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**DOCLINE: Journal Copy**

Title: Journal of the American Veterinary Medical Association  
Title Abbrev: J Am Vet Med Assoc  
Citation: 1986 Jun 15;188(12):1426-31  
Article: Rebound hyperglycemia following overdosing of insu  
Author: McMillan FD;Feldman EC  
NLM Unique ID: 7503067 Verify: PubMed  
PubMed UI: 3528096  
ISSN: 0003-1488 (Print) 1943-569X (Electronic)  
Fill from: **Any format**  
Publisher: American Veterinary Medical Association, Schaumburg, Ill. :  
Copyright: Copyright Compliance Guidelines  
Authorization: hh  
Need By: N/A  
Maximum Cost: **Free**  
Patron Name: Poling LD, Melanie  
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Comments: **TaBaMLN, ESEA, SEND, FreeShare - PDF E-mail preferred! FAX accepted. Thank You!**  
Routing Reason: Routed to FLUPTJ in Serial Routing - cell 1  
Received: Aug 24, 2012 ( 09:21 AM ET )  
Lender: St Petersburg College/ Pinellas Park/ FL USA (FLUPTJ)

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# Rebound hyperglycemia following overdosing of insulin in cats with diabetes mellitus

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## SUMMARY

Posthypoglycemic hyperglycemia (rebound hyperglycemia) after overdosing of insulin was diagnosed in 6 cats with diabetes mellitus. Administration of excessive insulin induced hypoglycemia within 4 to 8 hours, followed by rebound hyperglycemia. Diagnosis was made by serial blood glucose determinations during a 20- to 24-hour period after insulin administration. Four cats had a history of difficulty in regulating the diabetic state. In 2 cats, rebound hyperglycemia was diagnosed on routine serial blood glucose determinations. All of the cats were hyperglycemic for most of the day. Rebound hyperglycemia was observed with both intermediate (neutral protamine hagedorn) and long-acting (protamine zinc iletin) insulins, and the range of insulin doses at which the disorder developed overlapped previously determined therapeutic doses for these insulins in the cat. Urine glucose and single afternoon blood glucose determinations were inadequate and potentially misleading in monitoring diabetic cats receiving excessive amounts of insulin.

ACUTE HYPOGLYCEMIA, which may develop as a result of overdosing of insulin, is corrected rapidly by several physiologic mechanisms. Glucagon, epinephrine, and the direct hepatic effects of hypoglycemia are believed to be the important immediate mechanisms responsible for rapid increase in glucose production, which often prevents the manifestation of clinical signs associated with hypoglycemia.<sup>1-3</sup> In the normal animal, the hyperglycemic response to hypo-

glycemia is limited and controlled by additional pancreatic release of insulin, maintaining blood glucose homeostasis.<sup>4</sup> Because the insulin-dependent diabetic animal lacks the ability to limit the rising blood glucose concentration, hyperglycemia results.

The administration of an insulin overdose, causing clinical or subclinical hypoglycemia that is followed by rebound hyperglycemia has been a recognized syndrome in human medicine for many years,<sup>5-7</sup> and recently has been described in the dog.<sup>8</sup> Human diabetic patients receiving excessive insulin are characterized by deterioration of diabetic regulation, with infrequent clinical hypoglycemia, but with frequent glycosuria, polyuria, and polydipsia.<sup>9</sup> Diabetic dogs that are receiving excessive insulin appear to be poorly regulated, with polyuria, polydipsia, glycosuria, polyphagia, lethargy, and rarely, seizures.<sup>8</sup> Hypoglycemia caused by insulin overdosage has been reported in cats<sup>10</sup>; however, diagnosis was based on clinical signs and blood glucose concentrations were not measured.

The objectives of this report were to document the rebound hyperglycemic response in diabetic cats that had received excessive insulin, and to document the necessity of serial blood glucose determinations for assessing the status of poorly controlled diabetic patients.

## Materials and Methods

Six cats with diabetes mellitus were included in this study on the basis of documented hypoglycemia (glucose <70 mg/dl) after insulin administration. Four cats were examined because of a history of difficulty in regulating their diabetic condition; 2 cats (cats No. 4 and 6) conditions were diagnosed on routine serial blood glucose determinations. Of the 4 cats in which there was difficulty in regulating their diabetes, owner complaints included persistent polydipsia/polyuria (4), persistent glycosuria (1), polyphagia (1), weight loss (1), weakness (1), and seizures (1). A standardized feeding protocol was not used during hospitalization, though most cats were fed canned food twice daily. Insulin was administered SC at 8 AM unless otherwise specified. Insulin was diluted with insulin diluent.<sup>\*</sup> Blood glucose concentrations were determined every 1 to 6 hours during a 24-hour period (20 hours in cat 4). Blood glucose

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\*Insulin diluent, Eli Lilly & Co, Indianapolis, Ind.

concentration was measured by the glucose-oxidase method.

### Case Histories

**Case 1**—A 13-year-old, 5.5-kg, castrated male Domestic Shorthair cat had been treated for diabetes mellitus for 1.5 months. Initially, treatment had consisted of 4 U (0.7 U/kg of body weight) U-40 neutral protamine hagedorn (NPH) insulin<sup>b</sup> administered SC at 8 AM. The dose had been increased slowly to 12 U (2.2 U/kg) after repeated findings of hyperglycemia on periodic single afternoon blood glucose determinations. The cat had polydipsia, polyuria, polyphagia, and weight loss.

Routine diagnostic laboratory evaluation revealed changes frequently observed in cats with diabetes mellitus.<sup>10-12</sup> Serial blood glucose determinations revealed low blood glucose concentration (55 mg/dl) 4 hours after insulin administration (Fig 1). Severe hyperglycemia was detected 10 hours after insulin administration.

The dose of insulin was changed to 3 U of U-100 protamine zinc iletin (PZI) insulin<sup>c</sup> (diluted to 10 U of insulin/ml; 0.56 U/kg SC SID) at 8 AM. The cat was fed 2 equal-sized meals, one at 8 AM and one at 6 PM. Polydipsia, polyuria, and polyphagia dissipated. Serial blood glucose concentrations were obtained after administration of the PZI insulin (Fig 1). The previously observed problem of wide fluctuations in the blood glucose concentration had resolved. The cat continued to do well 18 months after referral.

**Case 2**—An 8-year-old, 2.3-kg, spayed female Domestic Shorthair cat had been treated for diabetes mellitus for 9 months. The initial dose of insulin was 1 U (0.3 U/kg; the cat weighed 3.4 kg at the time of

<sup>b</sup>NPH Iletin, Eli Lilly & Co, Indianapolis, Ind.

<sup>c</sup>Protamine, Zinc, and Iletin, Eli Lilly & Co, Indianapolis, Ind.

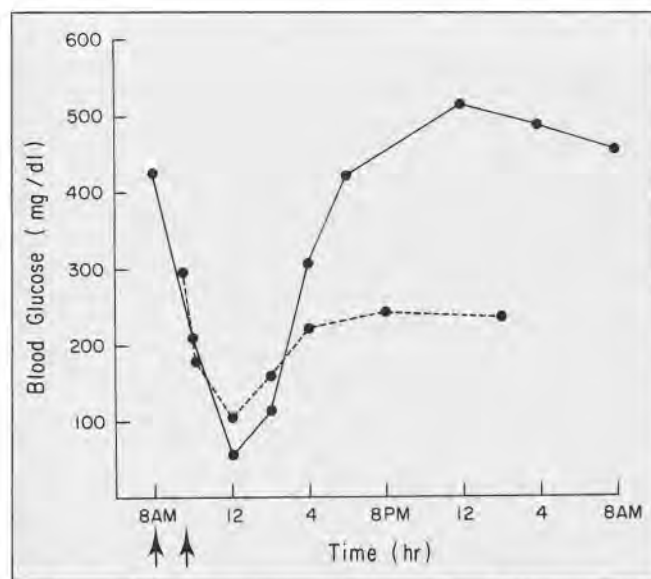


Fig 1—Blood glucose concentrations in a 5.5-kg Domestic Shorthair cat (case 1) after receiving insulin sc. Solid line—blood glucose concentrations after administration of 12 U (2.2 U/kg) NPH; broken line—concentrations after administration of 3 U (0.56 U/kg) PZI; ↑ = Insulin injection.

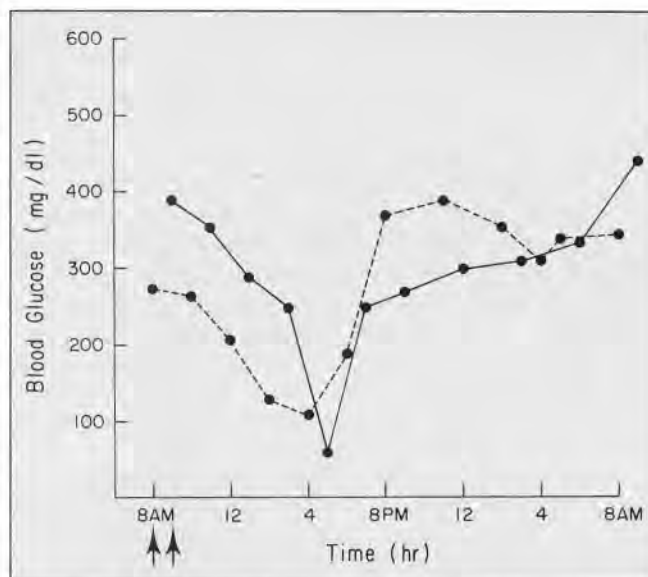


Fig 2—Blood glucose concentrations in a 2.3-kg Domestic Shorthair cat (case 2) after receiving PZI insulin sc. Solid line—blood glucose concentrations after administration of 3 U (1.3 U/kg); broken line—concentrations after administration of 2 U (0.87 U/kg); ↑ = Insulin injection.

initial examination) of U-100 PZI insulin (diluted to 10 U/ml) SC once daily. The dose was adjusted upward on the basis of degree of resolution of clinical signs and periodic urine glucose determinations by dipstick testing<sup>d</sup> at various times during the day. The dose of insulin had reached 5 U when the cat became depressed and anorectic. Laboratory evaluation revealed changes frequently observed in feline diabetes mellitus. With the decreased appetite, the dose of insulin was reduced to 2 U SID. The cat improved clinically. Periodic determination of glucose in the urine revealed glycosuria (500 to 2,000 mg/dl) at various times during the day. The dose of insulin again was raised to 3 U. The cat remained well for the following 5 months until polyuria and polydipsia redeveloped. Serial blood glucose concentrations were determined after administration of 3 U (1.3 U/kg) of PZI insulin. Blood glucose concentration was low (60 mg/dl) 8 hours after insulin administration (Fig 2). Severe hyperglycemia had redeveloped by the following morning.

The owner was instructed to decrease the dose to 1 U SID and to return the cat in 2 weeks for repeat serial sampling. At that time, serial glucose determinations were begun after administration of 1 U (0.44 U/kg) of PZI insulin. Because the first 3 glucose concentrations revealed that there was no appreciable response to the insulin, the test was aborted and repeated the following day, using 2 U (0.87 U/kg) of PZI insulin. Eight hours after insulin was administered, blood glucose concentration was in the euglycemic range (110 mg/dl), but hyperglycemia developed within 12 hours of insulin administration.

The cat was discharged, with instructions to the owners to administer 2 U of insulin BID. Eighteen

<sup>d</sup>Ketodiastix, Miles-Ames Division, Miles Laboratories, Elkhart, Ind.



months later, the cat continued to do well on 2.3 to 2.7 U of PZI insulin BID.

**Case 3**—A 10-year-old, 3.6-kg, castrated male Domestic Shorthair cat had been treated for diabetes mellitus for 2 months. Treatment had consisted of U-40 NPH insulin administered sc in the morning. The dose of insulin was adjusted several times after periodic assessment of single afternoon blood glucose concentrations. The initial insulin dose of 5 U (1.4 U/kg) had been progressively increased to 22 U (6.1 U/kg) because of repeated findings of hyperglycemia. The cat was referred after it had experienced a generalized motor seizure of 2 to 3 minutes' duration one morning. Other clinical signs included persistent polydipsia, polyuria, and episodic weakness.

Routine diagnostic laboratory evaluation revealed changes frequently observed in feline diabetes mellitus. Serial blood glucose determinations obtained after administration of 22 U of NPH insulin revealed low blood glucose concentrations 4 and 6 hours after insulin administration (41 and 38 mg/dl, respectively; Fig 3). Severe hyperglycemia had redeveloped 10 hours after insulin administration.

The cat was returned to the owner with instructions to administer 2 U of U-100 PZI insulin (diluted to 10 U/ml) SID. Two weeks later, clinical signs of hyperglycemia had dissipated and the owners had not observed weakness or seizures. Serial blood glucose concentrations were determined after administration of 2 U (0.56 U/kg) of PZI insulin (Fig 3). Though the previous wide fluctuation of blood glucose concentrations was no longer apparent, these blood glucose concentrations were mildly higher than desired. The dose of insulin was increased to 2.5 U and 15 months later the cat was continuing to do well.

**Case 4**—An 8-year-old, 6-kg, castrated male

Maine Coon cat had been treated for diabetes mellitus for 7 weeks, after an episode of diabetic ketoacidosis. The initial maintenance dose of insulin was 1 U (0.2 U/kg) of U-40 NPH insulin (diluted to 10 U/ml) SC SID. The dose was adjusted upward on the basis of periodic single afternoon blood glucose determinations, and reached 5 U on week 7.

Routine diagnostic laboratory evaluation revealed changes frequently observed in feline diabetes mellitus. Serial blood glucose determinations were made after administration of 5 U (0.83 U/kg) of NPH insulin SC. The blood glucose concentration was 48 mg/dl 6 hours after insulin administration (Fig 4). Severe hyperglycemia developed 12 hours after insulin administration.

The cat was discharged with instructions to the owners to administer 1.5 U of insulin SID. The dose was increased subsequently on the basis of repeated blood glucose determinations made over a period of 2 years. The type of insulin had been changed to PZI (U-100, diluted to 10 U/ml) because the duration of action of NPH insulin in this patient was less than 16 hours, as determined by serial blood glucose determinations. Signs of hypoglycemia were recognized in the fourth year of treatment. Progressive resolution of the diabetic condition followed repeat blood glucose determinations and subsequent reductions in the dose of insulin. Ultimately, insulin therapy was discontinued. Twelve months later, the cat continued to do well without receiving further treatment with insulin.

**Case 5**—A 12-year-old, 6.3-kg, castrated male Domestic Shorthair cat had been treated for diabetes mellitus with U-40 NPH insulin for 3 weeks. Previously, the cat had been treated with glucocorticoids topically and parenterally for anterior uveitis of unknown cause. After 3 weeks of treatment with glucocorticoids, diabetes mellitus was diagnosed. The cat

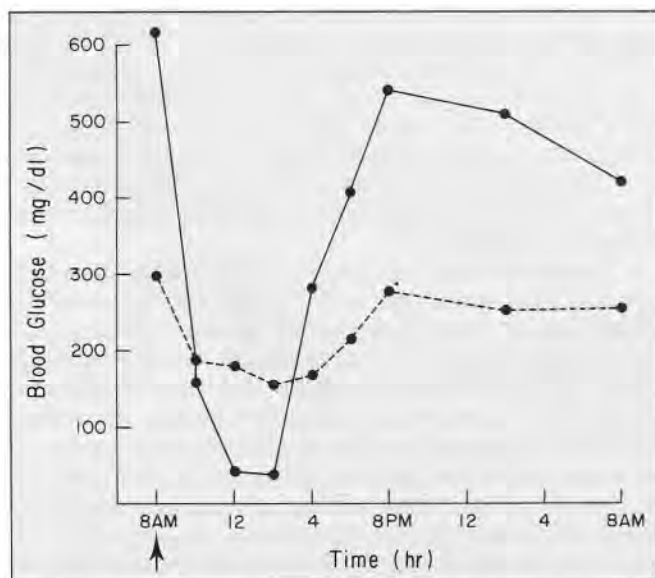


Fig 3—Blood glucose concentrations in a 3.6-kg Domestic Shorthair cat (case 3) after receiving insulin sc. Solid line—blood glucose concentrations after administration of 22 U (6.1 U/kg) NPH; broken line—concentrations after administration of 2 U (0.56 U/kg) PZI; ↑ = Insulin injection.

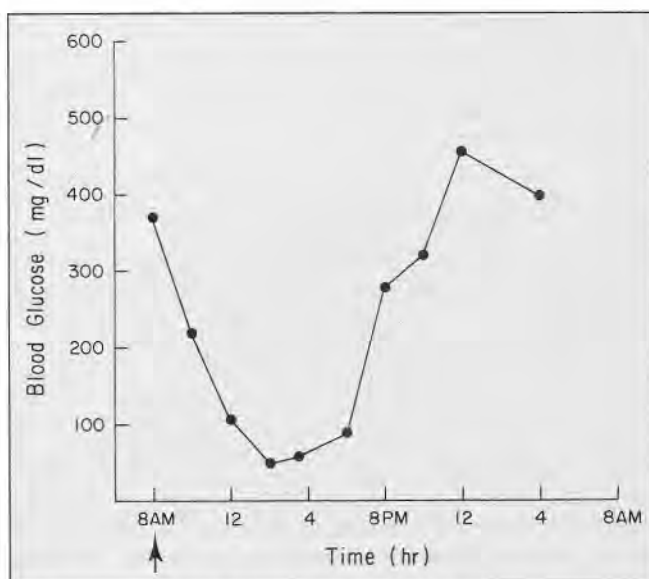


Fig 4—Blood glucose concentrations in a 6.0-kg Maine Coon cat (case 4) after receiving 5 U (0.83 U/kg) of NPH insulin sc. ↑ = Insulin injection.

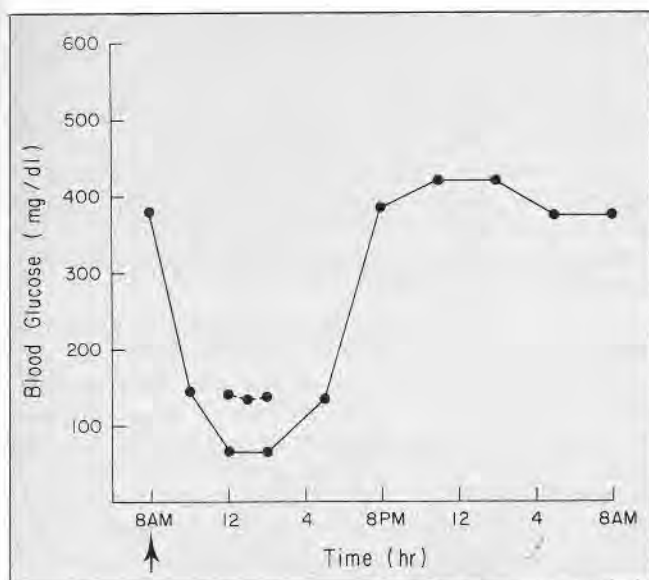


Fig 5—Blood glucose concentrations in a 6.3-kg Domestic Shorthair cat (case 5) after receiving NPH insulin sc. Solid line—blood glucose concentrations after administration of 12 U (1.9 U/kg); broken line—concentrations after administration of 6 U (0.95 U/kg); ↑ = Insulin injection.

received no steroids parenterally after diabetes was diagnosed, but remained on topical treatment with ophthalmic glucocorticoid preparations. The initial dose of insulin was 2 U of NPH insulin sc SID. The dose was increased subsequently in increments to 12 U because of consistent 2,000 mg/dl urine glucose concentrations determined by dipstick testing<sup>d</sup> at various times during the day. The cat was referred because of uncontrolled diabetes mellitus (polydipsia, polyuria, and persistent high glycosuria).

Physical examination revealed anterior and posterior uveitis in both eyes. Routine diagnostic laboratory evaluation revealed serum alanine aminotransferase concentration of 143 IU/L (normal, 21 to 102 IU/L), glycosuria (2,000 mg/dl), and 15 mg of ketones/dl of urine. Results of testing for FeLV antigen and feline infectious peritonitis virus antibody were negative. The toxoplasmosis titer was 1:64. Serial blood glucose concentrations were obtained after administration of 12 U (1.9 U/kg) NPH insulin. The blood glucose concentrations were low (65 mg/dl) 4 and 6 hours after insulin administration (Fig 5). Hyperglycemia developed 12 hours after insulin administration. The insulin dose was reduced to 6 U (0.95 U/kg) the following morning and serial blood glucose concentrations were obtained at the time of peak insulin activity (determined from the previous day's results). After administration of this lower dose of insulin, the lowest blood glucose concentration was 133 mg/dl.

To effect a longer duration of insulin activity,<sup>11</sup> the type of insulin was changed from NPH to PZI (U-100, diluted to 10 U/ml). Because of potential insulin antagonism, the dose of ophthalmic glucocorticoid medication had been reduced, as was the dose of insulin. The cat was discharged with instructions for the owner to administer 3 U of PZI insulin SID. The cat's insulin requirements steadily declined over a 2-

month period. Insulin was discontinued ultimately, and 14 months later, the cat was alive and well, receiving no medication.

**Case 6**—A 12-year-old, 5.5-kg, male Domestic Shorthair cat was admitted with an 8- to 12-week history of polydipsia, polyuria, and weight loss. Initial polyphagia had progressed to inappetence and finally anorexia. The cat remained polydipsic and polyuric. Physical examination revealed no abnormal findings. Routine laboratory evaluation revealed glycosuria and serum changes observed frequently in feline diabetes mellitus. Treatment with insulin was initiated, using U-100 PZI insulin (diluted to 10 U/ml) at a dose of 2.5 U (0.45 U/kg) sc daily. On the fourth day of treatment, blood glucose concentrations were determined hourly (Fig 6). The cat's appetite was normal at the time. The blood glucose concentrations revealed suboptimal control of diabetes mellitus (lowest blood glucose concentration, 240 mg/dl). The cat was discharged to the owner, with instructions to administer 3.5 U of PZI insulin SID. Seven days later, the owner reported that the cat was eating, gaining weight (gained 0.3 kg), and was less polydipsic and polyuric. Serial blood glucose determinations, after administration of 3.5 U (0.6 U/kg) of PZI insulin sc, revealed an apparent insulin-induced hypoglycemia and rebound hyperglycemia (Fig 6). The insulin dose was decreased, and 3 months later the cat remained well on 2.9 to 3.1 U of PZI insulin SID.

## Discussion

In the 6 cats described, blood glucose concentration was high (>370 mg/dl) at the time of insulin

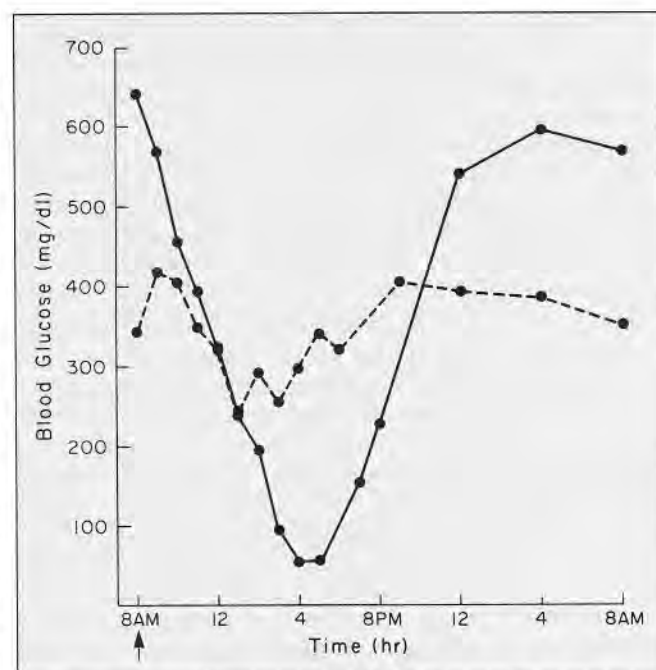


Fig 6—Blood glucose concentrations in a Domestic Shorthair cat (case 6) after receiving PZI insulin sc. Solid line—blood glucose concentrations after administration of 3.5 U (cat weighed 5.8 kg, 0.6 U/kg); broken line—concentrations after administration of 2.5 U (cat weighed 5.5 kg, 0.46 U/kg); ↑ = Insulin injection.



administration, and hypoglycemia ( $<70$  mg/dl) developed within 4 to 8 hours of insulin administration, followed by hyperglycemia. The duration of time that the blood glucose concentrations were above the suspected diabetic feline renal threshold value ( $\sim 200$  mg/dl)<sup>13</sup> ranged from 15.25 to 21.25 hours per 24-hour period (64% to 89% of the day). Therefore, patients receiving insulin in excessive quantities had glycosuria, polyuria, and obligate polydipsia for most of each day. Veterinarians should be aware that many of the signs of insulin underdosing (polydipsia, polyuria, persistent glycosuria) also may be signs of insulin overdosing.

Cats with rebound hyperglycemia have clinical signs similar to those observed in dogs. Morning glycosuria and polyuria/polydipsia were observed in these cats in spite of administration of high doses of insulin. As with dogs, seizures rarely are observed by the owners of insulin-overdosed cats. This is particularly important, because seizures represent one of the only signs suggestive of hypoglycemia. Therefore, it is often impossible to differentiate insulin underdosage from insulin overdosage without performing serial blood glucose determinations.

The dose of insulin that will induce rebound hyperglycemia is highly variable and not predictable. Two cats treated with PZI insulin were overdosed on 3 and 3.5 U (1.3 and 0.6 U/kg). The range of doses of NPH insulin that produced rebound hyperglycemia was 5 U to 22 U (0.83 to 6.1 U/kg). One report on insulin therapy in cats revealed the therapeutic range of PZI insulin to be 0.3 to 1.1 U/kg (3 cats), and the therapeutic range of NPH insulin to be 0.2 to 1.4 U/kg (7 cats, five of which received this dose twice daily).<sup>10</sup> Therefore, an overlap exists between the ranges of therapeutic and excessive doses for PZI and NPH insulin in the cat. On the basis of the previous report<sup>10</sup> and our experience, cats receiving  $>1$  U of insulin/kg of body weight and having persistent and/or severe glycosuria, clinical signs of hypoglycemia, or experiencing poor diabetic regulation are likely to have rebound hyperglycemia. If rebound hyperglycemia is suspected, it is best diagnosed by serial measurement of the blood glucose concentration. As in dogs, hypoglycemia ( $<65$  mg/dl) followed by hyperglycemia ( $>300$  mg/dl) within the 24-hour period after insulin administration confirms the diagnosis.<sup>14</sup>

In dogs experiencing posthypoglycemic rebound hyperglycemia, single afternoon blood glucose determinations are potentially inadequate to assess the patient's condition.<sup>8</sup> Using the reported findings of the time of lowest blood glucose concentration after insulin administration in the cat, it can be determined whether the same holds true for this species. The time of lowest blood glucose concentration has been determined to be approximately 6 hours (range, 4 to 8 hours) after injection of intermediate-acting insulin (NPH) and approximately 9 hours (range, 6 to 12 hours) after injection of long-acting insulin (PZI).<sup>10</sup> Single blood glucose determinations obtained at these times in 2 of the cats of this report would have yielded the following conclusions about the insulin dose: cat 1—correct dose (glucose, 115 mg/dl), and cat

2—dose too low (glucose,  $\approx 150$  mg/dl). In addition, 3 of the cats in this report (cats 1, 3, and 4) developed rebound hyperglycemia while being monitored by periodic single blood glucose determinations. We also determined that peak insulin effect develops at a highly variable time interval after injection of insulin. It is evident, then, that single blood glucose determinations are potentially inadequate and/or misleading in assessing feline diabetic patients with rebound hyperglycemia.

The futility of using urine glucose to assess rebound hyperglycemia was evident from the data regarding the percentage of the day (64% to 89%) during which the blood glucose of these patients exceeded 200 mg/dl. Equally important, all cats had blood glucose concentrations in excess of 375 mg/dl at 8 AM the following morning (except cat 4, which had a blood glucose concentration of 398 mg/dl at 4 AM; a sample was not obtained at 8 AM). This indicates that most cats with rebound hyperglycemia have morning glycosuria. Therefore, morning urine glucose concentrations are not useful in distinguishing between underdosage and overdosage of insulin in cats with diabetes mellitus.

Treatment of rebound hyperglycemia is straightforward in that the insulin dose must be reduced. We arbitrarily reduce the dosage by 50% to 75% and return the cat to the owner. After 5 to 14 days on the new insulin dose, serial blood glucose concentrations should be reevaluated. The proper insulin dose results in a decrease of the blood glucose concentration to 80 to 120 mg/dl at the time of peak insulin action.<sup>8,14</sup>

Reports of a syndrome in the cat termed the "transient response to insulin" describe an episode of hypoglycemia followed by hyperglycemia.<sup>15-17</sup> On the basis of its description, this syndrome appears to be posthypoglycemic rebound hyperglycemia. In contrast, the syndrome of transient insulin response results from rapid metabolism of insulin<sup>14</sup> and is well illustrated in Figure 3 (at the lower of the 2 insulin doses). The blood glucose concentrations illustrate the duration of insulin activity to be 12 hours, after which the glucose concentration stays relatively constant. The treatment in these cats involves repeating the morning dose of insulin at 8 PM. We believe that the term "transient response to insulin" is best suited for these cases and that "rebound hyperglycemia" be used for cases in which insulin overdosing leads to hypoglycemia followed by hyperglycemia.

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