

## SEVERE SULFONYLUREA-INDUCED HYPOGLYCEMIA: A CASE REPORT

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## ABSTRACT

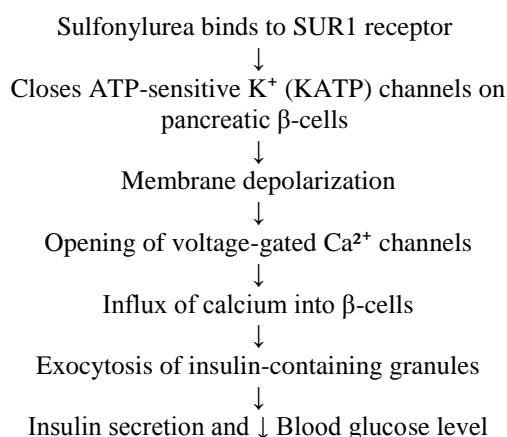
Sulfonylureas are commonly used medications in diabetes due to their lower cost. However, Sulfonylureas use is associated with severe hypoglycemia. Here is a case of 74 year old female with type 2 diabetes mellitus who was taking regular doses of glyburide 5mg daily and metformin 1000mg twice daily. She presented to emergency department after her family noticed acute onset of confusion, disorientation, and unresponsiveness, with an initial blood glucose reading of 45mg/dl. She appeared pale, was excessively sweating and had a slow heart rate. She had chronic type 2 diabetes mellitus, poorly controlled for the last 6 months. Her serum creatinine was increased to 3mg/dl from a baseline value of 0.9 mg/dl measured 2 weeks before admission. The patient had no signs of infection, trauma, or other acute illness and was diagnosed as severe hypoglycemia due to Sulfonylurea overdose. Immediately intravenous dextrose infusion was started with 50ml of 50% dextrose. The patient was closely monitored in ICU with frequent blood glucose levels measurements. According to Beers criteria, sulfonylureas are usually avoided in geriatric diabetic patients with renal or hepatic dysfunction due to the increased risk of severe hypoglycemia. After stabilization sulfonylurea medication (glyburide) was stopped and patient's diabetes regimen was modified to a lower dose of insulin therapy to avoid further hypoglycemic episodes.

**KEYWORDS:** Sulfonylureas, Hypoglycemia, Type2 Diabetes Mellitus, Beers Criteria.

## INTRODUCTION

A Severe Sulfonylurea-induced hypoglycemia is a potentially dangerous and life-threatening condition caused by the use of Sulfonylureas in diabetes mellitus type 2.<sup>[1]</sup> Sulfonylureas bind to sulfonylurea receptor in pancreatic beta cells and inhibit ATP-sensitive potassium channels, causing decreased potassium efflux and resulting in membrane depolarization. This depolarization opens calcium channels, allowing calcium influx which increases intracellular calcium levels, ultimately stimulating insulin secretion independent of blood glucose levels.<sup>[1][3]</sup> Hypoglycemia occurs when blood glucose levels drop below 70 mg/dl.<sup>[2]</sup> Hypoglycemia is suspected in patients with typical symptoms such as confusion, irritability, anxiety or nervousness, hunger, headache, sweating, blurring of vision, dizziness, fatigue, tingling around mouth. Common signs include diaphoresis, pallor, tremors, tachycardia, altered mental status, loss of consciousness, seizures, unresponsiveness, hypothermia in severe cases.<sup>[1][2][4]</sup> The American Geriatrics Society (AGS) released the 2023 update to Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, which recommends avoiding sulfonylureas in geriatric patients with type 2 diabetes mellitus and renal or hepatic dysfunction.<sup>[5]</sup> We report a case of severe hypoglycemia associated with Sulfonylureas in an elderly patient with

type 2 diabetes mellitus and acute kidney injury. Mechanism of action of Sulfonylureas is as follows in Figure 1.



**Figure 1: showing mechanism of action of Sulfonylureas.**

## Case Presentation

A 74-Year-old-female with a long history of atrial fibrillation, heart failure, anemia, type 2 diabetes mellitus, tobacco use disorder was admitted to emergency department with acute onset of confusion, disorientation and unresponsiveness as noticed by the

family with initial blood glucose level of 45 mg/dl. she was sweating profusely, appeared pale and had a bradycardiac pulse during presentation. there was no associated history of trauma, infection, recent illness or changes in diet or physical activity. her medical history included chronic type 2 diabetes mellitus, poorly controlled for last 6 months. she had a known history of sulfonylurea use (especially glyburide) for the past 5 years with regular doses of 5mg daily. previous episodes of mild hypoglycemia were reported, but none as severe as current episode. she was adherent to her diabetic medications, including glyburide 5mg daily and metformin 1000mg twice daily. Her blood glucose level 14 days before admission was 64mg/dl and on the day of admission was 51mg/dl. On the day of admission, her serum creatinine level was increased to 3 mg/dl from a

baseline value of 0.9mg/dl, blood urea nitrogen level was 47 mg/dl, EGFR level is 16 ml/min/1.73m<sup>2</sup>, renal function tests showed acute kidney injury, sodium was 137 mg/dl and potassium level was 4.5 mg/dl. EKG shows sinus bradycardia without any other changes. serum insulin levels were elevated, indicating excessive insulin secretion. Diagnosis of Severe hypoglycemia due to sulfonylurea overdose was made. Immediately intravenous dextrose infusion was started (50 ml of 50% dextrose) and the patient was closely monitored in ICU with frequent measurement of blood glucose levels. After stabilization, glyburide was stopped, and patients diabetes regimen was modified to insulin therapy to avoid further hypoglycemic episodes. Note: Table -1 shows laboratory findings.

**Table 1: showing Lab findings.**

Lab values	14days before this admission	Day 0 of this admission	Day 2 of this admission
Na (mmol/L)	142	135	137
K (mmol/L)	4.7	4.5	4.6
Cl (mmol/L)	100	92	101
CO <sub>2</sub> (mmol/L)	39	30	28
BUN (mg/dl)	16	47	30
Creatinine (mg/dl)	0.9	3	1.6
AnionGap (mmol/L)	3	13	1.6
EGFR(ml/min/1.73 m <sup>2</sup> )	>60	16	35
Lactic acid (mmol/L)	-	1.8	-
Glucose (mg/dl)	64	51	228
Ca (mg/dl)	8.3	8.7	8.3
Total Protein (g/dl)	-	6.8	6.0

### Outcome and Follow up

The patient gradually regained cognition, and her blood glucose levels are increased gradually. She was monitored for the next 24 hours and remained stable with no further episodes of hypoglycemia. Blood glucose level on day 2 after admission was 228 mg/dl. The patient was discharged after 48 hours with her diabetes regimen modified to low dose insulin therapy and appropriate follow-up for diabetes management.

### DISCUSSION

Severe hypoglycemia occurs when blood glucose levels fall below 50 mg/dl. Sulfonylureas due to their action of increased insulin secretion leads to drop in blood glucose levels.<sup>[1][3]</sup> Sulfonylureas induced hypoglycemia is a significant concern in older adults, particularly in presence of multiple comorbidities such as chronic kidney disease, heart failure, and autonomic dysfunction.<sup>[1][3]</sup> Hypoglycemia complications include arrhythmias, cardiac arrest, myocardial infarction, increased loss of vision, seizures, dementia, neurocognitive dysfunction, coagulation abnormalities, multi organ failure, permanent brain damage, falls and fractures especially in elderly patients, recurrent episodes of hypoglycemia requiring multiple hospitalizations.<sup>[2][3][6][7][8]</sup> American Diabetic Association has issued new recommendations for managing of hypoglycemia particularly in older adults.<sup>[8]</sup> New

guidelines particularly stress the importance of individualized drug therapy using glucose lowering agents with low hypoglycemia risk, proven cardiovascular benefits, avoiding overly aggressive treatment and simplifying regimens while maintaining appropriate HbA<sub>1c</sub> levels. Less stringent glycemic goals may be appropriate for older adults as a part of individualized treatment and care.<sup>[8]</sup>

Management of hypoglycemia includes treatment of hypoglycemia and prevention of hypoglycemia. treatment of hypoglycemia is based on symptoms and blood glucose levels.<sup>[7]</sup> mild to moderate hypoglycemia is treated with 15-15 rule : consume 15 grams of glucose tablets or fruit juice or candies (carbohydrates) and check blood glucose levels after 15 minutes.<sup>[7]</sup> intramuscular glucagon or intravenous dextrose are used in treatment of severe hypoglycemia. check for medications causing hypoglycemia and they were stopped and drug regimen was modified to another anti diabetic medication with low or absent risk of hypoglycemia. adhering to guidelines such as beers criteria and considering alternative therapies can help mitigate the risks of sulfonylurea induced hypoglycaemia.<sup>[7][8][9]</sup>

Preventive strategies include :- involves a multifaceted approach as follows,

- A) patient education- educate patients on recognizing early signs of hypoglycemia and importance of regular meal patterns
- B) medication review – regularly review the patients medication regimen to initially identify potential drug interactions that may increase hypoglycemia risk
- C) dose adjustment – start sulfonylureas with low dose and titrate cautiously, especially in older adults and those with renal or hepatic impairment
- D) alternative therapies - consider newer anti-diabetic such as DPP4 inhibitors or SGLT2 inhibitors, which may have low hypoglycemia risk
- E) monitoring – continuous and regular blood glucose monitoring to detect and address hypoglycemia early and prevent recurrent hypoglycemic episodes.<sup>[7]</sup>

In this case, a 74 year old female experienced life threatening hypoglycemia attributed to long term glyburide use- an agent which is classified as a potentially inappropriate medication for older adults by 2023 Beers Criteria issued by American Geriatrics Society (AGS).<sup>[5]</sup> Goals of beers criteria are to improve quality of care by reducing the use of inappropriate medications.<sup>[5]</sup> The Beers Criteria recommend avoiding sulfonylureas like glyburide and chlorpropamide in elderly patients due to their prolonged half life and increased risk of severe hypoglycaemia.<sup>[5]</sup> this risk is further amplified by common age related factors like impaired renal clearance, polypharmacy, and comorbid conditions like heart disease and neuropathy which can mask early symptoms of hypoglycaemia.<sup>[1][5]</sup> Beers criteria risk factors for medication induced hypoglycemia included in Table -2.

**Table 2: showing Beers criteria -risk factors.**

<b>Beers Criteria-Risk factors for medication induced hypoglycemia include:</b>
1)Overuse of Sulfonylureas (unintentional overdose or inappropriate dose adjustment)
2)Renal Insufficiency, which impairs the clearance of sulfonylureas and increases the risk of prolonged hypoglycemia
3)Drug interactions (alcohol, beta-blockers, certain antibiotics)
4)Age and comorbid conditions like heart disease and neuropathy which mask symptoms of hypoglycemia

In this patient, acute kidney injury significantly reduced the clearance of glyburide, resulting in sustained insulin secretion and severe hypoglycaemia.<sup>[1]</sup> Impaired renal function can affect the pharmacokinetics of diabetic medications by reducing drug clearance and increasing plasma levels which increases risk of severe hypoglycemia.<sup>[1]</sup> Patient's history of cardiovascular disease and autonomic dysfunction made her more vulnerable to adverse effects of hypoglycemia including bradycardia, loss of consciousness, unresponsiveness, altered mental status, reduced awareness of hypoglycemic episodes.<sup>[2][4][6]</sup> The cause of medication failure or side effects is autonomic dysfunction. this is age related and also caused by long standing and uncontrolled diabetes. This manifestations highlight the need for individualized management in older adults. Recent clinical guidelines increasingly recommend newer anti diabetic agents such as GLP-1 receptor agonists and possibly avoiding sulfonylureas, SGLT2 inhibitors, DPP4 inhibitors which have a risk of hypoglycemia. HbA1c targets have been raised upto 8.6% in elderly patients, this does not justify the continued used of high risk agents like sulfonylureas. Safer glycemic control strategies must be prioritized to prevent avoidable complications such as those observed in this patient.<sup>[8][9]</sup>

## CONCLUSION

Prescribing Sulfonylureas by neglecting contraindications most commonly hepatic and renal dysfunction in elderly patients contributes to increased hypoglycemia risk.<sup>[1][7]</sup> According to beers criteria, sulfonylureas are not used as first line therapy and should

be avoided in geriatric diabetic patients with renal and hepatic dysfunction due to impaired clearance and increased plasma levels of sulfonylureas leading to increased hypoglycaemia.<sup>[5]</sup> So in this women with 74 years of age with a pre-existing history of heart disease and acute kidney injury on chronic kidney disease, sulfonylureas are contraindicated. Patient was discharged after 48 hours after considering low dose insulin therapy as safe for elderly patients of age >65 years with appropriate follow up for diabetes management, patient education about early detection of signs and symptoms of hypoglycemia and periodic blood glucose measurements.<sup>[7][8][9]</sup>

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