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Hypersensitivity reaction associated with subcutaneous glargine insulin therapy in a cat

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Abstract

Case summary A 14-year-old, domestic shorthair cat was treated for transient diabetes mellitus for 3 months with glargine insulin, which was discontinued when the diabetes mellitus resolved. Approximately 36 months later the diabetes mellitus recurred and glargine insulin was restarted. Within 2–3 mins of the first injection the cat collapsed, developed profuse vomiting and diarrhea, as well as facial swelling and diffuse erythema. A hypersensitivity reaction was suspected and the cat was treated with antihistamines, aggressive fluid therapy and gastrointestinal support. The cat made a full recovery and was discharged 3 days later. Six months later the cat re-presented for relapse of its diabetes mellitus and an intradermal skin challenge with 1:20 diluted insulin was performed confirming a hypersensitivity to glargine. The cat continues to be well regulated on porcine zinc insulin without any hypersensitivity reactions noted.

Relevance and novel information Hypersensitivity reactions to insulin administration are rarely described in human medicine. This is the first reported case of a hypersensitivity reaction secondary to glargine insulin in a cat. Clinicians should be aware of this potential complication, particularly in animals with a previous history of insulin administration and the potential to utilize intradermal testing with insulin.

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Introduction

Hypersensitivity reactions (HRs) most commonly occur after an allergen binds to IgE on the surface of mast cells and basophils precipitating release of vasoactive substances such as histamine, chymase, tryptase and other chemokines.[1–3] It is usually associated with prior exposure to the antigen causing sensitization of the immune system.[1–3] Clinical manifestations can range from facial pruritis and urticaria, to cardiovascular collapse and death.[2,3] Previous reports of suspected HRs to pharmaceuticals in veterinary medicine include dexamethasone,[4] ophthalmic medication[5] and human albumin[6] among others.[7,8]

HRs to insulin have been rarely reported in human medicine.[9–11,12] To our knowledge, an HR to insulin has not been previously reported in the veterinary literature. The purpose of this case report is to describe the clinical manifestation and management of a cat with an HR to subcutaneous glargine insulin (GI) administration.

Case description

A 14-year-old, female, spayed, domestic shorthair cat weighing 5.68 kg presented on referral to our hospital for evaluation of acute collapse. The cat had a history of diabetes mellitus (DM), which was first treated with GI in 2013. The cat was treated for diabetes, which became transient after 3 months of treatment. One week prior to presentation at our institution, the DM had recurred and re-initiation of GI was recommended. The owners had purchased a new bottle of GI from a local pharmacy. The

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bottle had not been opened prior to use and it was stored in a refrigerator. The evening of presentation the cat had ingested all of its meal (which had not been changed in over a year), according to the owner, and received 1 unit of GI subcutaneously for the first time since 2013. Approximately 2–3 mins after administration, the cat collapsed and started panting. The cat also demonstrated projectile vomiting and diarrhea. On presentation to the primary veterinarian, the cat was noted to be laterally recumbent and was exhibiting horizontal nystagmus. A blood glucose (BG) was not obtained, but the cat was given dextrose submucosally as there were concerns about a hypoglycemic crisis. The cat was then referred to our facility.

On presentation to our institution, the cat was noted to be obtunded, was tachycardic (heart rate of 220 beats per minute) and tachypneic (respiration of 50 breaths per minute). Rectal temperature was normal (101.2ºF). The respiratory effort was increased and infrequent stridor noted. The face and muzzle were swollen and edematous. The cat again produced a large amount of vomiting and diarrhea; at this time hematochezia was also noted. Though mentation was dull, the nystagmus had resolved and no cranial nerve deficits were noted.

BG was measured on presentation with a handheld glucometer (AlphaTrak; Abbott Animal Health) and was noted to be 517 mg/dl (reference interval [RI] 75–116 mg/dl); this was approximately 2 h after the GI had been administered. The cat had no measurable systolic blood pressure on Doppler measurement (Parks Doppler Machine) and a 10 ml/kg bolus of crystalloids was administered. Systolic blood pressure measured after the crystalloid bolus was noted to be 120 mmHg. Owing to the concerns about an HR to the insulin, diphenhydramine (2 mg/kg) was administered intramuscularly. Within an hour, the muzzle swelling and erythema had improved after antihistamine administration. The cat continued to experience recurrent systemic hypotension in the subsequent hours and after receiving a 3 ml/kg synthetic colloid bolus, was started on a continuous crystalloid (75 ml/kg/day) and colloid infusion (8 ml/kg/day) and the systemic hypotension resolved. Blood work performed on admission revealed hyperglycemia (666 mg/dl; RI 75–116 mg/dl), hypokalemia (3.36 mEq/l; RI 3.62–4.60 mmol/l) and hyperlactatemia (5.4 mmol/l; RI 0.7–2.8 mmol/l). The serum was evaluated for ketones at presentation and none were noted. A complete blood count was also performed and was unremarkable.

Treatment for her gastrointestinal signs consisted of maropitant (1 mg/kg SC q24h), dolestron (0.6 mg/kg IV q24h) and ampicillin (20 mg/kg IV q8h).The cat continued to experience a large volume of diarrhea and hematochezia over the first 24 h after admission, but the vomiting resolved.

An abdominal ultrasound was performed 1 day after presentation and revealed an enlarged and hyperechoic liver with few small hypoechoic nodules throughout the parenchyma, assessed as consistent with a diabetic hepatopathy. The gallbladder was within normal limits. Both kidneys had a mild decrease in corticomedullary definition, and the left and right adrenal glands were noted to have normal shape and size. No other abnormalities were noted. Blood work was also repeated at this time and showed normalization of the lactate and potassium levels. During hospitalization, the BG continued to be monitored and ranged from 107–355 mg/dl; the cat's appetite remained poor. No insulin was administered while hospitalized, owing to the poor appetite, persistent diarrhea and the concerns about an HR to GI. Serum ketones were monitored daily and continued to be negative. The cat was discharged 3 days after presentation on metronidazole (10 mg/kg PO q12h) and famotidine (1 mg/kg PO q24h). The owners continued to monitor the cat's BG at home with a handheld glucometer and it ranged between 88 and 380 mg/dl. The owners tended to measure the BG if they felt the cat appeared lethargic; they did not have a set protocol of when and how frequently to measure its BG. At this time the cat was still not consuming its full caloric needs and we recommended that the owners continue to monitor the cat's BG at home to determine when it would require insulin again. The owners infrequently measured the cat's BG 1–2 times weekly and it was never greater than 200 mg/dl.

Six months later, the cat re-presented for recurrence of polyuria/polydipsia and being lethargic at home. The owners were continuing to measure the cat's BG at this time and were intermittently obtaining values greater than 250 mg/dl. Fructosamine was found to be elevated (400 µmol/l; RI 142–450 µmol/l), and the cat was also exhibiting intermittent glucosuria. The cat was sedated with ketamine (0.5 mg/kg IV) and valium (0.3 mg/kg IV), and the fur over the lateral left thorax was clipped. One unit of GI and porcine zinc insulin (PZI) were each diluted into 20 units/0.2 ml of 0.9% NaCl and from each of these mixtures, 0.05 ml/5 units was injected intradermally. As a negative control, 0.05 ml/5 units of 0.9% NaCl was also injected. All intradermal injection sites were approximately 2 cm apart. Within 30 mins of the procedure, a palpable swelling was noted over the GI site. The cat also developed erythema and swelling of its muzzle (Figure 1) and vomited; diphenhydramine (2 mg/kg IM) was administered and the clinical signs resolved. Two hours after the procedure, the cat's BG was 410 mg/dl (RI 90–180 mg/dl) and it was elected to administer 0.5 units PZI subcutaneously, owing to the hyperglycemia. The cat tolerated the injection of PZI well and no adverse effects were noted. The cat was kept overnight for monitoring and was noted to be painful

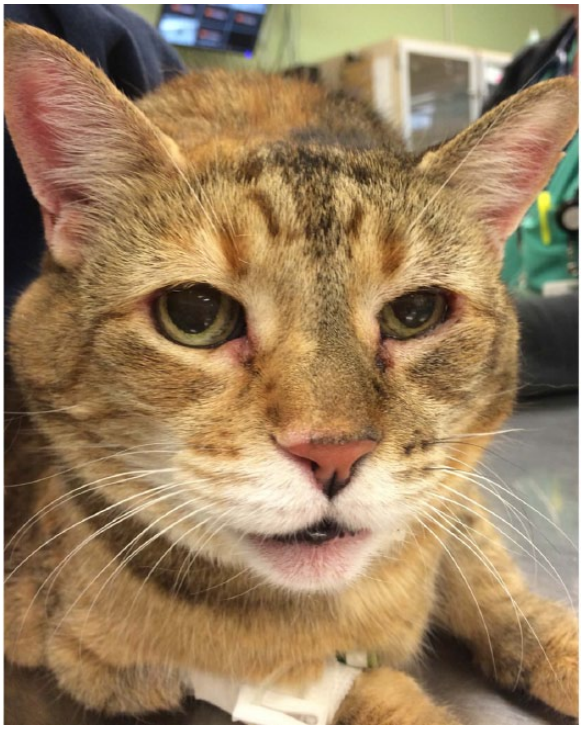

Figure 1 Evidence of cutaneous anaphylaxis after the administration of glargine insulin; note the generalized erythema and swelling over the muzzle and periocular regions

and intermittently pruritic over the injection site. The cat was discharged the following day and continues to be on subcutaneous PZI every 12 h and has not exhibited any recurrent signs of systemic or cutaneous HR.

Discussion

Three types of HRs to insulin have been described in human medicine.[11,12,13,14] Type I HRs, as previously noted, can vary in severity from urticaria to anaphylaxis. This can occur as a biphasic reaction, with immediate itching and burning at the injection site, followed by a more sustained generalized reaction 4–8 h later with a combination of cutaneous, gastrointestinal and/or respiratory symptoms reported.[10,13] Less commonly, type III HRs are mediated by IgG, causing insulin–antibody complex formation, resulting in complement fixation and activation. This presents as small, localized tenderness and painful non-erythematous nodules and central hematomas at injection sites, occurring around 6–8 h after insulin injection and lasting for 48 h.[10,13] Clinical examples of type III HRs include serum sickness, adenopathy and insulin resistance.[12] Finally, type IV HRs correspond to T lymphocyte-mediated delayed hypersensitivity. The cutaneous nodules associated with a type IV HR can be distinguished from a type III HR as the former usually occurs 24 h or more after the insulin injection and last for 4–7 days.[10,13] In humans, type IV HRs are usually associated with a reaction to the retarding agents in commercial insulin preparations.[15] It appears, given the acute presentation and history of prior exposure to insulin, the cat in this case demonstrated a type I HR, but this was not conclusively proven. Severe anaphylactic reactions in cats can cause a multitude of signs, but dyspnea is most common as the lungs are believed to be the shock organ of cats.[16] In the case presented here, the cat exhibited both respiratory and gastrointestinal signs. Previous case reports of anaphylactic reactions in cats have also shown that some will also exhibit simultaneous gastrointestinal and respiratory signs.[5] While a gastrointestinal infection or toxin cannot be fully ruled out, the cat's diet was strictly controlled by its owners, owing to its DM, and an infection also seemed less likely as it was kept indoors only and there were no other pets in the house. Also, the association of the signs with the administration of the GI is also indicative of an HR.

Confirmation of a cutaneous HR to insulin administration is performed by intradermal testing using a 1:20 dilution of insulin preparation.[13] Appearance of a cutaneous lesion within 60 mins of injection indicates a type I HR, as exhibited by the cat in this case, whereas a type III or IV HR would be suggested by a response seen between 2 and 24 h.[12,13] Human protocols were used as intradermal testing with insulin had never been performed in a cat prior to this. There was subjectively more swelling and discomfort noted at the GI injection site; the GI site also appeared more erythematous. The increased swelling and erythema over the GI site also provides more evidence that the cat was more sensitive to the GI than the PZI. The cat in this case exhibited more severe cutaneous and gastrointestinal signs than the typical human patients who undergo intradermal testing. Should this protocol be utilized in the future in small animal patients, the insulin may need to be further diluted to reduce the severity of adverse effects. Other diagnostic modalities for HRs reported in dogs include identification of an elevated alanine transaminase and increased gallbladder wall thickness and a striated wall pattern on abdominal ultrasound.[17] It is unknown if such abnormalities are identified in cases of feline insulin HR; the abdominal ultrasound performed in the cat reported here failed to identify any gall bladder abnormalities.

Management of insulin HR involves exclusion of poor injection technique, use of alternative forms of insulin, splitting the dose and injection into separate sites, and addition of antihistamines.[13,15] If these methods fail, a local injection of dexamethasone in combination with insulin is sometimes used.[18] Steroid therapy was not pursued in this cat as we were concerned it

would further complicate the management of the DM. Similarly, we also did not attempt to divide the dose or inject it in separate sites as the cat had exhibited such severe clincial signs of hypersensitivity initially. Poor injection technique or improper storage of insulin was not considered likely as the owners had successfully managed the cat's DM for 3 years. Desensitization, using gradually increasing dilutions of insulin intradermally in a controlled setting, can be successful in type I HR, but can require long periods of time to be beneficial.[19] Desensitization in people appears to be less successful in patients with the biphasic type I HR.[18] Use of newer insulins such as aspart or GI has also been recommended,[11,12,14,15] but HRs to these insulins have also been recently recognized in human medicine.[20,21] In the cat reported here, management of the HR included diphenhydramine and fluid therapy. Corticosteroids and epinephrine have been recommended for HRs in veterinary patients but were considered potentially contraindicated given the preexisting DM, severe hyperglycemia and potential to cause ketosis.[16] The cat appears to be well managed on PZI without any reported signs of an HR.

Insulin HRs were much more common in human patients prior to the use of human insulin analogues when bovine and porcine insulin were more commonly administered. It is believed that humans that have an HR to insulin are reacting to the type of protein in the insulin given that there are molecular differences between insulin from different species.[22,23] We elected to use PZI, a protamine-containing recombinant human insulin, in this cat rather than GI, a recombinant human insulin analogue, as this contains a different form of protein. Both GI and PZI also contain different adjuvants, with PZI mostly containing zinc and GI mainly containing metacresol. As such, it is unclear if the HR developed secondary to the adjuvants rather than the different insulin protein molecules. In human medicine it is much more common to react to the insulin molecule rather than the adjuvants. Furthermore, while we cannot completely rule out improper storage or poor administration, the bottle of GI was newly purchased, stored in a refrigerator and had never been used prior to the suspect HR event. The owners had also successfully managed the cat's DM for 3 years and were well versed in subcutaneous administration of insulin, so poor technique does not seem likely. We cannot rule out that cats do not naturally develop pruritis and erythema from intradermal GI injections and further studies should evaluate intradermal GI injections in healthy cats.

Conclusions

Clinicians should be aware of the possibility of HRs to insulin administration in cats, particularly in cats with a previous history of insulin administration. The incidence of HRs to insulin and use of intradermal insulin testing for confirmation in veterinary medicine requires further evaluation.

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References

1 Bochner BS and Lichtenstein LM. **Anaphylaxis**. *N Eng J Med* 1991; 324: 1785–1790.
2 Muelleman RL and Tran TP. **Allergy, hypersensitivity and anaphylaxis**. In: Marx JA, Hockberger RS, Walls RM, et al (eds). Rosen's emergency medicine – concepts and clinical practice. 5th ed. St Louis, MO: Mosby, 2002, pp 1619–1624.
3 Lieberman P. **Anaphylaxis and anaphylactoid reactions**. In: Middleton E, Ellis EF, Yunginger JW, et al (eds). Allergy principles and practice. 5th ed. St Louis, MO: Mosby; 1998, pp 1079–1092.
4 Schaer M, Ginn PE and Hanel RM. **A case of fatal anaphylaxis in a dog associated with a dexamethasone suppression test**. *J Vet Emerg Crit Care* 2005; 15: 213–216.
5 Plunkett SJ. **Anaphylaxis to ophthalmic medication in a cat**. *J Vet Emerg Crit Care* 2000; 10: 169–171.
6 Trow AV, Rozanski EA, deLaforcade AM, et al. **Evaluation of use of human albumin in critically ill dogs: 73 cases (2003–2006)**. *J Am Vet Med Assoc* 2008; 233: 607–612.
7 Jasani S, Boag AK and Smith KC. **Systemic vasculitis with severe cutaneous manifestation as a suspected idiosyncratic hypersensitivity reaction to fenbendazole in a cat**. *J Vet Intern Med* 2008; 22: 666–670.
8 Elliott J. **Hypersensitivity reaction during epirubicin infusion in a cat**. *J Small Anim Pract* 2015; 56: 356.
9 Schernthaner G. **Immunogenicity and allergenic potential of animal and human insulins**. *Diabetes Care* 1993; 16 Suppl 3: 155–165.
10 Radermecker RP and Scheen AJ. **Allergy reactions to insulin: effects of continuous subcutaneous insulin infusion and insulin analogues**. *Diabetes Metab Res Rev* 2007; 23: 348–355.
11 Richardson T and Kerr D. **Skin-related complications of insulin therapy: epidemiology and emerging management**. *Am J Clin Dermatol* 2003; 4: 661–667.
12 deShazo RD, Boehm TM, Kumar D, et al. **Dermal hypersensitivity reactions to insulin: correlations of three patterns to their histopathology**. *J Allergy Clin Immunol* 1982; 69: 229–237.
13 Bodtger U and Wittrup M. **A rational clinical approach to suspected insulin allergy: status after five years and 22 cases**. *Diabet Med* 2005; 22: 102–106.
14 Rosenwasser LJ. **Immunologic reactivity to insulin: animal models and clinical syndromes**. *Clin Immunol Rev* 1981–1982; 1: 311–335.
15 Moyes V, Driver R, Croom A, et al. **Insulin allergy in a patient with type 2 diabetes successfully treated with continuous subcutaneous insulin infusion**. *Diabet Med* 2006; 23: 204–206.

16 Loeb JA, Herold KC, Barton KP, et al. **Systematic approach to diagnosis and management of biphasic insulin allergy with local anti-inflammatory agents**. *Diabetes Care* 1989; 12: 421–423.
17 Thompson DM and Ronco JJ. **Prolonged densensitisation required for treatment of generalized allergy to human insulin**. *Diabetes Care* 1993; 16: 957–958.
18 JiXiong X, Jianying L, Yulan C, et al. **The human insulin analog aspart can induce insulin allergy**. *Diabetes Care* 2004; 27: 2084–2085.
19 Durand-Gonzalez KN, Guillausseau N, Pecquet C, et al. **Glargine insulin is not an alternative in insulin allergy**. *Diabetes Care* 2003; 26: 2216.
20 Quantz JE, Miles MS, Reed AL, et al. **Elevation of alanine transaminase and gall bladder wall abnormalities as biomarkers of anaphylaxis in canine hypersensitivity patients**. *J Vet Emerg Crit Care* 2009; 19: 536–544.
21 Shmuel DL and Cortes Y. **Anaphylaxis in dogs and cats**. *J Vet Emerg Crit Care* 2013; 23: 377–394.
22 Kumar D. **Insulin allergy: difference in the binding of porcine, bovine and human insulins with anti-inulin IgE**. *Diabetes Care* 1983; 4: 104–107.
23 Heinzerling L, Raile K, Rochlitz H, et al. **Insulin allergy: clinical manifestations and management strategies**. *Allergy* 2008; 63: 148–155.