An Uncontrolled Diabetic Dog

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CONSIDER THIS CASE

Buster, a 7-year-old male castrated beagle mix weighing 18 kg, was presented for evaluation of uncontrolled diabetes.

HISTORY

Previous Diagnosis

Six months before presentation, Buster was presented to his primary veterinarian for polyuria, polydipsia, and weight loss. Physical examination and complete blood count (CBC) were unremarkable, while the serum biochemical profile (Table 1) demonstrated:

- Mildly increased alkaline phosphatase (ALP)
- Mild hypercholesterolemia
- Hyperglycemia

The urinalysis showed glucosuria, with no evidence of ketones, white blood cells, or bacteria. Based on these findings, Buster was diagnosed with diabetes mellitus.

Medical Therapy

After diagnosis, Buster’s primary veterinarian initiated therapy with neutral protamine Hagedorn (NPH) insulin at 9 U (0.5 U/kg) SC q12h. Intermittent spot

TABLE 1 Buster: Historical Serum Biochemical Profile Results

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>RESULT</th>
<th>REFERENCE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>860</td>
<td>14–91</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>360</td>
<td>139–353</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>538</td>
<td>86–118</td>
</tr>
</tbody>
</table>

QUESTIONS: Investigating the Unstable Diabetic Dog

1. What are possible causes of poor diabetic control in this dog?
2. Are there problems with insulin handling and administration?
3. Is this dog receiving an appropriate insulin type and dose?
4. What and when is the dog being fed, and does the dog receive any additional treats or table scraps?
5. What are possible causes of insulin resistance in this dog?
6. What additional diagnostics would help in better assessing diabetic control?

Turn to page 52 for the answers to these questions.
blood glucose monitoring was used to determine adjustments in insulin dose and, based on variably high results (>350 mg/dL), Buster’s insulin dose was increased approximately every 3 days.

Upon presentation for a second opinion on diabetic control, Buster was receiving 30 U of NPH insulin q12h. The insulin was from a new prescription, stored in the refrigerator, and the administration technique (visualized as part of history collection) appeared appropriate.

Buster had no other known medical conditions and was not receiving any other drugs or supplements.

**Diet & Exercise**

Buster was receiving a maintenance diet (daily requirements calculated at 700 calories/day; he was receiving approximately 800 calories/day), divided and fed in equal amounts roughly 10 to 12 hours apart. The diet and exercise pattern had been consistent since diagnosis.

**CLINICAL SIGNS**

The owners noted that Buster was polyphagic, polyuric, and polydipsic, with no obvious improvement since initiation of insulin therapy. Buster had no recent vomiting, diarrhea, or alterations in appetite.

**PHYSICAL EXAMINATION**

Physical examination revealed a symmetrically muscled dog with mild muscle atrophy, with a body condition score of 7/9. Buster had moderate periodontal disease, a grade III/VI left apical systolic heart murmur, incomplete bilateral diabetic cataracts, and a tense, nonpainful abdomen on palpation. No additional abnormalities were appreciated.

**TABLE 2** Buster: Serum Biochemical Profile & Urinalysis Abnormalities at Presentation

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>RESULT</th>
<th>REFERENCE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine aminotransferase (IU/L)</td>
<td>38</td>
<td>21–72</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>444</td>
<td>14–91</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>608</td>
<td>139–353</td>
</tr>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>519</td>
<td>86–118</td>
</tr>
<tr>
<td>Glucosuria</td>
<td>3+</td>
<td>0</td>
</tr>
<tr>
<td>Pyuria</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urine specific gravity</td>
<td>1.015</td>
<td></td>
</tr>
</tbody>
</table>
**DIAGNOSTIC APPROACH**

Buster’s problem list of conditions—both related and unrelated to his diabetes mellitus—included:

- Poorly controlled diabetes mellitus
- Bilateral incomplete diabetic cataracts
- Grade III/VI systolic heart murmur
- Periodontal disease

Suspected causes of poor diabetic control included:

- Insulin overdose
- Inappropriate insulin type (eg, short duration of action)
- Insulin resistance caused by concurrent disease

**Initial Laboratory Analysis**

Routine CBC, serum biochemical profile, and urinalysis with urine culture were performed. The CBC was unremarkable and urine culture was negative for bacterial growth. The primary abnormalities noted on the serum biochemical profile were elevated ALP, hypercholesterolemia, and hyperglycemia (Table 2).

**Glucose Monitoring & Curves**

The patient was hospitalized in order to better assess diabetic control through serial blood glucose curves and monitoring.

**Day 1:** Blood glucose was assessed in-hospital on the night of admission (Table 3), before insulin administration.

**Day 2:** Blood glucose monitoring began the next morning (Table 3). Because blood glucose was lower than anticipated at 8 am, Buster received 25 U of NPH insulin SC after a complete meal, with blood glucose measurements taken 2 hours later and then q2h.

Buster significantly responded to insulin while in the hospital, with a relatively low blood glucose at 8 pm. Buster was fed and no additional insulin was administered on Day 2. Blood glucose monitoring continued overnight until blood glucose was >200 mg/dL.

**Day 3:** Buster received 10 U of NPH insulin SC after a complete meal in the morning, with response monitored throughout the day (Table 3).

**Figure 1** depicts the blood glucose measurement trends revealed over the 3 days of in-hospital monitoring.

![Figure 1](image-url)

**TABLE 3 Buster: Blood Glucose Measurements (mg/dL) During Hospitalization**

<table>
<thead>
<tr>
<th>TIME</th>
<th>DAY 1: NPH 30 U</th>
<th>DAY 2: NPH 25 U</th>
<th>DAY 3: NPH 10 U</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 am</td>
<td>252</td>
<td>328</td>
<td></td>
</tr>
<tr>
<td>Meal/insulin</td>
<td>Meal fed; then insulin administered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 am</td>
<td>107</td>
<td>394</td>
<td></td>
</tr>
<tr>
<td>12 pm</td>
<td>148</td>
<td>256</td>
<td></td>
</tr>
<tr>
<td>2 pm</td>
<td>169</td>
<td>227</td>
<td></td>
</tr>
<tr>
<td>4 pm</td>
<td>129</td>
<td>246</td>
<td></td>
</tr>
<tr>
<td>6 pm</td>
<td>129</td>
<td>217</td>
<td></td>
</tr>
<tr>
<td>8 pm</td>
<td>528</td>
<td>132</td>
<td>251</td>
</tr>
<tr>
<td>Meal/insulin</td>
<td>Meal fed; then insulin administered</td>
<td>Meal fed; NO insulin administered</td>
<td></td>
</tr>
<tr>
<td>10 pm</td>
<td>245</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Unstable Diabetic Dog: Diagnostic Approach**

For a patient with uncontrolled diabetes mellitus, the goal of the diagnostic evaluation is to establish a problem list of conditions related and unrelated to the animal’s diabetes mellitus.

In addition, determine the suspected causes of poor diabetic control, which may include:

- Problems with owner administration
- Activity of the insulin
- Insulin overdose or underdose
- Prolonged or short duration of insulin effect
- Concurrent disease causing insulin resistance
On the basis of serial blood glucose curves and monitoring in the hospital, it was suspected that Buster was exhibiting clinical signs consistent with poor control caused by rebound hyperglycemia, also known as the Somogyi response.

This diagnosis was based on Buster’s clinical response (reduced clinical signs and increased body weight) and improved blood glucose values, both of which were associated with a significant reduction in insulin dose. See The Somogyi Response, page 51, for further details on diagnosis of rebound hyperglycemia.

Challenges in Diagnosis

The specific criteria for a Somogyi response (page 51) were not demonstrated on Buster’s blood glucose curves performed in the hospital. However, these criteria can be challenging to identify in hospital, and may not be identified at all because of:

• Infrequent sampling in the hospital
• The fact that diabetogenic hormones released during the response can have lingering effects—up to 24 to 72 hours following the period of hypoglycemia
• Increased stress caused by hospitalization

According to the blood glucose values obtained in hospital for Buster, once the insulin dose was reduced significantly, Buster’s blood glucose values improved, leading to suspicion of insulin overdose.

Definitive Diagnosis

In this dog, if the previous high insulin dose had been administered repeatedly, a Somogyi response with rebound hyperglycemia may have been documented in subsequent blood glucose curves.

Treatment & Follow-up

Buster’s Day 3 dosage of NPH insulin (10 U SC q12h) was continued for 7 to 10 days, with a plan for the owner to return with Buster in 1 week for a blood glucose curve.

**Blood Glucose Curves**

Blood glucose concentrations can vary significantly in diabetic animals. Blood glucose curves can, therefore, provide more useful impressions of how diabetic animals respond to insulin administration than single measurements alone.

Concurrent monitoring of body weight, clinical signs (water consumption, urination, appetite), and fructosamine measurements should accompany blood glucose monitoring, as blood glucose curves are best evaluated with this additional information in hand.

Key questions to ask when evaluating blood glucose curves include:

1. **Is the insulin effective at decreasing the blood glucose?** If ineffective, consider insulin underdose, overdose causing rebound hyperglycemia or Somogyi response, or insulin resistance. It is also important to review the animal’s history and physical examination findings to help prioritize possible causes of poor diabetic control.

2. **What is the nadir?** If the nadir is too high or too low, consider an insulin dose that alternates.

3. **What is the duration of action of the insulin?** If too short or too long, consider changing the insulin type.

Clinicians must recognize the variability between blood glucose curves performed at home and those obtained in the hospital setting. Many owners may alter a pet’s daily routine (eg, feeding schedule, exercise) to accommodate the hospital visit. In addition, pets exhibiting fear or stress in a hospital setting are unlikely to be good candidates for in-hospital blood glucose curves. At-home blood glucose monitoring or other approaches (for example, continuous glucose monitors) must be considered.
At Buster’s follow-up appointment, his clinical signs had improved but not resolved. A blood glucose curve was performed, revealing a nadir of 260 mg/dL at 4 pm. The insulin was effective, but the nadir was not ideal. Thus, the dose was increased to 12 U of NPH insulin SC q12h.

Additional follow-up showed that, with this dose, Buster’s clinical signs had resolved and his condition was controlled.

**IN SUMMARY**

Unstable diabetic animals can be a struggle to manage in clinical practice. Thorough communication with the owner and examination of the animal, along with careful monitoring, are the key to successfully stabilizing these animals. Making small, infrequent insulin dose changes and allowing time to assess the animal’s response are the best ways to prevent insulin overdose. **TVP**

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**The Somogyi Response**

The Somogyi response, also called rebound hyperglycemia and insulin-induced hyperglycemia, is the physiologic response to impending hypoglycemia. This response is characterized by stimulation of hepatic gluconeogenesis and secretion of diabetogenic hormones, including catecholamines and glucagon.

**Incidence & Risk Factors**

Limited literature supports the documentation of the Somogyi response in dogs and cats. A recent study suggests that, in cats receiving long-acting insulin analogs (eg, insulin glargine, insulin detemir), the Somogyi response is less common than initially suspected.

Factors that may increase risk for the Somogyi response in dogs and cats include:

- Insulin adjustments made very frequently, which does not give the patient time to equilibrate between doses
- Insulin adjustments made in large increments
- Lente insulin therapy q12h.

**Clinical Signs**

Clinical signs of hypoglycemia are often subtle and overshadowed by signs of hyperglycemia that go unnoticed by the client. Table 4 provides a list of common clinical signs of hyperglycemia and hypoglycemia.

**Diagnosis**

Diagnosis of the Somogyi response requires documentation of hypoglycemia (glucose <65 mg/dL) followed by hyperglycemia (glucose >300 mg/dL) after insulin administration.

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**TABLE 4 Common Clinical Signs of Hyperglycemia & Hypoglycemia in Dogs**

<table>
<thead>
<tr>
<th>HYPERGLYCEMIA</th>
<th>HYPOGLYCEMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polydipsia</td>
<td>Abnormal behavior or mentation changes</td>
</tr>
<tr>
<td>Polyphagia</td>
<td>Collapse</td>
</tr>
<tr>
<td>Polyuria</td>
<td>Polyphagia</td>
</tr>
<tr>
<td>Weight loss despite a good appetite</td>
<td>Tremors, seizures</td>
</tr>
<tr>
<td></td>
<td>Weakness, lethargy</td>
</tr>
</tbody>
</table>

Rebound hyperglycemia is often between 400 and 800 mg/dL. It is suspected that patients exhibit sustained hyperglycemia and insulin resistance (up to 24–72 H) after a hypoglycemic event.

The Somogyi response should be suspected when:

- Blood glucose rapidly drops regardless of nadir.
- Duration of insulin is greater than 12 hours.
- The patient is receiving a high dose of insulin (>1.5 U/kg).
- There is a cyclic history of good glycemic control for 1 to 2 days, followed by poor glycemic control for several days.
- The patient has gained weight despite suboptimal diabetic control.
- The patient has failed to improve despite increasing the insulin dose.

**Challenges with Recognition**

Several challenges surround diagnosis of a Somogyi response. The Somogyi response:

- Is rare in dogs and cats. Previously believed to be more common in cats on lente insulins. Perceived to be less common in feline patients receiving new analog insulin preparations, although there is limited literature describing prevalence in diabetic animals.
- Does not happen in every episode of hypoglycemia. Reasons for this are unclear, but may include lack of a counterregulatory hormone response and duration of hypoglycemia.
- Can be challenging to detect with blood glucose curves because the period of hypoglycemia can be very short and easily missed.
- Is associated with unpredictable serum fructosamine measurements. Usually, a concentration greater than 500 mcmol/L confirms poor diabetic control.

Because of these challenges, when insulin overdose is suspected, but not documented on a blood glucose curve, consider reducing the insulin dose. Once the dose has been reduced, instruct the owner to carefully monitor clinical signs for any subtle change and repeat monitoring at least 4 to 7 days after reducing the insulin dose.
Ann Della Maggiore
Ann Della Maggiore, DVM, DACVIM, serves as an assistant professor of clinical internal medicine at the University of California, Davis School of Veterinary Medicine, with a specific interest in small animal endocrinology. She received her veterinary degree from UC Davis, then completed a residency in small animal internal medicine at the same institution.

References

ANSWERS:
Investigating the Unstable Diabetic Dog
1. What are possible causes of poor diabetic control in this dog?
   Insulin overdose, inappropriate insulin type, insulin resistance caused by concurrent disease.
2. Are there problems with insulin handling and administration?
   Not in this case.
3. Is this dog receiving an appropriate insulin type and dose?
   Insulin dose is too high and does not provide good diabetic control; the insulin type should be appropriate, but duration of action cannot be assessed currently.
4. What and when is the dog being fed, and does the dog receive any additional treats or table scraps?
   Appropriate caloric intake is provided twice daily, with no treats or table scraps.
5. What are possible causes of insulin resistance in this dog?
   Hyperadrenocorticism, hypertriglyceridemia, insulin antibodies, periodontal disease, or other concurrent disease.
6. What additional diagnostics would help in better assessing diabetic control?
   Blood glucose curve (performed in hospital or at home), fructosamine concentration; further diagnostics can be based on findings and may include systemic evaluation for concurrent disease or continuous glucose monitoring, if available.