Old, But Not Outdated: Tolbutamide-Induced Refractory Hypoglycemia

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Sulfonylureas have been used to treat patients with diabetes for the last 80 years. The main side effect of this drug class is hypoglycemia, which might be severe and protracted. With the emergence of new medications with improved safety and better efficacy in preventing diabetes complications and cardiovascular morbidity and mortality, the use of these agents is waning.

Sulfonylureas are historically classified into two generations. The first generation includes drugs such as tolbutamide and chlorpropamide, which are no longer used. The second generation includes glibenclamide and glimepiride, which have different pharmacokinetic properties and active metabolites.

In this case report, we present a patient with diabetes and end-stage renal disease (ESRD) who developed prolonged hypoglycemia following the unauthorized use of a food supplement containing the first-generation sulfonylurea - tolbutamide.

PATIENT DESCRIPTION

A 68-year-old man presented to our emergency department due to a syncopal episode. He had a history of long-standing uncontrolled type 2 diabetes and ESRD, which required hemodialysis. He also had hypertension and severe peripheral vascular disease and had previously undergone a below-left knee amputation.

Prior to his admission, his wife noticed that he had developed drowsiness. His capillary blood glucose level was 30 mg/dl (1.7 mmol/L). He was aroused after a glucagon injection followed by a meal, and his glucose increased to 220 mg/dl (12.2 mmol/L). Nevertheless, he experienced another episode of hypoglycemia with drowsiness a few hours later. He was referred for evaluation at a local emergency medical center. He was treated with intravenous (IV) glucose and showed rapid but transient recovery. He was then referred to the emergency department of our medical center, where his glucose level was 41 mg/dl (2.3 mmol/L). The patient's wife mentioned that he was taking an unauthorized food supplement called Vedanate, known to contain the sulfonylurea tolbutamide [1]. Further evaluation demonstrated a morning cortisol level of 1092 nmol/l, and no signs of infection. He has treated with IV glucose infusion and subcutaneous octreotide 50 mg and admitted to the intensive care unit for close monitoring of blood glucose levels and octreotide treatment every 6 hours. After 24 hours, octreotide was discontinued, and the glucose infusion rate was reduced. C-peptide and insulin levels during hypoglycemia were 281 pmol/l (reference range 22–180 pmol/l) and 5476 pmol/l (reference range 268–1274), respectively. During the next 7 days, any attempt to stop the glucose infusion resulted in recurrent hypoglycemia [Figure 1].

Screening for sulfonylureas in plasma was negative; however, it turned out that the assay could detect second-generation, but not first-generation, sulfonylureas and therefore failed to identify tolbutamide.

On his 16th day of admission, an abdominal computed tomography (CT) scan was performed to further evaluate the persistent hypoglycemia. No pancreatic lesion or any other suspicious tumor was identified. A second course of octreotide was initiated, and the hypoglycemia gradually resolved over the next few days, allowing for discontinuation of the glucose infusion. Subsequently, the patient was transferred from the intensive care unit to the medical ward, and the octreotide was stopped.

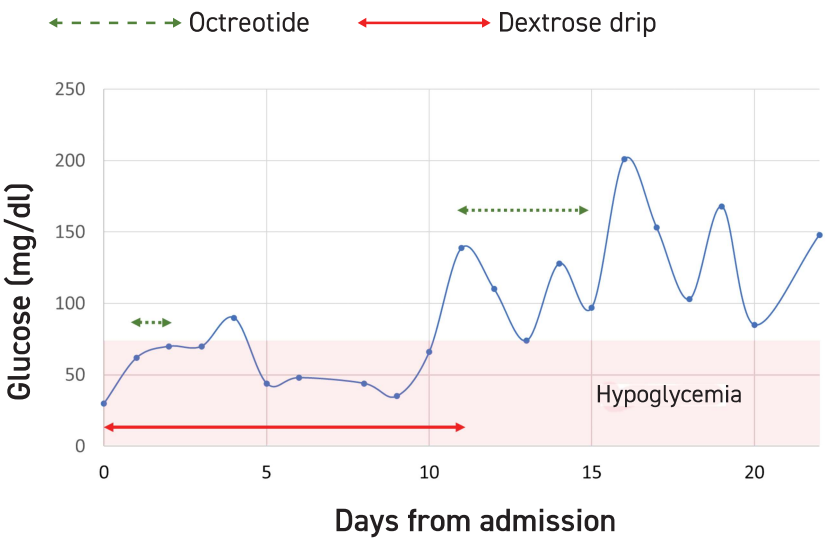
The patient was discharged after 21 days with no evidence of repeated hypoglycemia.

COMMENT

Tolbutamide is a first-generation sulfonylurea that acts as an insulin secretagogue by closing of the ATP-sensitive K+ channels. It is metabolized in the liver by CYP2C9. The medication and its metabolites are mainly excreted by the kidneys (75–85% are excreted in the form of its metabolites). The use of tolbutamide was abandoned in the 1970s due to concerns regarding its cardiovascular safety [2]. This treatment was associated with an increased risk for hypoglycemia due to its long half-life and multiple drug interactions with salicylates.

In our case, the patient informed the medical staff that he was consuming a herbal remedy for the treatment of diabetes, which turned out to contain tolbutamide. Tolbutamide is metabolized in the liver into two active molecules: hydroxymethyl tolbutamide, which has a mild glucose

Figure 1. Glucose level and treatments during hospitalization. Treatments included dextrose 5% or 10% drip (solid line) and octreotide (dotted line). The cutoff for hypoglycemia was below 70 mg/dl (3.9 mmol/L).



lowering effect, and carboxytolbutamide, which is inactive. We assumed that, in our case, delayed clearance of tolbutamide and its active metabolite due to the presence of ESRD resulted in prolonged, refractory severe hypoglycemia.

Genetic alterations of genes regulating tolbutamide metabolism can probably cause the patient to develop hypoglycemia. Scott and colleagues [3] found approximately 12 mutations that affect the activity of the drug's metabolizing enzymes, which might have marked effects on the rate of tolbutamide clearance.

The patient was treated with low-dose aspirin for primary prevention of cardiovascular disease. Regarding the pharmacological interaction between tolbutamide and acetylsalicylic acid, Cattaneo and co-authors [4] demonstrated that in addition to the known effect of high-dose ASA on pancreatic beta cells causing insulin secretion, it may increase free-tolbutamide concentrations in the plasma and therefore can further exacerbate hypoglycemia.

CONCLUSIONS

We described an unusual case of severe hypoglycemia in a patient with type 2 diabetes and ESRD who had taken a food supplement containing tolbutamide, an outdated sulfonylurea. This case emphasizes the importance of recognizing the potential risks associated with obsolete drugs, their metabolism, and potential drug interactions. Furthermore, it highlights the need for caution when using food supplements, as they may contain potentially harmful compounds. Healthcare professionals should be vigilant in identifying and managing adverse drug events, and patients should be educated about the potential risks of using unregulated products.

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Capsule

Old selection affects modern health

The immune system is a constant and repeated target of natural selection. **Kerner** and colleagues used a wide array of ancient and modern European DNA to assess selection on immune-related alleles in humans. The authors modeled allele frequency trajectories for over 1 million variants, finding 89 independent loci predicted to be under positive selection since the Neolithic period. Many of these variants were associated with hematopoietic traits such as platelet and reticulocyte counts, autoimmune diseases, and infection. This finding indicates that these traits have been directly affected by selection in Europeans and supports the idea that increased protection from infectious disease may concomitantly increase the risk for autoimmunity.

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