Severe Hypoglycemia Associated With Trimethoprim-Sulfamethoxazole Therapy

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Abstract: Hypoglycemia associated with sulfamethoxazole therapy in patients with chronic renal insufficiency has previously been documented. We report the case of an elderly patient with relatively normal renal function who developed severe hypoglycemia associated with trimethoprim-sulfamethoxazole therapy. (JABFP 1988; 1: 143-5.)

Severe hypoglycemia has been reported as an unusual adverse reaction associated with sulfamethoxazole therapy as well as other sulfonamides. Two previously reported patients had significant chronic renal insufficiency,[1,2] but our report describes a patient without overt renal failure who developed severe hypoglycemia associated with sulfamethoxazole.

Case Report

An 88-year-old woman was seen in the emergency department for recurrent urinary tract infection secondary to an indwelling Foley catheter for longstanding urinary incontinence. Her other problems included a nonfunctioning right kidney (congenital), right hip prosthesis, anemia of chronic disease, and chronic back pain from osteoporosis. Her only medication was an acetaminophen-propoxyphene combination as needed for pain. A combination antibiotic containing 160 mg trimethoprim and 800 mg sulfamethoxazole (Bactrim DS™) was prescribed, one tablet twice a day, and she was discharged to her home.

Four days later, while eating lunch, the patient dropped her milk and overturned her plate. Her eyes rolled back, and she apparently had a seizure with tonic-clonic movements. En route to the hospital, ambulance personnel counted her heart rate in the mid-forties, with occasional ventricular premature beats. Her speech was garbled, but she was alert. A 5 percent dextrose solution was started at 40 mL/hr intravenously.

The initial exam revealed a chronically ill elderly woman with kyphosis, whose speech was unintelligible but who seemed alert. She was not oriented to time and place but had no other focal neurological findings. Her blood pressure, respiration, and pulse were stable. Cardiac exam revealed a slightly irregular rhythm at 55/min without murmur. A stat glucose was 33 mg/dL, and she was given 50 mL of 50 percent dextrose solution intravenously. Her mental status improved promptly, and the intravenous (IV) solution was subsequently changed to 10 percent dextrose in half normal saline.

During the next 24 hours, the patient's glucose measurements dropped as low as 28 mg/dL, with most ranging from 40 to 90 mg/dL. Hypoglycemia persisted even though she received 270 grams of intravenous dextrose and approximately 1,000 calories of a regular diet. After 24 hours, the patient was maintained on 10 percent dextrose in half normal saline IV with blood glucose ranging from 126–200 mg/dL. The IV was discontinued at 72 hours, and the patient then maintained normal serum glucose.

After admission, the trimethoprim-sulfamethoxazole combination was discontinued. Blood and urine cultures were negative, and the patient received no additional antibiotics. Myocardial enzymes were not elevated, and subsequent electrocardiograms revealed no changes from admission except disappearance of the premature ventricular contractions and resolution of the bradycardia. During hospitalization, the patient's mental status remained clear. The only medication she received on a regular basis was

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the acetaminophen-propoxyphene combination for pain.

Other than the severe and persistent hypoglycemia, most of the patient's laboratory tests were normal during her hospitalization. Abnormal values included a hemoglobin 11.8 g/dL, hematocrit 35 percent, albumin 2.9/dL, and gamma-glutamyltranspeptidase (GGTP) 76 IU/L. Serum and urine drug screens, including ethanol, were negative. Urinalysis revealed occasional hyaline casts, innumerable white blood cells per high-power field, one to two red blood cells per high-power field, a few budding yeasts, but a negative culture. Computerized tomography of the abdomen was unremarkable. Serum cortisol on admission was normal. Insulin and C-peptide levels were drawn initially, but subsequently lost. The patient's BUN/creatinines on admission were 20 mg/dL/1.2 mg/dL, and on discharge, they were 14 mg/dL/0.9 mg/dL. The creatinine clearance was 35 mL/min.

Discussion

This patient presents an unusual complication of sulfamethoxazole therapy, namely, severe hypoglycemia without chronic renal failure in contrast to two other reports of patients who had chronic renal failure; one of whom was given large doses of sulfamethoxazole.[1,2] Renal failure predisposes to hypoglycemia,[4-6] and these patients had creatinines that were 6.1 mg/dL and 11.0 mg/dL, respectively. Our patient had a normal creatinine, although her creatinine clearance was decreased.

Other causes of hypoglycemia include sepsis, liver failure, endocrinologic dysfunction, and inanition. Although our patient was chronically ill and was not a vigorous eater, she had a breakfast of toast, jelly, and juice on the morning of admission. She also ingested vegetables and milk just before her mental status deteriorated, so there is no reason to believe she was in a fasting state. Moreover, there was no laboratory evidence of endocrinologic dysfunction, and the patient has not required hospital treatment in 13 months since the reported admission. Although hypoglycemia has been reported with propoxyphene,[7] our patient has continued to take this drug without any problem.

Elevated blood insulin levels were reported in the two other patients cited[1,2]; this was attributed to decreased catabolism and increased secretion of endogenous insulin caused by sulfonamide therapy.

Sulfonamide was first observed to produce hypoglycemia in 1942 during a study on the treatment of typhoid fever; however, no practical use was made of this until 1955 when carbutamide, an antibacterial, was shown to reduce blood glucose.[8] This opened the way for the development of sulfonylurea compounds now used in the treatment of diabetes mellitus. Sulfamethoxazole is structurally similar to sulfonylurea in possessing an amine group attached to a sulfur molecule.

The sulfonylurea compounds stimulate insulin secretion from the beta cells in the pancreas. They may also have indirect long-term extrapancreatic effects that include increasing the number of peripheral insulin receptors and reducing hepatic glucose production.[9] The sulfonylurea compounds and sulfonamides are metabolized by the liver, and their metabolites are excreted by the kidneys.[8] Considering the similar chemical structure and metabolism of these compounds, the hypothesis that sulfamethoxazole could function in the same manner as the sulfonylureas seems tenable. This hypothesis could account for the increased insulin levels noted in the previous reports and is the most likely reason for our patient experiencing severe hypoglycemia. It is also interesting that our patient remained hypoglycemic during the first 24 hours despite receiving what seemed adequate glucose intravenously and taking calories by mouth. The half-life of sulfamethoxazole is 6 to 12 hours,[8] which would fit the hypoglycemic profile of our patient.

Our patient had a number of risk factors that might have predisposed her to hypoglycemia. Her appetite was poor, and her glycogen stores were probably marginal. Although her creatinine was normal, her creatinine clearance was decreased, as would be expected in an 88-year-old person with only one functioning kidney. While the dose of trimethoprim-sulfamethoxazole was the standard dose for treatment of urinary tract infection, it may have been excessive for a chronically ill elderly woman with impaired renal function. Although serum levels of sulfamethoxazole were not measured in our patient, they were probably elevated, which could easily account for hyperinsulinemia and prolonged hypoglycemia.

Summary

An elderly patient was treated with sulfamethoxazole and developed severe and prolonged hypoglycemia. Previously reported cases involved

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individuals with significant decreases in renal function. This patient had relatively normal renal function as measured by BUN and creatinine, but there was an age-related decrease in creatinine clearance. Given the frequency of trimethoprim-sulfamethoxazole therapy, it seems appropriate to recommend decreasing the dosage for elderly patients with impaired renal function, and to call attention to hypoglycemia as a possible adverse reaction.

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