

# Successful Treatment of Prolonged Sulfonylurea-Induced Hypoglycemia with Octreotide in a Patient with Chronic Renal Failure: Case Report

## Kronik Böbrek Yetmezlikli Bir Hastada Sülfonilüreye Bağlı Uzamış Hipoglisemide Oktreotid'le Başarılı Tedavi

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**ABSTRACT** Patients who present to the emergency department after ingestion of excessive amounts of sulfonylurea medications have hypoglycemia refractory to dextrose administration. Recently, the use of octreotide was described as an alternative treatment in such patients. A diabetic patient with chronic renal failure who ingested excessive amounts of sulfonylurea medications causing refractory hypoglycemia resistant to treatment with large doses of intravenous dextrose was presented here. Octreotide administration rapidly reversed hypoglycemia allowing the patient's stabilization and eventual discharge without any significant adverse events. We believe that octreotide may be an effective therapy in refractory sulfonylurea-induced hypoglycemia.

**Key Words:** Sulfonylurea receptor; kidney failure, chronic; hypoglycemia; octreotide

**ÖZET** Aşırı miktarda sülfonilüre alımından sonra acil servise başvuran hastalar dekstroz uygulamasına dirençli hipoglisemiye sahiptirler. Son zamanlarda bu hastaların tedavisinde yeni bir alternatif olarak oktreotidin kullanımı tanımlanmıştır. Burada aşırı miktarda sülfonilüre alan yüksek dozda intravenöz dekstroz tedavisine dirençli hipoglisemiye sahip kronik böbrek yetmezlikli bir hasta sunuldu. Oktreotid uygulaması herhangi bir yan etki olmaksızın hastanın stabilizasyonu ve taburcu olmasını sağladı. Biz sülfonilüreye bağlı olarak gelişen dirençli hipoglisemide oktreotidin alternatif bir tedavi olabileceğini öne sürüyoruz.

**Anahtar Kelimeler:** Sülfonilüre; böbrek yetmezliği; hipoglisemi; oktreotid

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Sulfonylurea (SU) agents are commonly used to treat hyperglycemia in type II diabetes mellitus (DM). The predictable major side effect of these agents is hypoglycemia.<sup>1</sup> Hypoglycemia was defined as a glucose level less than 60 mg/dL (3.33 mmol/L).<sup>2</sup> Second generation SU drugs are glyburide, glipizide, and gliclazide. These newer drugs have a greater hypoglycemic effect per miligram than previous agents.<sup>3</sup>

In patients with chronic renal failure (CRF) using these drugs, the risk of hypoglycemia is high and it may often be prolonged.<sup>4,5</sup> Traditional therapies in patients who develop hypoglycemia with the use of SU agents include intravenous (iv) and oral glucose, glucagon and diazoxide. In spite of

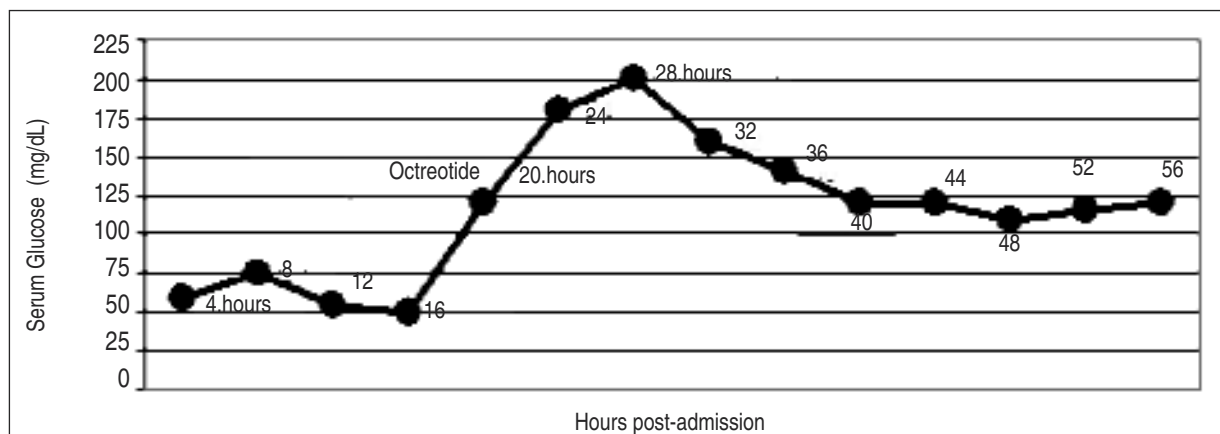


FIGURE 1: Changes in serum glucose over time before and after octreotide therapy.

these treatments, hypoglycemia frequently recurs, because glucose is a potent stimulus for the release of more pre-formed insulin.<sup>5</sup> Numerous studies show that longer-acting SU drugs are associated with a higher risk of hypoglycemia, including serious hypoglycemia.<sup>6</sup> Gliclazide (second generation SU) has been widely used as therapy for hyperglycemia in type 2 diabetes in our country, and its duration of action is 12 h.<sup>1</sup> Gliclazide and glipizide were shown to cause less hypoglycemia than glibenclamide, and one study suggested that glimepiride was safer than glibenclamide. There are no published reports comparing glimepiride directly with gliclazide or glipizide for hypoglycemia.<sup>7</sup> Octreotide acetate is a synthetic octapeptide analogue of human somatostatin that directly inhibits insulin secretion from the pancreas and prevents rebound hypoglycemia.<sup>8,9</sup>

We present a case of a 46-year-old man who ingested 2400 mg of gliclazide causing refractory hypoglycemia resistant to treatment with iv dextrose.

A 46 year-old man with a history of attempting suicide after ingesting 30 tablets (80 mg tablet) of gliclazide (approximately 2400 mg) less than 4 h previously was admitted to the emergency department (ED). He had two more episodes of hypoglycemia over the next 4 hours until arriving ED. He had a history of type 2 DM for 10 years, managed with diet and sustained-release gliclazide (Diamicron 80 tb) 160 mg daily. In addition, he had a history of CRF for 5 years, managed as End Stage

Renal Disease (ESRD). He had had ESRD 2 days previously. On admission his blood pressure was 130/70 mmHg. The heart rate was 90 beats/min, respiratory rate 24/minute and axillary temperature 36.8°C. Finger prick glucose recorded 10 min after admission was 40 mg/dL (glucose measurements were obtained using a calibrated bedside glucometer). Serum electrolytes (Na, K, Ca, Cl) were measured in the normal range. He had no other medical problems. He was noted to be tremulous and diaphoretic but was alert and oriented. Due to the lack of inpatient beds, the patient was managed entirely in the ED observation unit. He was started on iv 10% dextrose at 100 cc/h. He was monitored in the ED with vital signs and finger prick glucose determinations every hour. The patient continued to have recurrent hypoglycemia not responsive to repeated administration of iv 10% dextrose. Approximately 8 h after ED admission, the measured glucose did not improve to greater than 75 mg/dL. After 16 h in the ED and with recurrent hypoglycemia, the patient was administered subcutaneous (sc) octreotide 50 µg along with iv 10% dextrose for a finger prick glucose of 50 mg/dL. Following the administration of octreotide, there was prompt improvement in the blood sugar level, with abolition of hypoglycemic episodes. The changes in blood glucose levels after octreotide were shown in Figure 1. His blood sugar normalized and iv 10% dextrose infusion was stopped over the next 8 hours. Once he started to tolerate oral feeding, he was discharged from the ED observation unit 56 h after

admission, in good condition. In addition to at least two meals and oral dextrose supplementation, the patient had received a total of 2400 mL (240 grams) of 10% dextrose before stabilization with sc 50 µg octreotide. Psychiatric evaluation of the patient in the ED revealed no indication for inpatient care, and follow up with the psychiatric service was arranged. He later agreed to receive hemodialysis, and he continues to receive maintenance hemodialysis at our facility. We monitored C-peptide levels by radioimmunoassay to assess the impact on insulin release. The levels of C-peptide, which were initially high, were suppressed.

## DISCUSSION

SU agents are widely used as therapy for hyperglycemia in type 2 DM and they may cause potentially life-threatening hypoglycemia with overdose. These agents produce hypoglycemia primarily by depolarizing pancreatic  $\beta$  cells and facilitating preformed insulin release.<sup>1</sup> Treatment of SU-induced hypoglycemia includes iv administration of dextrose and frequent monitoring of blood glucose concentrations. Dextrose infusion, which is readily available in most hospitals is cheap and is the first line treatment for SU-induced hypoglycemia. Unfortunately, dextrose itself is a potent stimulus for additional insulin release in SU-exposed patients and frequently results in rebound hypoglycemia that may be recurrent and prolonged.<sup>9-12</sup> Patients with significant SU poisoning require intensive monitoring, central venous access for hypertonic dextrose administration, and blood glucose measurements every 20 to 60 minutes because of recurrent hypoglycemia. Diazoxide, an antihypertensive drug, is the traditional second line agent for severe SU-induced hypoglycemia. It was used to reduce insulin release and limit rebound hypoglycemia; however, its efficacy appears limited primarily by significant side effects, which include hypotension, nausea, vomiting, reflex tachycardia and fluid retention.<sup>9,13</sup> Glucagon, a naturally occurring hormone, works by recruiting hepatic glycogen stores and inducing gluconeogenesis, although its success is partially dependent on the adequacy of glycogen stores.<sup>14,15</sup> Iv glucagon may also release insulin, an

unwanted effect in the setting of SU-induced hypoglycemia.<sup>16</sup> Although the use of glucagon may transiently increase blood glucose levels, hyperinsulinemia may be exacerbated and hypoglycemia may again recur. Despite these therapies hypoglycemia may recur, or persist for several reasons. First, the administration of iv dextrose may be a potent stimulus for further insulin release.<sup>10,11</sup> Second, in CRF some SUs many have altered pharmacodynamic effects that predispose to hypoglycemia.<sup>17,18</sup> Third, reduced insulin degradation in CRF predisposes to hypoglycemia.<sup>5</sup> In this patient, the hypoglycemia was most likely of multifactorial origin; though the use of SU in the face of severe CRF was the most dominant factor. The patient had decreased oral intake, which is a well known risk factor for hypoglycemia.<sup>2,16-17</sup> Octreotide, a synthetic somatostatin analog, is known to suppress the secretion of numerous hormones including glucagon, growth hormone, gastrin, vasoactive intestinal peptide and most importantly here insulin.<sup>10</sup> It has been used for a variety of gastrointestinal, endocrine, and surgical indications. In the setting of SU-induced hypoglycemia, octreotide directly inhibits insulin secretion from the pancreas and prevents rebound hypoglycemia.<sup>9,10</sup> Octreotide has been successfully used to treat hypoglycemia due to hyperinsulinemic state associated with SU overdoses and insulinomas.<sup>2,9,10,13,14,19-25</sup> The rapid improvement in the neurological status and resolution of hypoglycemia in our patients was consistent with the experience with this agent in other previous reports of hyperinsulinemic hypoglycemia. The precise mechanisms of the hyperglycemic effect of octreotide in our patient is unknown, but suggestions include suppression of insulin release (with decreased C peptide levels), increased hepatic glucose output, and decreased peripheral glucose uptake.<sup>20,24</sup> Octreotide was administered approximately 20 h after ingestion of 2400 mg gliclazide. Yet, our view is supported by the fact that our patient had refractory hypoglycemia despite the administration of 2400 mL (240 grams) of 10% dextrose and only after the addition of octreotide the glucose level stabilized in the normal range for any duration. Boyle et al. concluded that octreotide was superior to both

dextrose and diazoxide in the treatment of SU-induced hypoglycemia.<sup>9</sup> McLaughlin et al. found that recorded hypoglycemic episodes were significantly less common after octreotide administration in 9 patients with SU overdose.<sup>2</sup> Moreover, the patients' dextrose requirements were much less after octreotide administration. The fact that C peptide levels decreased in our patient favors a role for decreased insulin release in this effect. Experimental data support the view that in pancreatic  $\beta$  cells, octreotide binds to the somatostatin (sub-type 2) receptor, which is attached to the voltage gated calcium channel via a G-protein.<sup>25,26</sup> Inhibition of this calcium channel reduces calcium influx, leading to inhibition of insulin release. Octreotide is well absorbed through sc or iv route. The elimination half life is

reported to be 1.5 hours.<sup>8</sup> Side effects reported with this agent included headache, nausea, abdominal discomfort and pain at injection site.

## CONCLUSION

Based on our case report and previous reports, we suggest that octreotide should be considered for first-line therapy in the treatment of hypoglycemia secondary to SU overdose in diabetic patients with CRF. All patients must be carefully monitored for recurrent hypoglycemia during octreotide therapy and for perhaps 24 hours following termination of octreotide therapy before discharge.<sup>7</sup> Continuing research is required to better define the optimal dose, dosing interval, and inpatient monitoring requirements.

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