Alerts, Notices, and Case Reports

Hypoglycemia Associated With the Use of Fluoxetine

MARK A. DEEG, MD, PhD
EDWARD W. LIPKIN, MD, PhD
Seattle, Washington

HYPOGLYCEMIA HAS many causes in patients who do not have diabetes mellitus, in contrast to patients with diabetes mellitus, in whom hypoglycemia is most often due to the use of insulin or oral hypoglycemic agents. We report a case of symptomatic hypoglycemia associated with fluoxetine use in a patient with non–insulin-dependent diabetes mellitus. Symptoms of sweating, tremor, or anxiety occur in 10% or more of patients taking fluoxetine[1,2] and can easily be confused with hypoglycemia that occurs in diabetic patients.[3] In the case reported here, symptomatic hypoglycemia was associated with increased blood insulin levels during a 72-hour fast while the patient was taking fluoxetine. This case emphasizes the importance in evaluating the occurrence of hypoglycemia of discontinuing all nonessential medications during a 72-hour fast.

Report of a Case

The patient, a 53-year-old man diagnosed with non–insulin-dependent diabetes mellitus six years before admission, was treated with glyburide, 20 mg per day. Four months before admission, treatment with fluoxetine, 20 mg per day, was started for depression. The patient began having episodes of confusion, fatigue, dry mouth, and blurred vision. During some of these episodes, his blood glucose level was reportedly as low as 2.36 mmol per liter (43 mg per dl) as determined by self-monitoring. These episodes occurred paroxysmally, but his symptoms were relieved with food. A trial of discontinuing the glyburide was attempted, but his symptoms continued. In addition, while taking fluoxetine, the patient lost 13 kg (29 lb).

The patient was admitted to an outside hospital for a 72-hour fast to evaluate his hypoglycemia. He had stopped taking glyburide two weeks before admission but continued taking fluoxetine during the fast. During the second and third days of the fast, episodes of symptomatic hypoglycemia were noted. One episode occurred about 48 hours into the fast, with a blood glucose level of 2.1 mmol per liter (normal, 4.2 to 6.4) and a simultaneous serum insulin level of 129 pmol per liter (18 μU per ml; normal, 35 to 145 pmol per liter). A second episode occurred after 60 hours of fasting, with a blood glucose level of 2.4 mmol per liter, a serum insulin level of 237 pmol per liter, and a C-peptide value of 4.1 μg per liter (normal, 0.5 to 2.0). Insulin and C-peptide levels were determined by radioimmunoassay (Diagnostic Products Corporation). A urine specimen collected during the fast was negative for sulfonylureas as determined by high-performance liquid chromatography using an ultraviolet light detector (National Medical Services, Inc). Thyroid, liver, and renal function test results were normal, and anti-insulin antibodies were absent. An abdominal computed tomographic scan showed no pancreatic abnormality. Esophagogastroduodenoscopy and endoscopic ultrasonography revealed mild heterogeneity of the pancreatic head. The patient was referred to the University of Washington School of Medicine (Seattle) for further evaluation of an insulinoma.

The patient was admitted two months later for a second 72-hour fast. Glyburide had not been used between the fasts, and fluoxetine was discontinued 24 hours before the second fast. During the second fast, no hypoglycemic symptoms were noted. Blood glucose levels ranged from 3.8 to 7.8 mmol per liter, with serum insulin concentrations of 43 to 108 pmol per liter. No further testing was done, and the patient was discharged.

Hyperglycemia later developed, and glyburide therapy was reinstituted at a lower dose. At the discretion of the practicing physician, the use of fluoxetine was continued for depression. The patient continued to have episodes of hypoglycemia, albeit less severe.

Discussion

Hypoglycemic symptoms result from the release of counterregulatory hormones and neuroglycopenia. As blood glucose levels begin to decrease, the initial symptoms of hypoglycemia, including tremors, diaphoresis, and palpitations, occur from the release of epinephrine. Neuroglycopenic symptoms of lethargy, confusion, and loss of consciousness occur with further decreases in the blood glucose concentration. Causes of hypoglycemia include drugs, excess insulin production—insulinoma—anti-insulin antibodies, and concomitant diseases that may compromise glucose production.

In evaluating hypoglycemic symptoms, the documentation of hypoglycemia (<2.2 mmol per liter) at the time of symptoms is required (one of the diagnostic criteria in Whipple's triad[4]). Occasionally this can be accomplished on an outpatient basis, but the standard protocol is a 72-hour fast with frequent taking of blood specimens to correlate symptoms with glucose, insulin, and C-peptide levels.[5] Insulin-mediated hypoglycemia is associated with an inappropriately elevated insulin level (>43 pmol per liter) at the time of hypoglycemia. Other pancreatic islet β-cell peptides can be used to differentiate between the various insulin-mediated hypoglycemias.[5]

In the case reported here, the hypoglycemia was clearly associated with symptoms and, by history, relieved with food. The elevated serum insulin and C-

(Deeg MA, Lipkin EW: Hypoglycemia associated with the use of fluoxetine. West J Med 1996; 164:262-263)

From the Division of Metabolism, Endocrinology, and Nutrition, Department of Medicine, University of Washington School of Medicine, Seattle.

Reprint requests to Mark A. Deeg, MD, PhD, Division of Metabolism, Endocrinology, and Nutrition, University of Washington School of Medicine, Box 356426, Seattle, WA 98195-6426.

peptide concentrations during the first 72-hour fast are consistent with an endogenous insulin-mediated hypoglycemia. Oral hypoglycemic agent use seems unlikely because sulfonylureas were absent in the urine. These laboratory results mimic those expected for an insulinoma. When fluoxetine was discontinued before the second 72-hour fast, however, no hypoglycemia was noted, suggesting that fluoxetine use during the first 72-hour fast contributed to the disorder.

It is unclear whether fluoxetine use per se induced the hypoglycemia or if it potentiated a glyburide-induced hypoglycemia. Hypoglycemia from sulfonylureas can occur 48 to 72 hours after the last dose.[6] Because by history the patient discontinued glyburide use two weeks before fasting, glyburide-induced hypoglycemia seems unlikely. The absence of sulfonylureas in the urine is consistent with this conclusion, but sulfonylurea use during the fast cannot be entirely discounted because assays for sulfonylureas may not have the sensitivity for low levels of second-generation sulfonylureas and their metabolites.[7]

Many drugs have been shown to potentiate the hypoglycemic effects of sulfonylureas by altering either the pharmacokinetics of sulfonylurea metabolism or pharmacodynamic interactions.[6] Pharmacokinetic data suggest that with multiple dosing of glyburide, the drug equilibrates with a slowly turning over compartment, possibly adipose tissue.[8] It is conceivable that fluoxetine use potentiated the hypoglycemic effect of glyburide by displacing glyburide from this compartment. Discontinuing glyburide 14 days before the fast would seem to rule out this possibility because the slowly turning over compartment would have to have a half-life of more than three days.

Numerous drugs can induce hypoglycemic symptoms with or without hypoglycemia. The side-effect profile of fluoxetine overlaps with hypoglycemia, and this appears to be a common property of selective serotonin-reuptake inhibitors. In this case, however, hypoglycemic symptoms associated with the use of fluoxetine appeared to be caused by a low-blood glucose level. A poorly documented case of symptomatic hypoglycemia associated with fluoxetine use has been reported elsewhere.[9]

Fluoxetine has been used to treat obese patients with non–insulin-dependent diabetes to induce weight loss.[10,11] These studies noted an improvement in glycemic control with the administration of fluoxetine, 60 mg per day, as manifested by a decrease in hemoglobin A_{1C} levels in conjunction with a decrease in caloric intake and an average weight loss of 4 to 6 kg (9 to 13 lb). No episodes of hypoglycemia were reported in these studies. The improvement in glycemic control in these studies is likely due to weight loss. The weight loss this patient experienced likely accounted for the improved glycemic control, allowing the discontinuation of glyburide before and the normal glucose levels during the second fast, but it would not account for the hypoglycemia. In addition, fluoxetine has been shown to improve peripheral insulin action and decrease hepatic glucose production in insulin-resistant patients.[12]

In prescribing selective serotonin-reuptake inhibitors to diabetic patients, the American Hospital Formulary Service recommends careful monitoring of blood glucose levels in all patients with diabetes initiating or discontinuing these agents.[13] This seems practical advice concerning the use of this class of agents in these patients, especially those on concomitant sulfonylurea therapy, as illustrated in this case. We also recommend that in evaluating hypoglycemic symptoms in patients taking selective serotonin-reuptake inhibitors, stopping the medication should be an initial diagnostic maneuver. This case also emphasizes that in evaluating hypoglycemia, all nonessential medications should be stopped during the 72-hour fast.

REFERENCES

1. Wernicke JF: The side effect profile and safety of fluoxetine. J Clin Psychiatry 1985; 46(pt 2):59-67

2. Cooper GL: The safety of fluoxetine—An update. Br J Psychiatry 1988; 153(suppl 3):77-86

3. Lear J, Burden AC: Fluoxetine side-effects mimicking hypoglycaemia (Letter). Lancet 1992; 339:1296

4. Whipple AO: The surgical therapy of hyperinsulinism. J Int Chir 1938; 3:237-276

5. Service FJ: Hypoglycemic disorders. N Engl J Med 1995; 332:1144-1152

6. Jackson JE, Bressler R: Clinical pharmacology of sulphonylurea hypoglycaemic agents: Part 2. Drugs 1981; 22:295-320

7. Rogers HJ, Spector RG, Morrison PJ, Bradbrook ID: Pharmacokinetics of intravenous glibenclamide investigated by a high performance liquid chromatographic assay. Diabetologia 1982; 23:37-40

8. Balant L, Zahnd GR, Weber F, Fabre J: Behaviour of glibenclamide on repeated administration to diabetic patients. Eur J Clin Pharmacol 1977; 11:19-25

9. Katz LM, Fochtmann LJ, Pato MT: Clomipramine, fluoxetine, and glucose control. Ann Clin Psychiatry 1991; 3:271-274

10. O'Kane M, Wiles PG, Wales JK: Fluoxetine in the treatment of obese type 2 diabetic patients. Diabet Med 1994; 11:105-110

11. Gray DS, Fujioka K, Devine W, Bray GA: Fluoxetine treatment of the obese diabetic. Int J Obes 1992; 16:193-198

12. Potter van Loon BJ, Radder JK, Frölich M, Krans HMJ, Zwinderman AH, Meinders AE: Fluoxetine increases insulin action in obese nondiabetic and in obese non-insulin-dependent diabetic individuals. Int J Obes 1992; 16:79-85

13. McEvoy GK (Ed): American Hospital Formulary Service 1995: Drug Information. Bethesda, Md, American Society of Health-System Pharmacists, 1995, pp 1483-1495

Conflict of Ethics and Practice in Hospitalized Patients Who Want to Smoke

JAMES CHAPPELL, MD
MARLON ILAGAN, MD
RICHARD L. ALLMAN, MD
ETIENNE J. PHIPPS, PhD
Philadelphia, Pennsylvania

THE MEDICAL PROFESSION views smoking as a major health hazard and encourages physicians to help patients

(Chappell J, Ilagan M, Allman RL, Phipps EJ: Conflict of ethics and practice in hospitalized patients who want to smoke. West J Med 1996; 164:263-266)

From the Department of Medicine, Albert Einstein Medical Center, Philadelphia, Pennsylvania.

Reprint requests to Etienne J. Phipps, PhD, Dept of Medicine, Albert Einstein Medical Center, 5401 Old York Rd, Philadelphia, PA 19141.