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CASE REPORT

Severe and recurrent hypoglycemia in an elderly patient with type 2 diabetes: the role of Glibenclamide and urinary tract infection

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ABSTRACT

Background: Hypoglycemia is an acute complication of diabetes especially in elderly patients and a leading cause of emergency room visits and hospital admissions. Several risk factors, such as age, polypharmacy, inadequate food intake, and infections, can further increase the risk of recurrent hypoglycemia and complicate its management. **Objective:** This report aims to present a case of severe and recurrent hypoglycemia induced by Glibenclamide in an elderly patient with concurrent infection. **Case:** A 66-year-old female was admitted to the emergency department (ED) in an unconscious state. After a thorough history taking and examination, the patient was diagnosed with profound hypoglycemia induced by sulfonylurea and urinary tract infection. Recurrent episodes of hypoglycemia were observed during treatment despite the administration of Dextrose 40%. **Conclusion:** Severe hypoglycemia is a common and life-threatening complication. Glibenclamide is a known cause of severe hypoglycemia, although other risk factors may also contribute to its occurrence. Infections can exacerbate hypoglycemic episodes, making them more difficult to manage. Clinicians must remain vigilant about recurrent episodes of hypoglycemia as prompt treatment is associated with a good prognosis.

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Highlights

1. Severe hypoglycemia is a life-threatening condition that can be effectively managed with glucose infusion. However, clinicians must be aware of the risk of recurrent hypoglycemic episodes.
2. Identifying and addressing the risk factors that contribute to recurrent hypoglycemia are essential.

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BACKGROUND

Hypoglycemia is the most common metabolic complication in patients with diabetes mellitus (Kaaniche et al., 2022), leading to emergency department (ED) visits and hospital admissions (Kim et al., 2020), posing a threat not only to the patient's health but also causing distress to their family and placing a significant burden on the healthcare system (Amiel et al., 2008). Diabetes-related emergencies include hyperosmolar hyperglycemic state (HHS), diabetic ketoacidosis (DKA), and hypoglycemic episodes (Amiel et al., 2008). Hypoglycemic episodes occur due to the use of glucose-lowering drugs such as insulin, sulfonylureas, or glinides (Nakhleh and Shehadeh, 2021). Several factors, such as age, impaired renal function, inadequate food intake, infections, and polypharmacy, increase the risk of hyperglycemic episodes. Sulfonylureas, a class of oral antidiabetic agents, are widely prescribed for type 2 diabetes mellitus (T2DM) in Indonesia due to their effectiveness, affordability, and tolerability. Despite these advantages, the strong hypoglycemic effects of sulfonylureas, which stimulate insulin secretion from the pancreas, can contribute to severe hypoglycemic episodes, particularly in vulnerable populations such as the elderly (Elsayed et al., 2023).

Hypoglycemia is a condition characterized by blood glucose levels falling below the normal range, defined as less than 70 mg/ dL (Sircar et al., 2016; Soelistijo, 2021). As a result, insulin secretion from the pancreas decreases, followed by an increase in glucagon production (Sircar et al., 2016). Because glucose is the primary fuel for the brain, hypoglycemic episodes trigger the release of hormones such as adrenaline, glucagon, cortisol, and growth hormone, which contribute to the manifestation of hypoglycemic symptoms. Hypoglycemic symptoms are categorized as autonomic and neuroglycopenic. Autonomic symptoms include sweating, hunger, paresthesia, and catecholamine-mediated adrenergic responses, such as palpitations, anxiety, changes in systolic blood pressure, and tremors. Meanwhile, neuroglycopenic symptoms include weakness, difficulty in thinking, fatigue, drowsiness, dizziness, blurred vision, slurred speech, and loss of consciousness (Lin et al., 2010). The prevalence of hypoglycemia is higher among individuals with type 1 diabetes (T1DM) than those with T2DM. However, serious complications are more frequently observed in T2DM patients. Therefore, clinicians must be adept at managing hypoglycemic episodes and identify other factors that may exacerbate the condition.

Infections are common in T2DM patients and contribute to increased morbidity and mortality. Infections caused by the disruption to the immune system due to hyperglycemic environment impairs the antibacterial activity in the urine as well as gastrointestinal and urinary motility (Casqueiro et al., 2012). Immune system alterations render individuals with T2DM more susceptible to infections and predispose them to more aggressive infectious diseases caused by bacteria, such as *Chlamydophila pneumoniae, Haemophilus influenzae*, and *Streptococcus pneumoniae*, as well as viruses such as CoV-2, Influenza A, and Hepatitis B. Hyperglycemia is thought to alter the microenvironment of immune cells and affect factors such as pH, blood viscosity, energy supply to bacteria, inflammatory response, and oxidative stress due to bacterial proliferation and metabolism (Chávez-Reyes et al., 2021). Urinary tract infections (UTIs) are common and more severe in T2DM patients and, with worse outcomes due to resistant pathogens (Nitzan et al., 2015). A meta-analysis reported the prevalence of UTIs in T2DM patients to be 11.5% (Salari et al., 2022). One contributing factor is incomplete bladder emptying due to autonomic neuropathy (Nitzan et al., 2015).

OBJECTIVE

This case report presents a case study of a 66-year-old female admitted to the ED of EWA Pangalila Hospital in an unconscious state. After a thorough history taking and examination, the patient was diagnosed with profound hypoglycemia induced by sulfonylurea and urinary tract infection. Recurrent episodes of hypoglycemia were observed during treatment despite the administration of Dextrose 40%.

CASE

A 66-year-old female was brought to the ED by her family due to unconsciousness. Her daughter found her unresponsive one hour prior to hospital admission. Before losing consciousness, the patient experienced dizziness, nausea, and vomiting twice. The patient had a history of mild fever and myalgia, which were managed with over-the-counter (OTC) drugs. There was no history of headache, dysarthria, paresis, cough, rhinorrhea, or diarrhea. The patient was diagnosed with T2DM three years before, but her condition remained uncontrolled. She had recently begun taking Glibenclamide 4 mg which was obtained from a social charity event the week before. Her last dose of Glibenclamide 4 mg was taken 12 hours prior to hospital admission. The patient also had history of uncontrolled hypertension.

Upon clinical examination, the patient was unconscious but responsive to pain (GCS: E2-V2-M4). Stridor was present, which was alleviated with an airway maneuver. Vital signs showed hypertension with a blood pressure of 174/96 mmHg. The pupils were normal and reacted to light. Other systems were also normal. The patient's blood glucose level, measured using a capillary glucometer for random blood sugar (GRBS), was 47 mg/dl. Immediate resuscitation was initiated with a rapid administration of Dextrose 40% 50 ml intravenously, followed by Dextrose 10% at 100 ml/hour for five hours. After 15 minutes, the patient slowly regained consciousness and her blood glucose level was 272 mg/dl. No Dextrose 40% was administered and the patient's blood glucose level was rechecked one hour later.

Laboratory examinations revealed leukocytosis of 17,140 uL with neutrophilia at 84.5%. Kidney function tests (BUN and Cr) were within normal limits. Urinalysis revealed leucocytes (+1), a pH of 8, glucose (+), nitrites (+3), calcium oxalate (+), and epithelial cells (+2), suggesting a urinary tract infection (UTI). Ceftriaxone 1 g was given twice daily as empirical treatment for the infection.

After the patient regained consciousness, she vomited twice. As a result, 4 mg of ondansetron was administered to relieve the symptoms. One hour later, the patient became unresponsive again (GCS: E3-V3-M5). Her blood glucose level was 48 mg/dL. Therefore, 50 ml of Dextrose 40% was readministered. After 15 minutes, the patient regained full consciousness and her blood glucose level was 238 mg/dL. Blood glucose level was monitored twice hourly and showed levels above 100 mg/dL (161 mg/dL and 123 mg/dL). After the patient's blood glucose stabilized, she was transferred to the ward. During ward treatment, the patient reported one mild hypoglycemic episode, with a blood glucose level of 69 mg/dL, which was alleviated with 25 ml of Dextrose 40% and sweet foods. Subsequently, the patient remained hemodynamically stable. Oral feeding was initiated and intravenous Dextrose was tapered down slowly. No further hypoglycemic episodes occurred after the patient was able to eat well. After 72 hours of stable blood glucose levels, the patient was discharged from the hospital.

DISCUSSION

The use of insulin is associated with hypoglycemia (Emral et al., 2018), as is the use of sulfonylureas (Bolanle Ademolu, 2019), both of which contribute to morbidity and mortality (Alsahli and Gerich, 2015). Most patients are not aware of hypoglycemia as a significant barrier which has negative impacts on adherence, dosing, quality of life, and economic productivity (Emral et al., 2018). The causes of hypoglycemia include alterations in renal or hepatic function (Alsahli and Gerich, 2015), disease duration (T2DM), age, frailty (Hölzen et al., 2024), cognitive impairment, lack of awareness (Hölzen et al., 2024), counter-regulatory response (Nakhleh and Shehadeh, 2021), knowledge of diabetes management, T1DM (Aljumaidi et al., 2024), physical and intellectual disability, alcohol consumption, multiple drug consumption (Asplund et al., 1983), and history of severe hypoglycemia (Elsayed et al., 2023). Hypoglycemia can result in seizures, physical and cognitive disfunction, frailty, disability, and poor outcomes. Severe cases may lead to coma and cardiac arrhythmias (Abdelhafiz et al., 2015).

An individual is categorized as hypoglycemic if their blood glucose level falls below the threshold of 70 mg/ dL or 3.9 mmol/l (Abdelhafiz et al., 2015; Aljumaidi et al., 2024; Seaquist et al., 2013). The American Diabetes Association categorized hypoglycemic episodes into three levels: level 1 (blood glucose level between 54 mg/dl and 70 mg/dL), level 2 (blood glucose level less than 54 mg/dL), and level 3, which requires third-party intervention (Elsayed et al., 2023). Level 3, also known as severe hypoglycemia, refers to hypoglycemic episodes requiring the administration of carbohydrates,

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glucagon, or resuscitation. These episodes can induced seizures or coma due to neuroglycopenia, with blood glucose levels ranging between 40-50 mg/dL (Tsai et al., 2011).

The severe hypoglycemia in this patient was caused by the consumption of 4 mg of Glibenclamide, a sulfonylurea, obtained from a social charity event. A study noted that 12% of participants experienced hypoglycemia as a side effect of Glibenclamide, while 4% experienced weight gain (Rani et al., 2014). Similarly, a case report noted this side effect in a 77-years old male with a blood glucose level of 45 mg/dl with fever, loose motions, and drowsiness, which lead to emergency admission (Hussain et al., 2016). In 57 cases of hypoglycemia, hypoglycemic episodes mostly occurred during the first month of treatment, at a daily dose of 10 mg. The clinical signs of hypoglycemia included coma or altered consciousness, with the lowest blood glucose level of 1.3 mmol/1, resulting in 10 fatalities (Asplund et al., 1983).

The patient was admitted to the ED with altered mental status (GCS: E2-V2-M4), a three-year history of T2DM, and hypertension (BP: 174/96 mmHg). Physical and neurological examinations were normal with a blood glucose level of 47 mg/dL, which was classified as severe hypoglycemia. The prompt administration of intravenous Dextrose led to a rapid improvement in her consciousness, confirming the diagnosis.

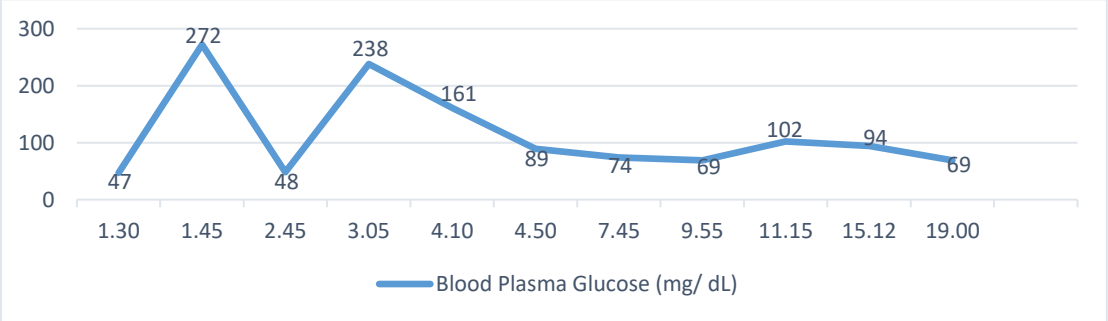

Figure 1. Patient's blood plasma glucose on day 1 (October 11st, 2024)

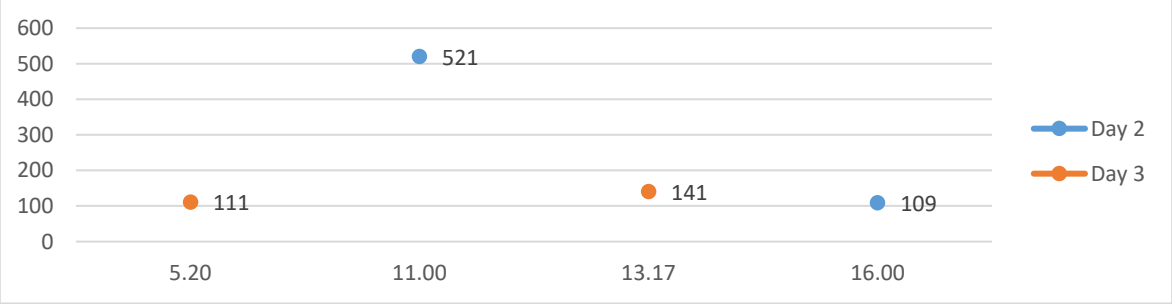

Figure 2. Patient's blood plasma glucose on day 2 and day 3 (October 11st to 12rd, 2024)

After one hour, the patient experienced a recurrent episode of hypoglycemia (GCS: E3-V3-M5). Blood glucose showed a level of 48 mg/dL. As a result, Dextrose 40% was readministrated and her consciousness rapidly improved. During the treatment, four episodes of hypoglycemia were documented, including two episodes of severe hypoglycemia and two episodes of level 1 hypoglycemia. The cause of hypoglycemia in this patient was Glibenclamide, a second-generation sulfonylurea known for its strong hypoglycemic effects by stimulating insulin secretion from the pancreas (Asplund et al., 1983). Glibenclamide has been associated with more frequent hypoglycemia than other sulfonylureas (Gangji et al., 2007). This is consistent with the findings of this case. Small doses of Glibenclamide (2.5-5 mg/day) led to severe outcomes in the form of hypoglycemia (Asplund et al., 1983), with episodes lasting for 12-48 hours (Asplund et al., 1983; Hussain et al., 2016). In this patient, the hypoglycemic episodes resolved after 12 hours. Another factor contributing to the recurrent hypoglycemic episodes in this patient was inadequate intake due to nausea and vomiting, which were rapidly alleviated with routine intravenous administration of ondansetron 4 mg three times daily and

omeprazole 40 mg once daily. A multivariate logistic regression study found that less food intake increases the risk of hypoglycemia by 9.33-fold (Silbert et al., 2017).

To rule out other causes and risk factors that contribute to recurrent hypoglycemia, blood and kidney function tests were conducted. The results showed normal kidney function (BUN and Cr). Urinalysis revealed leucocyte (+1), a pH of 8, glucose (+), nitrites (+3), calcium oxalate (+), and epithelial cells (+2), suggesting UTI. Ceftriaxone 1 g was administered twice daily as empirical treatment for the disease. Diabetic patients are prone to infections, including UTI (Silbert et al., 2017), and certain antidiabetic drugs, such as dapagliflozin (10 mg/day), have been shown to increase the risk of UTI by 1.17-fold (Zheng et al., 2023). The cause of UTI in T2DM patients include glucosuria, bacterial adhesion to the uroepithelium, and immune dysfunction, particularly in those receiving sodium-glucose cotransporter-2 (SGLT2) inhibitors (Geerlings et al., 2014). Glibenclamide may also increase susceptibility to UTI in diabetic patients by reducing the proinflammatory response in polymorphonuclear neutrophils (PMNs), especially interleukin (IL)-1β and IL-8 (Kewcharoenwong et al., 2013).

Hypoglycemia with concurrent infection is prevalent in elderly females. Infection can serve as a hazardous factor in patients with hypoglycemia, even those without a history of diabetes (Lin et al., 2010). The incidence of hypoglycemia is higher with the presence of infections (13.6%) than without the presence infection (8.4%). The mechanism for this association is that infections deplete glycogen stores, impair gluconeogenesis, and increase glucose utilization by the infecting pathogens. (Lin et al., 2010). A study found that infection (47%) as a comorbidity in patients with T2DM contributed to recurrent hypoglycemia ($p < 0.001$). The possible mechanism involves inflammatory stress induced by endotoxins, fever, increased metabolism, and increased energy consumption (Su et al., 2017). These findings supported the finding of this case report which found an association between recurrent hypoglycemic episodes and infections.

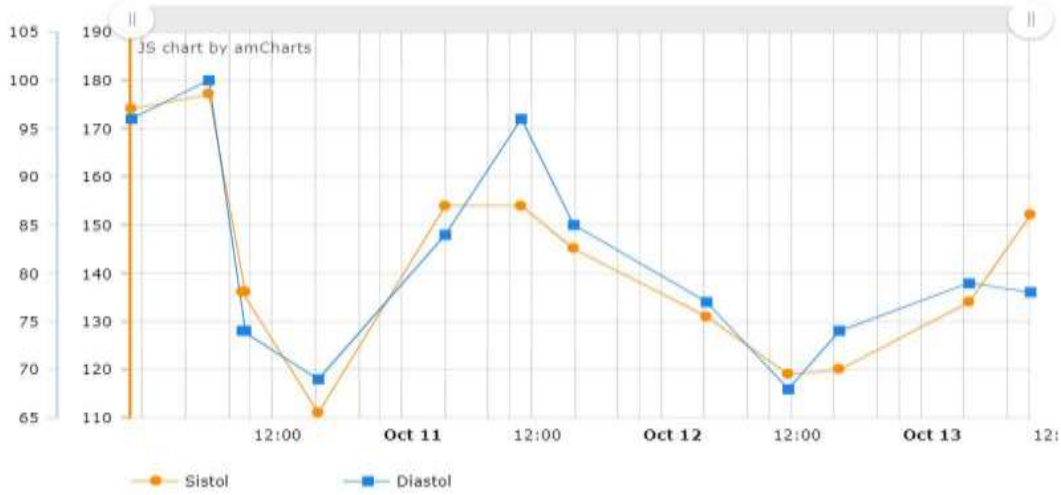

Figure 3. Patient's blood pressure during treatment

This patient had a history of hypertension, which was poorly controlled. Upon arrival at the ED, her blood pressure was 174/96 mmHg, categorized as stage II hypertension according to the Joint National Committee (JNC) 8 guidelines (James et al., 2014). Her guardian reported that her blood pressure had never been that high. Hypoglycemia activates the sympathoadrenal system, causing the secretion of catecholamines that exert significant hemodynamic effects. Specifically, activation of the sympathetic system leads to increased heart rate, systolic blood pressure, cardiac output, ejection fraction, and decreased diastolic blood pressure (Fisher et al., 1990). After the hypoglycemic episodes resolved, the blood pressure returned to baseline at 150-130 mmHg for systolic values and at 85-76 mmHg for diastolic values.

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Limitations

A thorough history and clinical presentation facilitated the diagnoses of the patient. This case report is supported by several studies and references. However, the limitation of this case report is the lack of long-term follow-up and minimal examination to identify other causes, due to cost-effectiveness considerations.

CONCLUSION

Severe hypoglycemia is a common and life-threatening complication in patients with T2DM, affecting not only the patient's health but also causing distress to their family. Glibenclamide is a known cause of severe hypoglycemia, although other risk factors may also contribute to its occurrence. Infections can exacerbate hypoglycemic episodes, making them more difficult to manage.

Acknowledgment

The authors would like to thank the patient and her family for providing consent for the publication of this case.

Conflict of Interest

All authors contributed to all processes in this study, including preparation, data collection and analysis, drafting, and approval for the publication of the manuscript.

Patient Consent for Publication

This case report has been approved by the patient and her guardian.

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