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A diabetic woman with worsening heart failure, hunger, and tremor

Her glucose level is 23. What is the cause?

A 57-YEAR-OLD WOMAN presents to the emergency department with severe shortness of breath after minimal exertion, which developed over the last several weeks. She also notices increasing peripheral edema, especially in her feet and legs, an increase in her body weight of about 5 kg over 3 weeks, and a marked decrease in urine output for several days. She does not have any chest pain, fever, chills, abdominal pain, nausea, or vomiting. While in the hospital she starts to complain of anxiousness and hunger.

Medical history

- Coronary artery disease: a myocardial infarction 9 years ago and coronary artery bypass grafting performed 2 years later
- Chronic atrial fibrillation
- Congestive heart failure: several episodes that required hospitalization; her latest echocardiographic examination showed a left ventricular ejection fraction of 25%
- Hypertension
- Hypercholesterolemia
- Stable chronic renal insufficiency (serum creatinine 2.0 mg/dL)
- Type 2 diabetes mellitus (diagnosed 7 years ago). Initially, she was treated with diet and exercise, but later required glimepiride (Amaryl), a sulfonylurea, to control her blood glucose levels. One year ago her primary care physician stopped the glimepiride, but restarted it 1 week ago. Her last glimepiride dose was about 36 hours ago. She has no known retinopathy, neuropathy, or nephropathy.

This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

Medications

- Glimepiride 4 mg/day
- Aspirin 325 mg/day
- Enalapril 10 mg/day
- Metoprolol 50 mg twice daily
- Simvastatin 40 mg/day
- Warfarin 2 mg/day.

Physical examination

She appears ill and weak but can talk in full sentences while lying in bed and receiving oxygen via nasal cannula at 4 L/minute. She has generalized massive edema. Her skin is moist, and her outstretched hands reveal a fine tremor.

Vital signs: pulse 124, respirations 28, blood pressure 106/67 mm Hg.

Cardiac examination: irregular rhythm, audible S3. Her jugular veins are distended to approximately 10 cm.

Chest: fine crackles over the lower two thirds of the posterior lung fields.

Abdomen: soft, nontender, no organomegaly.

The patient is admitted to hospital with the impression of exacerbation of congestive heart failure.

Serum laboratory results

- Sodium 135 mmol/L (normal 132–148)
- Potassium 3.8 mmol/L (3.5–5.0)
- Chloride 98 mmol/L (98–110)
- CO_2 25 mmol/L (24–32)
- Blood urea nitrogen 86 mg/dL (8–25)
- Creatinine 2.9 mg/dL (0.7–1.4)
- Glucose 23 mg/dL (65–110)
- Aspartate aminotransferase 21 U/L (7–40)
- Alanine aminotransferase 10 U/L (0–45)
- Bilirubin 0.6 mg/dL (0.0–1.5)
- Thyroid-stimulating hormone 4.387 µU/mL (0.4–5.5).

WHAT IS THE CAUSE OF HER HYPOGLYCEMIA?

1 Which of the following is the most likely cause of this patient's hypoglycemia?

- ❑ Insulinoma
- ❑ Glimepiride intoxication
- ❑ Adrenal insufficiency
- ❑ Poor food intake
- ❑ Inadvertent insulin administration

Insulinoma is a rare cause of hypoglycemia, and patients usually have a history of recurrent hypoglycemic episodes that are often associated with prominent neuroglycopenic symptoms (dizziness, headache, blurring of the vision, slurring of the speech, loss of fine motor skills, confusion, abnormal behavior, convulsions, or coma).

Patients also may report a weight gain over time that is the result of increased food intake to counteract the effects of hypoglycemia.

Of note, the typical autonomic signs and symptoms of hypoglycemia (eg, sweating, tremor, tachycardia, anxiety, and hunger) may be absent, because autonomic responses may become blunted after repeated episodes of hypoglycemia. Therefore, these signs and symptoms would occur at lower plasma glucose levels than in patients without insulinomas.

Insulinomas in patients with diabetes are extremely rare.[1] Although our patient gained weight over the past few weeks, this was not associated with symptoms of hypoglycemia. The association of weight gain with an increase in peripheral edema suggests fluid retention, not increased eating.

Glimepiride intoxication is the most likely cause of this patient's hypoglycemia. Most hypoglycemic episodes are caused by drugs, including alcohol. In patients with diabetes, hypoglycemia is by far most commonly related to therapy.[2] Sulfonylurea intoxications that cause hypoglycemia are usually due to accidental ingestions and suicide attempts, but also can be related to changes in the body's ability to metabolize or excrete this class of medications (liver failure or diminished kidney function) or to the administration of pills of the wrong (higher) strength.[3]

This patient presented with acute worsening of renal failure, which is known to cause protracted hypoglycemia in patients taking a sulfonylurea. Most cases of protracted hypoglycemia involve glyburide or chlorpropamide, but a few cases involving glipizide and glimepiride have been reported.[4,5]

Adrenal insufficiency should be considered in this patient, as it can present with hypoglycemia. The patient is taking warfarin and is thus predisposed to bilateral adrenal hemorrhage, which is a well-recognized cause of acute adrenal insufficiency.[6]

Acute adrenal insufficiency usually presents with adrenal crisis, while chronic adrenal insufficiency has nonspecific symptoms and signs such as fatigue, nausea, vomiting, abdominal pain, weakness, anorexia, salt craving, weight loss, hypotension, electrolyte abnormalities (hyponatremia in 85%–90% of cases and hyperkalemia in 60%–65%), hyperpigmentation, sexual dysfunction, and even psychiatric manifestations. None of these establish the diagnosis, either singly or in combination, but they should prompt the clinician to entertain this possibility.

In light of our patient's relatively normal pulse and blood pressure, normal electrolyte levels, and absence of other symptoms and signs, adrenal insufficiency would be unlikely, although its symptoms may be subtle and nonspecific.

Her physicians obtain a random cortisol level, which is 20.5 µg/dL, effectively ruling out adrenal insufficiency.

Poor food intake can cause hypoglycemia in cases of extreme malnutrition and in patients with severe underlying liver disease.[7] However, this patient's history does not suggest such a condition, making it unlikely as a cause of her hypoglycemia.

Inadvertent insulin administration is a rare cause of hypoglycemia but has been reported in hospital settings. Intentional insulin use by patients with psychiatric conditions or by malingerers is more common.[8] Nothing suggests these problems in our patient.

Case continued

The patient is given 50 mL of 50% dextrose intravenously. Her hypoglycemia and hypo-

Drugs—including alcohol—cause most hypoglycemic episodes

TABLE 1

Normal fasting values of glucose-related molecules

Glucose	65–110 mg/dL
Insulin	1–24 µU/mL
Proinsulin	2.1–26.8 pmol/L
C peptide	0.7–3.0 ng/mL
Cortisol (morning)	3.4–26.9 mg/dL
Cortisol (evening)	0.9–15.8 µg/dL

glycemic symptoms improve briefly, but then return.

Because she has severe congestive heart failure, her physicians want to minimize her fluid intake and avoid worsening her fluid overload. They therefore decide not to treat her hypoglycemia with a continuous glucose infusion, but instead to keep giving her bolus doses of 50% dextrose. However, each bolus raises her blood glucose level only briefly, with recurrent hypoglycemia within 1 to 1.5 hours. A blood sample is drawn during one of these hypoglycemic episodes to measure her glucose, insulin, C peptide, and cortisol levels simultaneously. (Normal values are shown in TABLE 1.)

Elevated insulin, C peptide, and cortisol are consistent with sulfonylurea-induced hypoglycemia

LABORATORY PATTERNS AND CAUSES OF HYPOGLYCEMIA

2 Which of the following sets of laboratory findings is most consistent with sulfonylurea-induced hypoglycemia in a patient whose glucose level is 32 mg/dL?

- ❑ Insulin 62.4, C peptide 24.6, cortisol 26.8
- ❑ Insulin 2.8, C peptide 0.6, cortisol 26.8
- ❑ Insulin 62.4, C peptide 0.6, cortisol 26.8
- ❑ Insulin 2.8, C peptide 0.6, cortisol 9.2

Elevated insulin, C peptide, and cortisol (the first pattern) is most consistent with sulfonylurea-induced hypoglycemia. The low glucose level and elevated insulin and C peptide levels indicate that the insulin is of endogenous origin, as injectable insulin preparations do not contain C peptide. The cortisol level is appropriately high as a reaction to the stress of hypoglycemia.

Of note: this pattern also fits hypoglycemia caused by insulinoma and other causes of endogenous hyperinsulinemia. The serum sulfonylurea concentration may need to be measured to establish the diagnosis in some instances.[9]

Low insulin, low C peptide, elevated cortisol (the second pattern) can be seen in cases of increased glucose utilization associated with certain tumors (large fibromas or sarcomas, renal cell carcinomas, or adrenal cancers) that are thought to cause hypoglycemia by hypersecretion of insulin-like growth factor 2 (IGF 2). Increased glucose uptake is also seen in states of systemic carnitine deficiency (Reye syndrome, deficiencies of enzymes of fat oxidation, and 3-hydroxy-3-methylglutaryl-CoA-lyase deficiency), which blocks the body's use of free fatty acids for energy production. Again, the cortisol level is appropriately high as a reaction to the stress of hypoglycemia.

Elevated insulin, low C peptide, elevated cortisol (the third pattern) is most consistent with exogenous administration of insulin. If the glucose level is low, a high insulin level is inappropriate. The low C peptide level suggests that insulin did not originate endogenously. The cutoff level of C peptide for distinguishing exogenous vs endogenous hyperinsulinemia is 0.6 ng/mL.[10]

Low insulin, low C peptide, low cortisol (the fourth pattern) is most consistent with adrenal insufficiency. In this condition the low glucose level is appropriately associated with low levels of insulin and C peptide, and the cortisol level is inappropriately low for the degree of hypoglycemia.

The most sensitive single test of the hypothalamic-pituitary-adrenal axis is the insulin tolerance test, which involves giving an intravenous dose of insulin to cause hypoglycemia and stimulate the hypothalamic-pituitary-adrenal axis. The normal response is an increase in serum cortisol to at least 18.5 µg/dL.[11]

HOW TO RAISE HER GLUCOSE LEVEL?

3 Faced with persistent hypoglycemia despite repeated doses of 50% dextrose, the patient's physicians decide to undertake additional measures to restore euglycemia. All of the following will increase

this patient's glucose level (at least temporarily) except which one?

- ❑ Glucagon injection
- ❑ Octreotide injection
- ❑ Adrenocorticotropic hormone injection
- ❑ Diazoxide, orally
- ❑ Dextrose 20% infusion

A glucagon injection usually increases blood glucose temporarily, but it has to be followed by additional measures to maintain euglycemia. Glucagon mobilizes hepatic glycogen and induces hepatic gluconeogenesis, but the higher blood glucose levels in turn stimulate the pancreatic beta cells to secrete more insulin, which lowers the glucose level again. Glucagon raises blood glucose levels more slowly than intravenous glucose infusions or bolus injections, and this therapy sometimes fails.[12] It should be reserved for patients without intravenous access.[13]

Octreotide (Sandostatin), a synthetic somatostatin analogue, has been used to achieve more prolonged increases in blood glucose in patients with protracted hypoglycemic episodes caused by a sulfonylurea.

In a study in eight healthy volunteers with hypoglycemia induced by glipizide overdose,[14] octreotide was superior to treatment with diazoxide or glucose infusion. Several case reports and one retrospective review of patients with sulfonylurea-induced hypoglycemia confirm this drug's efficacy.[15]

Adrenocorticotropic hormone injection (corticotropin) slightly increases plasma glucose levels in normal, unstressed subjects, but it would not in this patient. Her hypothalamic-pituitary-adrenal axis is already maximally stimulated by hypoglycemia, as shown by her elevated serum cortisol levels.

Diazoxide (Proglycem) also raises glucose levels in hypoglycemic episodes that are induced by hyperinsulinism (insulinoma, nesidioblastosis, factitious hypoglycemia due to sulfonylurea use). It decreases serum insulin concentrations by inhibiting insulin release from beta cells and also by increasing insulin metabolic clearance. It also appears to increase tissue resistance to insulin action.[16]

Up to 47% of patients experience side effects with diazoxide, however, most commonly fluid retention, followed by hirsutism, hypotension, and skin rashes (including Stevens-Johnson syndrome).[17] Most of the side effects do not occur during the short-term use required in cases of sulfonylurea overdose.

Diazoxide usually is taken three times a day.

Infusion of 20% dextrose seems like the obvious way to raise plasma glucose levels in patients with protracted hypoglycemia. However, sulfonylurea medications stimulate beta cells to release insulin, and they sensitize them to glucose. Thus, in patients with sulfonylurea intoxication, glucose infusion will correct the hypoglycemia but may result in severe rebound hypoglycemia when the infusion is stopped, due to continuing stimulation of insulin secretion.[18]

Case continued

The patient is started on subcutaneous injections of octreotide 50 µg every 8 hours.

Following the first octreotide injection, she requires two additional bolus doses of 50% dextrose, both within the first 6 hours. Thereafter, her plasma glucose level gradually increases and she needs no more doses of dextrose. Octreotide therapy is stopped after four injections, when her plasma glucose level reaches 185 mg/dL.

For the next 14 hours she remains hyperglycemic with blood glucose levels reaching 340 mg/dL, and she requires injections of regular insulin. Thereafter, her fasting plasma glucose levels decrease to the range of 120 to 150 mg/dL (FIGURE 1).

Glucagon raises glucose levels, which raise insulin levels, which lower glucose again

HOW DOES OCTREOTIDE RAISE GLUCOSE?

4 Octreotide counteracts the hypoglycemic action of sulfonylurea medications by which of the following mechanisms?

- ❑ Increasing glycogenolysis in the liver
- ❑ Increasing gluconeogenesis in liver
- ❑ Displacing the sulfonylurea from its receptors on pancreatic beta cells
- ❑ Inhibiting insulin release from beta cells
- ❑ Increasing catabolism of circulating insulin

Increasing glycogenolysis and gluconeogenesis are mechanisms by which *glucagon*

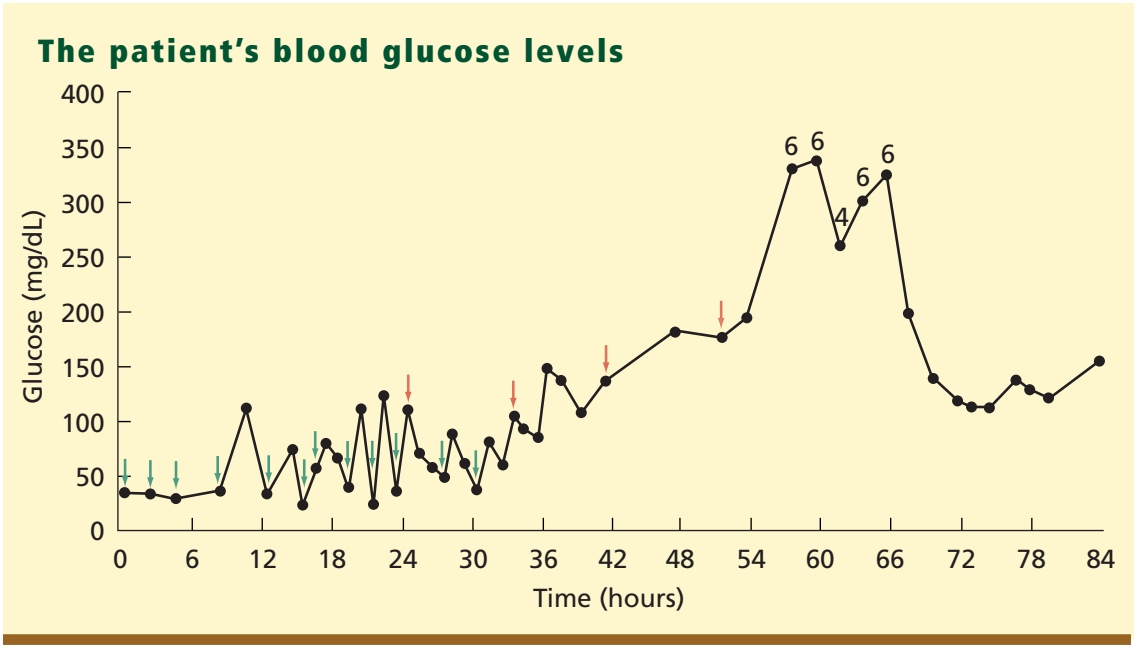

FIGURE 1. The patient's blood glucose values while in the hospital, as measured by bedside fingerprick monitoring. Green arrows indicate bolus intravenous injections of 50% dextrose 50 mL; red arrows indicate injections of octreotide 50 µg; black numbers indicate doses of regular insulin.

Octreotide inhibits insulin secretion in cases of sulfonylurea overdose

counteracts hypoglycemia,[19] but there is no evidence that octreotide has similar effects.

Displacing sulfonylurea is also incorrect—no known medication displaces sulfonylureas from their receptors on pancreatic beta cells.

Inhibiting insulin release is the correct answer. Octreotide is a powerful inhibitor of secretion of insulin from pancreatic beta cells. It also inhibits secretion of glucagon, growth hormone, gastrin, exocrine pancreatic enzymes, and many other hormones.[20] In cases of sulfonylurea overdose, octreotide directly suppresses insulin secretion, lowering serum insulin levels and resolving hypoglycemia.[15]

The optimal octreotide regimen is not clear at this time, but two or three doses per day appear to suffice in most cases.

Increasing insulin catabolism is one of the mechanisms by which *diazoxide* increases glucose levels,[16] but there are no data showing that octreotide does this.

Case continued

Before the patient receives octreotide, her insulin level is 62.8 µU/mL (normal 1–24), C peptide 24.8 ng/mL (0.7–3.0), and proinsulin 467.3 pmol/L (2.1–26.8).

During octreotide therapy, her insulin level drops to 12.4 µU/mL, C peptide to 0.9 ng/mL, and proinsulin to 2.3 pmol/L. (These values illustrate octreotide's effects, but these tests are not necessary in managing hypoglycemia caused by a sulfonylurea.)

As she starts eating, her blood glucose levels increase to 180 to 250 mg/dL, and she receives regular insulin with each meal.

HOW TO MANAGE HER DIABETES?

5 Which of the following antidiabetic medications is the best choice for continuing therapy for this patient?

- ❑ Rosiglitazone
- ❑ Pioglitazone
- ❑ Metformin
- ❑ Acarbose
- ❑ Insulin

Rosiglitazone and **pioglitazone** are both thiazolidinediones. They are primarily insulin sensitizers that act mostly on muscle and fat tissue, and should not pose a risk of hypo-

glycemia if used alone. They also increase the size of low-density lipoprotein (LDL) particles, lower triglycerides levels, increase high-density lipoprotein (HDL) cholesterol levels,[21] and decrease high-sensitivity C-reactive protein levels[22]—all effects that should decrease atherogenesis.

An important side effect of these medications is fluid retention and, sometimes, a marked increase in peripheral edema and worsening of congestive heart failure. Therefore, they are contraindicated in patients with congestive heart failure requiring therapy. They are also contraindicated in patients with liver impairment.

Metformin is also an insulin sensitizer (acting primarily on the liver), and it should not cause hypoglycemia if used alone. It is the only antidiabetic medication that is not associated with weight gain, and may actually promote some weight loss. Metformin, too, has favorable effects on the lipid profile and it inhibits coagulation factors, leading to antiatherogenic effects.[23]

However, renal insufficiency (serum creatinine levels ≥1.5 mg/dL in men and ≥1.4 in women) is a contraindication to its use because of the possible development of severe and sometimes lethal lactic acidosis.

Acarbose inhibits alpha-glucosidase, an enzyme within the lumen of the small intestine that breaks down disaccharides into easily absorbable monosaccharides. Acarbose thus blunts the postprandial peak in blood glucose levels, and it has been shown to lower hemoglobin A1c levels modestly (by 0.5 to 0.6% absolute percentage points).[24]

This medication often causes gastrointestinal side effects and is rarely used as monotherapy because of its modest effect.

Insulin is the most appropriate therapy for this patient at this moment. Advantages: the patient does not have any contraindications to it, it has a short duration of action, and the dose can be adjusted on a daily basis depending on the results of home blood glucose monitoring.

Short-acting insulin secretagogues. Once her condition stabilizes, she may also be a good candidate for one of the short-acting insulin secretagogues that inhibit adenosine triphosphate-sensitive potassium channels on beta cells and restore the first phase of insulin secretion in patients with type 2 diabetes mellitus.[25] Nateglinide and repaglinide are currently available medications from this group.

Case continued

The patient is taught how to give herself insulin, and her glucose levels are well controlled with two daily injections of medium-acting (NPH) insulin and small doses of regular insulin with meals. She is discharged home on this regimen after her congestive heart failure is stabilized.

Acarbose is rarely used as monotherapy for type 2 diabetes

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