Treatment of *Pieris* Ingestion in Goats with Intravenous Lipid Emulsion

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Abstract Seven goats and one ram presented with clinical signs including regurgitation, obtundation, anorexia, apparent pain, and bloat. The animals had escaped from their barn, and it was discovered that they had ingested leaves of *Pieris japonica*, Japanese pieris, a grayanotoxin-containing plant. Animals were treated with antibiotics, calcium borogluconate, B vitamins, and activated charcoal within the first 24-h post-exposure, which was followed by the recovery of the ram and two goats and the death of two goats. Approximately 36 h after Japanese pieris ingestion, one of the three remaining anorectic goats was dosed with intravenous lipid emulsion (ILE). This goat recovered within a few hours. The remaining two goats were given ILE the next day and appeared to recover, but one died a week later of aspiration pneumonia.

Keywords Grayanotoxin · Goats · Intravenous lipid emulsion · *Pieris*

Previous Presentation of Data at Meetings or in Abstract Form Portions of this case study were presented at the New York State Veterinary Conference in Ithaca, New York, on October 5, 2013.

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Introduction

The Japanese pieris (*Pieris japonica*) is a common ornamental broad-leaved evergreen shrub in the Northeastern United States. *Pieris* spp., native to Asia and North America, are in the family Ericaceae, the heaths. Like members of some other genera in this family, namely *Rhododendron* spp. and *Kalmia* spp., the Japanese pieris is prized for its showy spring flowers. These genera also contain cardiotoxic grayanotoxins. Grayanotoxin poisoning has been reported in humans and a variety of livestock, including goats [1, 2]. Treatment protocols for grayanotoxin poisoning have been based on the use of detoxification procedures such as oral administration of activated charcoal and saline or sorbitol cathartics and symptomatic and supportive care.

Intravenous lipid emulsion (ILE) therapy is used to treat patients intoxicated with lipid-soluble substances, particularly local anesthetics [3]. ILE therapy has recently been introduced in the treatment of the poisoned veterinary patient [4]. Although the use of ILE is still experimental and controversial because the mechanism of action is not well understood, ILE therapy is becoming more common in veterinary medicine in part because long-term hospitalization and many therapeutic options for the poisoned patient can be cost-prohibitive, whereas ILE is relatively inexpensive and, in some cases, has decreased hospitalization time [5].

This case report involves seven goats that experienced severe clinical signs after ingestion of Japanese pieris. Three goats were eventually treated with ILE, two of which survived.

Case Study

Thirteen yearling or mature goats, five goat kids, and five sheep escaped their barn one evening in August. The escaped

animals were discovered approximately 6 h after they had been observed to be confined. One ram was found bloated, and many adult goats were regurgitating. They were initially treated with B vitamins, milk of magnesia, and flunixin meglumine. The next morning, the ram had recovered but seven goats still had evidence of regurgitation. The most severely affected (goat A1, a 15-month-old Nubian doe) was down, vocalizing, and thrashing; three others (A2, B1, and C1) were unwilling to stand and obtunded, and the remaining three were standing but obtunded. The most affected goat (A1) was given 60 mL of calcium borogluconate subcutaneously followed by intravenous butorphanol for pain management but died a few minutes later. The other six affected goats were treated with 60 mL of 23 % calcium solution subcutaneously, 60 mL activated charcoal paste orally, and penicillin by subcutaneous injection. An investigation of the farm revealed a small Japanese pieris plant with evidence of browsing (Fig. 1).

Postmortem examination of goat A1 was performed within 30 min after death and revealed ecchymoses on the dorsal rumen serosa. The rumen was densely packed with ingesta which included fragments of approximately ten green, leathery leaves similar to those of the pieris. The abomasum contained green froth. Leaves from the rumen were submitted to the California Animal Health and Food Safety Laboratory in Davis, California. Goat B1 died that evening, but no necropsy was performed.

The next day, two of the remaining five goats no longer had clinical signs and were eating enthusiastically. One goat, E1 (a 17-month-old Nubian doe), was standing and somewhat alert but moaning and febrile (temperature 40 °C (104 °F)), and another goat, E2 (a 3-year-old Nubian doe), was standing but obtunded with a temperature of 39.7 °C (103.4 °F). Aspiration pneumonia was suspected based on physical exam and auscultation; these goats were treated with a single injection of tulathromycin subcutaneously, and daily penicillin was continued. The third goat, A2 (a 3-year-old Boer Nubian cross doe), was down, obtunded, and refused feed, but she was able to stand with encouragement. She was also grinding her teeth, consistent with pain. She had adequate rumen motility. This goat was judged to weigh 40 kg and was given an intravenous dose of 60 mL of 20 % lipid solution,¹ slowly over about 5 min through a temporary jugular catheter. Tulathromycin was also administered. Three hours later, goat A2 was no longer showing clinical signs. She was walking and eating. However, goat E1 remained obtunded and E2 began regurgitating again.

The third morning, goat A2 remained asymptomatic, but E1 continued to moan and E2 was still regurgitating. E1 and

Fig. 1 *Pieris japonica* plant from the farm, with evidence of browsing

E2 both had greatly decreased rumen motility. Goats E1 and E2 were given 60 mL of 20 % lipid solution (see footnote 1) intravenously. Additionally, they were dosed with calcium once as well as B vitamins to be repeated 12 h later. Goats E1 and E2 responded to treatment within 12 h and were released onto the pasture with the other goats. They were not behaving differently from the rest of the herd.

Eleven days after exposure to the pieris, goat E1 presented with nasal discharge and decreased appetite. She became progressively more obtunded and in pain and died that day. Postmortem examination revealed pyothorax and necrotizing pneumonia affecting the right cranial lung lobe. Intralesional plant material was noted on histopathology.

Leaves recovered from the rumen of goat A1 were submitted for analysis. The sample was extracted with methylene chloride. An aliquot of the extract was concentrated under nitrogen and reconstituted with 1:1 (v/v) methanol/water. Analysis was performed using a high-performance liquid chromatograph equipped with a reversed phase column coupled to a hybrid triple quadrupole/linear ion trap mass spectrometer. The mass spectrometer utilized an electrospray ion source in negative polarity mode with detection by multiple reaction monitoring of a single precursor ion and two product ions for each analyte. This analysis was positive for grayanotoxins I and III.

Discussion

Pieris, *Kalmia*, and *Rhododendron* contain the diterpenoid grayanotoxins. There are more than 25 known isoforms of grayanotoxin [6]. *Kalmia* is known to contain grayanotoxins I, II, and III, of which III and I are considered the most toxic with mouse LD₅₀ doses of ≤1 mg/kg and slightly >1 mg/kg, respectively [7]. Grayanotoxins are present in all parts of the plant, and the toxic dose of fresh rhododendron foliage for ruminants is reported to be between 0.1 and 0.6 % body weight, though the concentration varies with season, species, and plant [1, 7]. Assuming that pieris has similar toxicity, each of the eight affected animals would have had to ingest ≥40 g

¹ Intralipid® 20 %, distributed by Baxter Healthcare Corporation, Deerfield, IL, USA, is manufactured by Fresenius Kabi AB, Uppsala, Sweden.

foliage, which we estimate to be between 80 and 400 individual leaves, depending on leaf size. However, based on the size of the plant and the severity and duration of clinical signs, we suspect that the leaves on this pieris plant were more potent than rhododendrons in previous reports, though leaves from the original plant were disposed of before analysis could be performed. Leaves recovered from the rumen content had a trace amount of Grayanotoxin I with a reporting limit (RL) at 0.5 ppm, and was positive for Grayanotoxin III above a RL at 0.5 ppm. Poisoning is most common in the winter, when these plants remain green and other forage may not be as readily available [1, 6].

Grayanotoxins bind voltage-gated sodium ion channels in nerve cells and myocytes of the heart and skeletal muscle, preventing inactivation and leaving the cells depolarized [1, 6]. Onset of clinical signs in goats is usually within 6 h [1]. The clinical signs and postmortem lesions in these goats and the ram are similar to those that have been previously described for livestock: anorexia, bloat, obtundation, abdominal pain, regurgitation, and lateral recumbency, with mild gastrointestinal hemorrhage, plant material in the gastrointestinal tract, and secondary aspiration pneumonia [1, 2, 7]. Other reported lesions include necrosis of the renal tubular epithelium and hepatocytes [7]. Treatment includes removing access to the plant, administration of activated charcoal and a sorbitol or saline cathartic in animals that are not vomiting or regurgitating, and symptomatic and supportive care such as analgesics for pain and treatment of bloat and aspiration pneumonia, which are common causes of death in these individuals [1, 2, 7]. No previous reports of ILE therapy for grayanotoxin poisoning were found by the authors.

ILE is most commonly used as therapy in the poisoned patient who has been exposed to a lipophilic substance such as local anesthetics or, in veterinary cases, macrocyclic lactones such as ivermectin and moxidectin in dogs, cats, and horses, and pesticides such as permethrin in cats [3, 5, 8–10]. The mechanism of action of ILE is not known, and several theories have been put forward. The most promising is the lipid sink theory in which plasma lipid acts as a compartment that sequesters the lipophilic compounds. Lipid micelles are eventually taken up and stored in lysosomes in skeletal muscle, myocardium, and abdominal viscera, where they are no longer biologically available [3, 11]. However, plasma lipid post-ILE is not theoretically adequate to create an effective depot for lipophilic compounds [12]. Additionally, response to ILE is more rapid than expected based on rate of diffusion [13]. Another theory for the mechanism of ILE action is the metabolic/mitochondrial effect theory. Fatty acids are the preferred substrate for oxidative metabolism in cardiac myocytes, and ILE increases the availability of free fatty acids [14]. While this theory better explains the rapid action of ILE, it does not explain the efficacy of ILE for compounds with non-cardiac effects [3].

Based on the lipid sink theory, compounds with an octanol/water partition coefficient >1 will partition to the lipid phase of the plasma [8]. The octanol/water partition coefficient for

grayanotoxins was not available to the authors, but grayanotoxin I is soluble in some organic solvents with polar and nonpolar properties such as ethanol and acetic acid and moderately to very slightly soluble in some organic solvents such as hot chloroform, benzene, ether, and petroleum ether [15]. Based on the relative lipid solubility of grayanotoxin I and the lipid sink theory, it was expected that the grayanotoxin would partially partition to the lipid phase of posttreatment lipemic plasma, decreasing the bioavailability of these compounds, thus decreasing clinical signs.

A typical treatment protocol for use of ILE in the veterinary small animal patient is to give 1.5 mL/kg of 20 % lipid emulsion as a slow bolus and then 0.25 to 0.50 mL/kg/min continuous rate infusion (CRI) for 30 to 60 min or until the patient is stable without exceeding a dose of 10 mL/kg over 30 min. Plasma is monitored for lipemia every 2 to 4 h. Dosing can be repeated once or twice if there is no clinical response and the plasma is not lipemic [4, 12]. A similar protocol has been used in a pony [10]. Unfortunately, the goats were not admitted to a clinic; thus, the treatment protocol had to be simplified for use in the field. The goats in this case were dosed with approximately 1.5 mL/kg 20 % lipid emulsion, but the CRI portion of the protocol could not be attempted. Monitoring was also minimized due to circumstances in the field, and blood was not drawn to check for lipemia. Despite these limitations, all three goats recovered within 12 h of ILE administration, though the third goat died 8 days after ILE due to aspiration pneumonia.

Treatment of the poisoned veterinary patient can be complicated, costly, and prolonged, and constraints on time and resources often lead to euthanasia of patients that might eventually have recovered. ILE is a relatively low-cost and rapid-acting treatment for certain lipophilic compounds. However, ILE is not an established therapy, and inappropriate use of ILE can delay the use of proven therapeutic options and lead to adverse effects. The patient's owner should be made aware of the experimental nature of ILE before it is used. Thus far, there are relatively few reports of adverse effects due to ILE. Adverse effects reported in human patients treated using ILE include bronchospasm, elevated serum amylase in the absence of clinical pancreatitis, and transient erythema secondary to extravascular administration [5, 16]. However, <1 % of human patients given lipid emulsions as a part of parenteral nutrition develop fat overload syndrome, which can induce lipemia, fat emboli, hepatomegaly, icterus, hemolysis, increased coagulation times, splenomegaly, thrombocytopenia, leukopenia, and pancreatitis [4, 12]. Thrombophlebitis and pulmonary compromise have also been reported [12, 17], and allergic reactions are possible [4, 5]. Lipid emulsion should not be reused after opening to avoid microbial contamination [9, 12, 18]. Additionally, lipemia secondary to ILE can interfere with laboratory analyses, including glucose analyzers [4, 16]. It is possible that ILE can interfere with lipophilic drugs used therapeutically [5, 9]. Recurrence of clinical signs

after cessation of ILE therapy has also been reported [11]. Many common veterinary drugs are lipophilic and thus could potentially be affected by ILE. No interference with propranolol or methocarbamol has been reported when these drugs were used concurrently with ILE therapy, but an apparent interaction with epinephrine was reported [5, 9, 12]. None of these specific drugs were used on these goats, and no other interactions were noted.

ILE appeared to be an effective therapy in goats that ingested Japanese pieris leaves containing grayanotoxins. Seven goats were initially sickened, two of which died and two of which recovered after administration of activated charcoal and symptomatic care. The remaining three goats continued to show clinical signs, and ILE was administered on day 2 (one goat) and day 3 (two goats). The first goat was noted to respond to ILE within 3 h. The other two responded within 12 h, though one died 8 days later of aspiration pneumonia.

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Conflict of Interest The authors have no conflicts of interest.

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