

Hypoglycemia in the treatment of hyperkalemia with insulin in patients with end-stage renal disease

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Abstract

Background. Hypoglycemia is common in patients with end-stage renal disease (ESRD). We identified the incidence and timing of hypoglycemia and its risk factors in hospitalized patients with ESRD after the treatment of hyperkalemia with insulin.

Methods. We conducted a retrospective study of all hospitalized adult patients treated with hemodialysis who received intravenous insulin to treat hyperkalemia between 1 January 2011 and 31 December 2011. We identified patients who became hypoglycemic [blood glucose <3.3 mmol/L (60 mg/dL)] after insulin administration.

Results. Two hundred and twenty-one episodes of hyperkalemia were treated with insulin, resulting in 29 episodes of hypoglycemia (13%). Factors associated with a higher risk of hypoglycemia included no prior diagnosis of diabetes [odds ratio (OR) 2.3, 95% confidence interval (CI) 1.0–5.1, $P=0.05$], no use of diabetes medication prior to admission [OR 3.6, 95% CI 1.2–10.7, $P=0.02$] and a lower pretreatment glucose level [mean 5.8 ± 0.7 mmol/L (104 ± 12 mg/dL) versus 9.0 ± 0.6 mmol/L (162 ± 11 mg/dL), $P=0.04$]. Hypoglycemia occurred at a median of 2 h after insulin administration and persisted for a median of 2 h.

Conclusions. The treatment of hyperkalemia with insulin in hospitalized patients with ESRD may be complicated by hypoglycemia. Patients with a history of diabetes are less susceptible to this complication. Our study supports the use of a protocol to provide dextrose support and blood glucose monitoring for at least 3 h after insulin treatment of hyperkalemia.

Keywords: end-stage renal disease; hyperkalemia; hypoglycemia; insulin

Introduction

Hyperkalemia is a common and potentially life-threatening complication in patients with end-stage renal disease (ESRD) due to decreased renal excretion of potassium. Elevated extracellular potassium can cause cardiac conduction abnormalities including ventricular fibrillation and asystole [1]. The urgent treatment of hyperkalemia is used when patients have electrocardiogram abnormalities associated with hyperkalemia or a serum potassium ≥ 6 mmol/L (mEq/L) [2]. Treatment includes stabilizing the cardiac membrane with intravenous (IV) calcium, shifting potassium into cells with IV insulin and albuterol and promoting potassium excretion with sodium polystyrene sulfonate or hemodialysis. For insulin, the commonly used regimen as supported by the American Heart Association guidelines and the Washington Manual of Critical Care is 10 units of regular insulin given intravenously with 25 g dextrose [2, 3]. Despite dextrose with insulin, hypoglycemia is a recognized complication of this treatment. In one study of the use of 10 units regular insulin with 25 g dextrose for the treatment of hyperkalemia in patients with ESRD, 9 of 12 (75%) of the patients had a blood glucose <3.1 mmol/L

(55 mg/dL) 1 h after treatment [4]. Patients with ESRD are already at an increased risk of hypoglycemia due to reduced renal clearance of insulin and decreased renal and hepatic glucose production [5, 6]. We conducted a retrospective study to identify the incidence of hypoglycemia in the treatment of hyperkalemia with IV insulin in patients with ESRD. We evaluated when hypoglycemia occurred, the length of time it persisted, and how much dextrose was given in order to design a protocol for glucose monitoring and dextrose administration to decrease this complication.

Materials and methods

We retrospectively collected data for all adult patients at Rush University Medical Center who were treated with hemodialysis and received IV regular insulin to treat hyperkalemia during a hospitalization between 1 January 2011 and 31 December 2011. None of the patients had peritoneal dialysis. This study was approved by Rush University's Institutional Review Board. Data were collected from the hospital's electronic medical record system, including age,

sex, race, weight, body mass index (BMI), diagnosis of diabetes, home medications, hospital medications and blood glucose levels.

Episodes were excluded if there was no blood glucose ≥ 3.9 mmol/L (70 mg/dL) within 10 h before insulin or no blood glucose within 6 h after insulin administration. Hypoglycemia was defined as a blood glucose level < 3.3 mmol/L (60 mg/dL). Measurements of glucose from serum, plasma and point-of-care whole blood samples were included. Whole blood capillary glucose levels < 1.1 mmol/L (20 mg/dL) were analyzed as 1.1 mmol/L (20 mg/dL). All oral and IV doses of 25 g of dextrose were recorded if administered with insulin and in the 6 h after insulin for each episode.

Standard descriptive analyses are provided using mean and standard error for continuous variables or frequency counts or percentages for categorical variables. To analyze factors associated with hypoglycemia, the independent sample *t*-test was used for continuous variables and χ^2 for categorical variables. The analysis was performed using SPSS version 19 (Chicago, IL, USA).

Results

We identified 245 episodes where IV regular insulin was administered to treat hyperkalemia. One episode was excluded because there was no documentation of blood glucose within 10 h prior to insulin administration, and 23 episodes were excluded because there was no documentation of blood glucose within 6 h after insulin administration. Two hundred and twenty-one episodes were included in the final analysis. These episodes occurred in a total of 133 patients. Sixty-seven of the 133 patients (50%) had diabetes. Patient characteristics for the 221 episodes are summarized in Table 1. The numbers of patients (in parentheses) with multiple treatment episodes analyzed are as follows: two episodes (27), three episodes (19), four episodes (3), five episodes (2) and seven episodes (1). The administered dose of IV insulin ranged from 4 to 10 units, with 90% of episodes receiving 10 units.

Twenty-nine of the 221 (13%) episodes resulted in hypoglycemia. Blood glucose was between 2.8 and 3.3 mmol/L (51–60 mg/dL) in 16 episodes and ≤ 2.8 mmol/L (50 mg/dL) in 13 episodes. Subcutaneous insulin or a continuous IV insulin infusion was administered within 24 h of the index dose of IV insulin in 68 episodes; however, there was only one episode of hypoglycemia in this group. No patients received a sulfonylurea.

Seventy-five percent of hypoglycemic episodes occurred within 3 h after insulin administration. Hypoglycemia

occurred at a median of 2 h [interquartile range (IQR) 1–3 h] and persisted for a median of 2 h (IQR 2–3 h). Age, sex or race was not significantly different between the groups with and without hypoglycemia. Patients who experienced hypoglycemia tended to have a lower BMI.

Compared with those with an established diagnosis of diabetes, patients without a prior diagnosis of diabetes had an increased risk of experiencing hypoglycemia [odds ratio (OR) 2.3, 95% confidence interval (CI) 1.0–5.1, $P = 0.05$]. Similarly, the risk for hypoglycemia was significantly higher in those patients not receiving anti-diabetes medications prior to admission [OR 3.6, 95% CI 1.2–10.7, $P = 0.02$], compared with those who were taking them. The mean pretreatment blood glucose level was significantly lower in the nondiabetic patients 6.2 ± 1.9 mmol/L (111 ± 34 mg/dL) as compared with the diabetic patients [10.8 ± 10.3 mmol/L (194 ± 185 mg/dL), $P < 0.001$]. The mean pretreatment blood glucose level was significantly lower in the hypoglycemic group 5.8 ± 3.5 mmol/L (104 ± 63 mg/dL) as compared with the nonhypoglycemic group [9.0 ± 8.2 mmol/L (162 ± 148 mg/dL), $P = 0.04$]. Mean nadir blood glucose level after insulin was 2.6 ± 0.5 mmol/L (46 ± 9 mg/dL) in episodes with hypoglycemia versus [8.9 ± 5.7 mmol/L (160 ± 102 mg/dL), $P = 0.01$] in episodes without hypoglycemia.

In 94% of the episodes, dextrose was given with insulin. All patients with hypoglycemic episodes received 25 g of dextrose with insulin, while 7% of patients without hypoglycemia received insulin without concomitant dextrose. Three episodes of hypoglycemia occurred despite receiving dextrose with insulin and a second dose of dextrose 1 h later. Hypoglycemia occurred at 3, 4 and 6 h after insulin in these three episodes. Four patients had multiple episodes of hypoglycemia (three patients with two episodes and one patient with four episodes). All four of these patients were nondiabetic.

Discussion

Hypoglycemia is common in patients with ESRD and can occur by one or several mechanisms. First, renal insufficiency reduces insulin clearance and results in prolonged insulin action and hypoglycemia. Second, hepatic glucose production is reduced. In the nonfasting state, the liver is the site of all endogenous glucose production through glycogenolysis (75%) and gluconeogenesis (25%) [7]. Reduced caloric intake associated with uremia decreases glycogen stores and thus decreases glycogenolysis, and acidosis and uremia decrease gluconeogenesis [8]. Third, renal

Table 1. Comparison of patient characteristics and treatments between those with and without hypoglycemic episodes following insulin treatment for hyperkalemia

	Hypoglycemic (n = 29)	Nonhypoglycemic (n = 192)	P-value
Age (years)	51 \pm 14	56 \pm 14	0.07
Male (%)	63	62	0.47
African American (%)	62	49	0.19
BMI (kg/m ²)	25.9 \pm 5.5	28.6 \pm 7.4	0.06
History of diabetes (%)	34	54	0.05
Taking diabetes medication prior to admission (%)	14	70	0.02
Pretreatment glucose level mmol/L (mg/dL)	5.8 \pm 3.5 (104 \pm 63)	9.0 \pm 8.2 (162 \pm 148)	0.04
Nadir glucose level mmol/L (mg/dL)	2.6 \pm 0.5 (46 \pm 9)	8.9 \pm 5.7 (160 \pm 102)	0.01
Received dextrose with insulin (%)	100	93	0.17
Doses (25 g IV or oral) of dextrose given before hypoglycemia	1.2 \pm 0.4	1.2 \pm 0.5	0.20

Data are presented as mean \pm SD unless otherwise noted.

gluconeogenesis is reduced. In the fasting state, the kidney contributes 10–25% of glucose production [9]. This protective process is lost in ESRD and predisposes these patients to fasting hypoglycemia [10]. Fourth, uremia can blunt the release of counter-regulatory hormones such as glucagon and catecholamines further limiting the body's defense against hypoglycemia [11].

Schafers *et al.* [12] examined the incidence of hypoglycemia after treatment of hyperkalemia with insulin in hospitalized adults. This study found that hypoglycemia [blood glucose <3.9 mmol/L (70 mg/dL)] occurred in 19 of 219 patients (8.7%) and 58% of the hypoglycemia occurred with the commonly used regimen of 10 units of IV insulin with 25 g of dextrose. The results of their study and our study suggest the need for additional dextrose. Their study population included 67% of patients with acute renal injury or ESRD, and the risk of hypoglycemia was higher in this subset. Our study focused solely on patients with ESRD, likely explaining the higher frequency of hypoglycemia.

Our study showed a 13% risk of hypoglycemia despite dextrose with insulin, demonstrating that one dose of dextrose is not sufficient in some patients. This suggests the need for additional dextrose support. The administration of dextrose alone to stimulate endogenous insulin secretion is not advised because, if there is inadequate insulin secretion such as with insulin-dependent diabetes, the resultant hyperglycemia could increase plasma osmolarity, promote the exit of potassium from cells and worsen hyperkalemia [13].

We suggest administering 25 g of dextrose with insulin and 25 g of dextrose 1 h after insulin based on our result that hypoglycemia occurred 1–3 h after insulin with dextrose. We think this regimen is superior to 50 g of dextrose with insulin because it may lessen the initial hyperglycemia, and the second dose may be more effective at preventing hypoglycemia in the following 1–3 h. Another potential solution is to treat with the standard 10 units of regular insulin and dextrose 25 g followed by an infusion of 10% dextrose at 50 mL/h with close monitoring of blood glucose for at least 3 h or until dialysis is initiated [13].

Hypoglycemia in our study persisted for 2–3 h after insulin. This suggests the need for blood glucose monitoring for 3 h after insulin. Since three episodes of hypoglycemia in our study occurred despite dextrose with insulin and dextrose 1 h after insulin, extending blood glucose monitoring for 3 h after insulin will hopefully identify the patients who require additional dextrose.

Our study has limitations. It is a retrospective study that includes data from a time period when there was no set protocol to treat hyperkalemia. Therefore, glucose monitoring varied according to the treating physicians. It is possible that the hypoglycemia may have persisted longer than the median 3 h reported, and that the frequency of hypoglycemia may be underestimated. In addition, we do not have the data regarding the timing of hemodialysis. The dialysate used at our institution contains dextrose 5.6 mmol/L (100 mg/dL), therefore the initiation of hemodialysis soon after insulin administration could have prevented hypoglycemia. Also, without the timing of hemodialysis, we could not comment on the change in serum potassium with this treatment.

We used our data to design the Rush University protocol for blood glucose monitoring and dextrose support with IV insulin to treat hyperkalemia (Table 2). The protocol stipulates universal administration of 25 g of dextrose at 0 and 60 min after IV insulin, and hourly monitoring of blood glucose at 0, 60, 120 and 180 min. All blood glucose

Table 2. Rush University protocol for glucose monitoring and dextrose support for the treatment of hyperkalemia with IV insulin

1. Check blood glucose prior to insulin administration. If <3.9 mmol/L (70 mg/dL), give dextrose 25 g prior to insulin.
2. Give insulin 10 units IV with dextrose 25 g.
3. Recheck blood glucose 1 h after insulin and dextrose administration, and give dextrose 25 g irrespective of blood glucose level.
4. Recheck blood glucose at 2 and 3 h after insulin administration. Give dextrose 25 g if blood glucose is <3.9 mmol/L (70 mg/dL).

levels <3.9 mmol/L (70 mg/dL) at 120 or 180 min are treated with additional dextrose. Further study will explore the efficacy and safety of this protocol.

In conclusion, patients with ESRD are at higher risk for developing hypoglycemia than patients with normal renal function. Thus, extra caution is required in the use of IV insulin to treat hyperkalemia in this population. Our data suggest a novel enhancement of the standard inpatient hyperkalemia treatment protocol which could improve patient safety.

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Conflict of interest statement. None declared.

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