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Case Report

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Persistent gross lipemia and suspected corneal lipidosis following intravenous lipid therapy in a cat with permethrin toxicosis

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Abstract

Objective – To describe the observation of persistent gross lipemia and suspected corneal lipidosis following intravenous lipid therapy (IVLT) in a cat with permethrin toxicosis.
Case Summary – A 5-year-old, spayed female, domestic short-haired cat with permethrin toxicosis was treated with a high dose of IVLT as an adjunct treatment when it remained severely obtunded following traditional supportive care. The cat received intravenous 20% lipid emulsion as a 1.5 mL/kg bolus given over 10 minutes followed by a constant rate infusion of 0.25 mL/kg/min for 2 hours. The cat developed gross lipemia that persisted at least 48 hours after the single dose of IVLT. Changes consistent with corneal lipidosis were observed and resolved within 1 week after IVLT.
New or Unique Information Provided – This is the first report documenting the complications of persistent gross lipemia and suspected corneal lipidosis in a cat following IVLT. This report underscores the off-label, experimental nature of IVLT as a treatment for intoxication in cats.

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Keywords: corneal opacity, feline, intralipid, pyrethroid, toxicity

Abbreviations

CRI	constant rate infusion
ILE	intravenous lipid emulsion
IVLT	intravenous lipid therapy
PN	parenteral nutrition

Introduction

Permethrin toxicosis is well recognized and documented in cats. Clinical signs can include muscle tremors and fasciculations, dermal hyperesthesia, seizures, hyperthermia, ptyalism, ataxia, mydriasis, blindness, vomiting, and death.[1,2] Recommended treatment is supportive, and includes stabilization, decontamination, supportive care, and treatment with muscle relaxants and tranquilizers such as methocarbamol and benzodiazepines until clinical signs subside.[1,2] For patients with permethrin toxicosis that are refractory to standard therapies, that are life threatening, or in which cost prohibits the necessary hospitalization and supportive care, intravenous lipid therapy (IVLT) has shown promise as an adjunct treatment that may shorten treatment times and improve outcomes.[3–5]

Intravenous lipid emulsion (ILE) is a solution of medium- and long-chain triglycerides traditionally used to deliver essential fatty acids as part of parenteral nutrition (PN).[6] IVLT is the administration of a high-rate infusion of ILE over a short period of time to ameliorate clinical syndromes of drugs or toxins.[3,6] The exact mechanism of action of IVLT is unknown, but it is suspected that IVLT creates a lipid compartment (also known as a "lipid sink") in circulating plasma that sequesters lipophilic drugs or toxins, reducing or shortening their toxic effects.[3,6–9] IVLT may also improve myocardial performance, but such a mechanism would only be relevant for treatment of exposure to drugs that directly affect the heart, such as bupivacaine,[3,6–9] and would not easily explain its apparent success in the treatment of other intoxications.[3,6]

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ILEs are considered relatively safe in both people and companion animals.[3,6] Possible adverse effects of ILEs include hypersensitivity reactions, bacterial infection from contamination of the product, or complications of either hyperlipidemia or fat overload syndrome (eg, pancreatitis, hepatomegaly, icterus, embolism, and hemolysis).[3,6,10] In contrast to PN, IVLT involves the administration of a relatively high dose of ILE over a short period of time. Given the relatively recent application of IVLT for intoxications in veterinary medicine, little is understood about the physiologic consequences of ILE boluses in people and veterinary species. There is only a single study[10] evaluating the LD_{50} (67.72 ± 10.69 mL/kg bolus over 30 minutes) of high volume ILE administration, performed in rats. The American Society for the Prevention of Cruelty to Animals (ASPCA) Animal Poison Control Center (APCC) documented 1 occurrence of hemolysis following ILE administration in a dog.[3] There are no reports of adverse effects of IVLT in the cat, or of ophthalmologic complications of IVLT in any veterinary species. The purpose of this report is to describe persistent gross lipemia and ocular changes following the use of IVLT in a cat with permethrin toxicosis.

Case Summary

A 5-year-old, spayed female, domestic shorthair cat was presented as an emergency for evaluation of seizures. Physical examination revealed mental obtundation, lateral recumbency, and severe, generalized twitching or seizures. The initial rectal temperature was increased at 40.0°C (104°F). Cardiac auscultation was normal, with a heart rate of 180/min and no evidence of a murmur or arrhythmia. Pulses were palpated, and were strong and synchronous. Pulmonary auscultation was clear bilaterally in all fields with a respiratory rate of 60/min. The body weight was 4.4 kg. The gingival mucosa was pink, excessively moist from ptyalism, and capillary refill time was <2 seconds. Small amounts of vomitus were present in the oral cavity. Accurate orthopedic and neurologic evaluations could not be performed because of the presence of severe neuromuscular activity.

Immediately upon presentation, a 22-Ga peripheral intravenous (IV) catheter[a] was placed, through which 2 separate doses of midazolam[b] (0.57 mg/kg per dose) were administered. Minimal improvement in the neuromuscular activity was seen.

The owner described accidental application of a high concentration permethrin-based flea and tick product[c] intended for use on dogs. The product package contained 2.5 mL of solution, with 44% permethrin (250 mg/kg for this cat), 8.8% imidacloprid (50 mg/kg), and 0.44% pyriproxyfen (2.5 mg/kg). The cat developed ptyalism and mild twitching several hours after application. The owner had subsequently bathed the cat in water without soap and did not observe any worsening of signs. The next morning, the owner noted marked progression of signs, and her primary care veterinarian referred the cat to the emergency service at Red Bank Veterinary Hospital of Cherry Hill.

Upon learning that the patient was exposed to a high concentration pyrethrin product, methocarbamol[d] (56.8 mg/kg) was administered IV and was effective at decreasing the cat's muscle fasciculations. Immediately afterwards, the patient was mentally dull but responsive to stimulation. A menace response was inconsistent, palpebral and pupillary light reflexes were normal, and no ocular abnormalities were noted. The patient could sit sternally, but was unable to stand or walk. Spinal reflexes were normal. There was an oily residue noted between the scapulae, but the skin and fur were otherwise grossly normal.

The patient was decontaminated by bathing with tepid water and dishwashing soap,[e] and then dried with towels. Blood samples were obtained for complete blood count,[f] serum biochemistry panel,[g] packed cell volume, and total plasma protein. Results of this blood work revealed eosinopenia (0.04×10^9/L [40/μL]; reference interval $0.17–1.57 \times 10^9$/L [170–1570/μL]), hypokalemia (2.5 mmol/L [2.5 mEq/L]; reference interval 3.5–5.8 mmol/L [3.5–5.8 mEq/L]), and hyperchloremia (130 mmol/L [130 mEq/L]; reference interval 112–129 mmol/L [112–129 mEq/L]). The plasma appeared grossly clear in centrifuged microhematocrit tubes. Urine collection by cystocentesis at presentation was not attempted because the urinary bladder was small.

Intravenous isotonic crystalloid fluids[h] supplemented with 40 mEq/L of potassium chloride[i] were administered at 25 mL/h, and ondansetron[j] (0.2 mg/kg) was given IV. Fifteen minutes after the first administration of methocarbamol, severe muscle fasciculations returned and responded again to a dose of methocarbamol (57 mg/kg, IV). One hour later, severe muscle fasciculations recurred and were treated again with methocarbamol (57 mg/kg, IV). Following the third methocarbamol dose, the patient became mentally dull and minimally responsive. The patient was admitted to the hospital for monitoring and further supportive care. Vital signs (heart rate, pulse quality, mucous membrane color, capillary refill time, and rectal temperature) and continuous electrocardiogram (ECG) were monitored.

Because of the large dose of permethrin applied, the severity and frequency of relapse of clinical signs despite ongoing treatment, and the worsening mental obtundation, IVLT was instituted. A 20% ILE[k] was administered following a previously described protocol.[11] An initial ILE bolus of 1.5 mL/kg was given IV over

10 minutes followed by an IV constant rate infusion (CRI) of 0.25 mL/kg/min for 2 hours. Intravenous fluids were discontinued during administration of the ILE. During this time, the patient's vital signs and ECG remained unchanged.

Upon completion of the ILE infusion, the patient was evaluated hourly by technical staff until improvement was seen. Four hours after completion of the infusion, the patient's clinical condition was markedly improved. The mental status became quiet, alert, and responsive, and the patient began to stretch, paw at her face, and groom. Movements were hypermetric and were accompanied by intermittent mild twitching; however, the patient was normal during periods of rest. No further methocarbamol, midazolam, or ILE were needed for the remainder of hospitalization. Recheck electrolytes 10 hours after presentation and six hours after completion of ILE infusion revealed normalization of the serum potassium (3.6 mmol/L [3.6 mEq/L]; reference interval 3.5–5.8 mmol/L [3.5–5.8 mEq/L]). The plasma appeared grossly lipemic in centrifuged hematocrit tubes. Potassium supplementation in the IV fluids was discontinued and the rate of infusion was lowered to 15 mL/h.

On the second day of hospitalization (18 hours following IVLT), the neurologic examination was improved and revealed quiet and alert mentation, inconsistent menace response, ataxia and mild twitching during ambulation, and normal pupillary light reflexes. Methocarbamol was not continued because clinical signs (ataxia and mild twitching) were only seen during ambulation, not at rest. The eyes appeared grossly normal. The patient could drink water with assistance, but remained hospitalized for monitoring and IV fluid therapy because it was not eating. Plasma electrolyte concentrations were monitored daily while receiving fluid therapy, and remained within reference intervals. The plasma continued to appear lipemic in centrifuged hematocrit tubes. An area of red urine was noted in the patient's cage. A urine sample was collected via natural voiding and was notable for marked hematuria (>50 RBCs/HPF)[l]. No comments were made regarding the color of the supernatant.

On day 3 of hospitalization (42 hours following IVLT), the patient's ophthalmic examination notably changed. A centrally located, symmetrical, panstromal white opacity had formed in both eyes, covering a large surface area of both corneas. An ophthalmoscope[m] slit aperture revealed no aqueous flare through visible portions of the anterior chamber. A fundic examination was not attempted because of the corneal changes. A fluorescein dye stain[n] was performed and was negative for stain uptake bilaterally. No conjunctival hyperemia, blepharospasm, or epiphora were present. Pupillary light reflexes remained normal, and the menace response remained inconsistent. The patient was able to ambulate with mild ataxia and could navigate obstacles and track moving objects. The patient began eating and drinking without assistance. A recheck chemistry profile revealed a mild ALT elevation (156 U/L [156 U/L]; reference interval 12–130 U/L [12–130 U/L]) and mild hypophosphatemia (0.78 mmol/L [2.4 mg/dL]; reference interval 1.0–2.4 mmol/L [3.1–7.5 mg/dL]). The packed cell volume was 40% and the total plasma protein concentration was 64 g/L (6.4 g/dL). Serum cholesterol and triglycerides were not measured. The plasma remained grossly lipemic in centrifuged microhematocrit tubes. Fluid therapy was discontinued and no other supportive therapies were deemed necessary prior to discharge.

The patient was discharged on day 3, with instruction to pursue consultation with a board-certified ophthalmologist, which the owner declined. A follow-up phone call to the owner the day after discharge revealed the patient to be doing well; the owner reported the eyes appeared less cloudy. Examination by the primary care veterinarian a week after discharge revealed the patient to be clinically normal. Specifically, the patient was visual with clear corneas and no obvious ocular problems. As a result, no further diagnostic testing or treatments were recommended.

Discussion

IVLT is a relatively new therapeutic approach in veterinary medicine, and has been reported as successful and safe in at least 5 cases of feline permethrin toxicosis.[4,5] The ASPCA APCC has also reported the use of IVLT to treat intoxications with numerous toxins and drugs, including pyrethrins.[3] IVLT for intoxication is off-label, is considered experimental, and should probably only be used as a last resort treatment in veterinary species because so little is currently known about its mechanism(s) and safety.[3,6] For instance, with respect to pyrethrin toxicosis, it has been recommended that IVLT be reserved for use in patients that are refractory to standard therapies, have life threatening clinical effects, or whose owners cannot afford prolonged standard supportive care.[3–5]

The success of IVLT for treatment of permethrin intoxication is likely attributable to the high lipophilicity of permethrin[12] and the ability of ILEs to sequester lipophilic toxins. Because permethrin toxicosis is not thought to affect the heart, proposed mechanisms of IVLT suggesting improved myocardial function likely do not contribute to its efficacy in these cases. Although little is known about what happens to toxins once sequestered by ILE, it is likely that they are metabolized or eliminated from the body prior to the disappearance of the lipid sink.

The cat in this report suffered previously unreported adverse effects, likely secondary to IVLT. The first adverse effect was gross lipemia that persisted for more than 48 hours. Gross lipemia persisting greater than 3 days is a known complication of PN in small animals.[13] In contrast, available literature[3,6,10] regarding IVLT acknowledges the potential for transient gross lipemia, but not persistent lipemia, as an expected consequence of IVLT. This difference may be explained by the slow, continuous administration of PN versus the rapid, brief administration of IVLT.

One study in rats[10] documented the kinetics of triglyceride concentrations following moderate to high volume, high rate ILE administration. At dosages ranging from 20 to 60 mL/kg administered IV over 30 minutes, triglyceride concentrations were markedly elevated from baseline immediately after administration and had returned to normal when next measured 48 hours later.[10] Although other clinicopathologic parameters and histologic measurements were evaluated in the rats, no ocular pathologies were reported.[10] At this time, it is unknown how long it takes cats to clear gross lipemia or hypertriglyceridemia following IVLT or how much interindividual variability exists. As a result, it is unknown if the phenomenon observed in this patient was an isolated occurrence, or if IVLT has the potential to result in persistent lipemia in a large percentage of cats. It is also unknown if animals suffering from various toxicoses metabolize the large dose of ILE similarly or differently than healthy animals.

One author[3] reports continuing IVLT for up to three doses if toxicosis persists, as long as gross lipemia has cleared prior to subsequent administrations. Gross lipemia can be seen in centrifuged microhematocrit or serum separator tubes. Case reports have documented repeated dosing of IVLT in cats with no apparent adverse clinical consequences.[4,5] In these reports, Haworth et al[4] documented clearance of lipemia prior to repeat dosing whereas Kuo et al[5] did not report assessment of lipemia. Among these 5 cases, no adverse effects resulting from IVLT were noted.

Prior to intoxication, the cat in this report was apparently healthy with no prior disease history to suggest an abnormality in lipid metabolism. Although the initial serum chemistry did not measure triglycerides, the plasma was grossly clear. Additionally, the cat had no evidence to support a disease process (eg, idiopathic hypertriglyceridemia, hyperchylomicronemia, diabetes mellitus, or hepatic lipidosis[14]) to explain persistent gross lipemia. Given all available data and timing, the persistent lipemia was most likely a consequence of the IVLT. It is unclear if persistent lipemia occurs commonly in cats, or if it was a phenomenon isolated to this patient.

A second unique feature of this case was the occurrence of ocular changes, suspected to be corneal lipidosis. Gross lipemia was documented immediately following IVLT and persisted beyond the time of discharge. No ocular changes were noted during the 2nd day of hospitalization. On the 3rd day of hospitalization (42 hours after IVLT), the corneas developed a symmetrical, panstromal white opacity. Although uncommon, ocular complications secondary to hyperlipidemia are well established in veterinary species and include corneal lipidosis, lipemia retinalis, and lipemia aqueous.[15,16]

Gross inspection revealed that the change in transparency and color was present in the corneas. Corneal lipidosis is a nonspecific, bilateral lipid deposition in the cornea unassociated with signs of ocular inflammation, and best described the pattern seen in this cat.[15] Triglycerides create a diffuse change in corneal opacity, in contrast to the crystalline appearance associated with corneal cholesterol deposits.[15] Although lipemia aqueous is theoretically possible, uveitis is a prerequisite for lipid entry into the anterior chamber,[15,16] and this patient had no clinical signs of uveitis and no aqueous flare on examination. In this patient, the corneal opacity precluded fundic examination, so evaluation for concurrent lipemia retinalis was not possible.

The complications seen in this cat underscore the need for identification of safe maximum doses and administration rates for ILE in veterinary species. In people, Weinberg[17] has proposed a dosage for local anesthetic toxicosis consisting of a rapid ILE bolus of 1.5 mL/kg followed by a CRI of 0.25–0.5 mL/kg/min for 10 minutes, with an empirical upper limit of 10 mL/kg within the first 30 minutes. Current small animal dosing recommendations are similar (1.5 mL/kg bolus followed by a CRI of 0.25 mL/kg/min for 30–60 minutes[6] or 60–120 minutes[11]). The CRI can be repeated 1–2 more times as needed if the serum is free of gross lipemia. Although a recent LD_{50} study in rats[10] did not observe fatal consequences from ILE doses under 60 mL/kg, more studies are needed to determine safe dosing practices in veterinary species.

The ILE dose used in this cat was the maximum recommended amount described in 1 primary veterinary resource,[11] and exceeds the current initial dose recommended for use in people.[17] The dose also exceeds those used in other reports of feline pyrethrin toxicosis.[4,5] Dosages of ILE used for PN are similar to that of low-dose IVLT (2 g/kg/day = 10 mL/kg/day of a 20% ILE[6]). The main difference is the rate of administration; PN is given continuously over a 24-hour period, whereas IVLT is given over a much shorter period of time. If IVLT is repeated or the CRI continued beyond 30 minutes, the total ILE dose can exceed those used for PN. The duration of the ILE CRI (120 minutes) and hence the total amount

of ILE administered to this cat (31.5 mL/kg) may have contributed to the persistent gross lipemia and ophthalmologic changes reported here.

This report has limitations. The cat was not examined by a board-certified veterinary ophthalmologist, and no photographs were taken to document the ophthalmic changes for ophthalmologist review. A second limitation is that further diagnostic tests were not performed to eliminate other systemic or transient disease that may have contributed to a problem with lipoprotein metabolism. Although a definitive relationship between IVLT and the corneal changes cannot be established in this case, it is unlikely the ocular changes would have occurred otherwise, because IVLT by its very nature causes hypertriglyceridemia.

This case report provides evidence that adverse effects such as persistent gross lipemia and ocular changes suspicious for corneal lipidosis can occur in cats following treatment with a high rate of a large dose of ILE for treatment of lipophilic toxicosis. To the authors' knowledge, this is the first reported ocular complication associated with IVLT. Further research is needed to determine minimum effective and maximum safe doses of rapid ILE administration in small animals.

Footnotes

[a] Terumo Surflo IV Catheter, 22G × 1 inch, Terumo Corporation, Somerset, NJ.
[b] Midazolam Injection (5 mg/mL), Hospira the (5mg/ml) should follow the word injection, Inc., Lake Forest, IL.
[c] K9 Advantix II (for large dogs), Bayer Animal Health, Shawnee Mission, KS.
[d] Robaxin Injectable (100 mg/mL), Baxter Healthcare Corporation, Deerfield, IL.
[e] Dawn, Liquid Detergent, Procter and Gamble, Cincinnati, OH.
[f] Idexx Procyte DX, Idexx Laboratories, Wesbrook, ME.
[g] Idexx Catalyst Dx, Idexx Laboratories, Westbrook, ME.
[h] Lactated Ringer's Solution, Hospira, Inc.
[i] Potassium Chloride (20 mEq/10mL), Hospira, Inc.
[j] Ondansetron (2 mg/mL), Wockhardt, Mumbai, India.
[k] Intralipid (20%), Baxter Healthcare Corporation, Deerfield, IL.
[l] Antech Diagnostics. Pottstown, PA Regional Laboratory. Irvine, CA.
[m] Welch Allyn 3.5V Coaxial-Plus Ophthalmoscope, Welch Allyn, Skaneateles Falls, NY.
[n] Ful-Glo® (Fluoreceine Sodium Ophthalmic Strips, USP), Akorn, Inc., Lake Forrest, IL.

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