pressure, respiratory rate, rectal temperature, PCV, and blood glucose concentration. Results were compared with changes in norepinephrine, epinephrine, and cortisol concentrations.

**Results**—Cats that did not receive analgesics had higher cortisol concentration than did cats without surgery and cats that received butorphanol after surgery. Systolic blood pressure measured by ultrasonic Doppler was found to be predictive of cortisol concentration, using a multiple linear regression model.

**Conclusions**—Cortisol concentration increased in response to surgical stress and pain, and this increase was diminished by use of butorphanol.

**Clinical Relevance**—Systolic blood pressure was the best clinical predictor of postoperative pain. (Am J Vet Res 1996;57:1674–1678)