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ORIGINAL RESEARCH

Incidence of Hypoglycemia Following Insulin-Based Acute Stabilization of Hyperkalemia Treatment

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PURPOSE: The aim of this study was to assess the incidence of hypoglycemia in hospitalized patients following acute treatment of hyperkalemia with insulin. A characterization of the affected patients and the administered insulin/dextrose regimens was also performed.

METHODS: A retrospective search of the electronic records of a large university-based tertiary care hospital was conducted, from June 1, 2009 to December 1, 2009, to identify patients who developed hypoglycemia following acute stabilization of hyperkalemia treatment with regular insulin.

RESULTS: Of 219 hyperkalemic patients who met the criteria of the study, 19 patients (8.7%) were identified as hypoglycemic (blood glucose <70 mg/dl), and 5 of these patients (2.3% of study patients) were classified as severely hypoglycemic (blood glucose <40 mg/dl). Fifteen (79%) of the hypoglycemic patients had acute kidney injury or were end-stage renal disease patients on hemodialysis at the time of treatment. Fifty-eight percent of the hypoglycemic events occurred following the commonly employed 10 units of regular insulin and 25 gm of dextrose 50% treatment regimen.

CONCLUSION: Iatrogenic hypoglycemia, as a result of treatment for hyperkalemia, is a common occurrence. Hyperkalemia occurs disproportionately in patients with acute kidney injury or end-stage renal disease, and these patients are predisposed to an increased risk of hypoglycemia. The risk of severe hypoglycemia escalates in patients with lower body weight and creatinine clearance. Hypoglycemia risk can be minimized by providing sufficient dextrose in the treatment regimen, however, patient variability in treatment response dictates careful blood glucose monitoring before and after treatment. *Journal of Hospital Medicine* 2012;7:239–242. © 2011 Society of Hospital Medicine.

Hyperkalemia is a common condition in hospitalized patients and can be fatal if left untreated.[1] The incidence of hyperkalemia in hospitalized patients is 1-10%.[2] Hyperkalemia develops secondary to decreased renal excretion of potassium, increased potassium intake, or redistribution of potassium into the extracellular fluid. Patients with renal dysfunction, especially acute kidney injury (AKI) or end-stage renal disease (ESRD), are especially predisposed to hyperkalemia. Drug therapy (particularly inhibitors of the renin-angiotensin-aldosterone system, calcineurin inhibitors, potassium sparing diuretics, and heparin) may also predispose patients to elevated potassium levels.[2] High extracellular potassium adversely affects the resting membrane potential of the myocardial cell. This results in a slowing of ventricular conduction, and may precipitate ventricular fibrillation or asystole.[3,4] Due to this high risk of cardiac complications, the American Heart Association recommends treatment when potassium levels are ≥6.0 mEq/L.[5]

A threefold approach to the treatment of hyperkalemia is currently adopted by clinicians: (1) stabilizing the cardiac membranes using intravenous (IV) calcium; (2) redistribution of potassium using IV insulin and nebulized albuterol (in the setting of metabolic acidosis, IV sodium bicarbonate will also help to shift potassium into cells); and (3) elimination of potassium from the body via hemodialysis or Na-K exchange resin binders.[2]

The use of insulin is incorporated into most acute hyperkalemia stabilization treatment regimens and, with or without concomitant dextrose, can predispose patients to develop hypoglycemia. Dosing recommendations for insulin and dextrose for hyperkalemia vary among clinical references but commonly include 10 units of regular insulin IV and 25-50 gm of IV dextrose.[6,7] Hypoglycemia following insulin and dextrose administration has received limited documentation.[8–10] Furthermore, several factors account for an increased frequency of hypoglycemia in patients with end-stage renal disease, a group also predisposed to hyperkalemia.[11] This study assesses the incidence of hypoglycemia in hospitalized patients

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TABLE 1. Distribution of Hypoglycemic Events Among the Various Insulin/Dextrose Regimens

Insulin (units)/dextrose (grams)	10/0	5/25	10/12.5	10/25	10/50
<40 mg/dl cohort	1/5 (20%)	2/5 (40%)	0	2/5 (40%)	0
41-69 mg/dl cohort	0	0	4/14 (29%)	9/14 (64%)	1/14 (7%)
<70 mg/dl cohort (total)	1/19 (5.5%)	2/19 (10%)	4/19 (21%)	11/19 (58%)	1/19 (5.5%)
Diabetic patients	0	1	1	3	0

after acute stabilization treatment of hyperkalemia with insulin.

METHODS

A retrospective search of the electronic records of a large university-based tertiary care hospital was conducted from June 1, 2009 to December 1, 2009. Adult hospitalized patients met our study inclusion criteria if they received IV insulin as part of an acute hyperkalemia stabilization treatment regimen and their potassium level was 6 mmol/L or greater. A medical record search was performed by applying the following search criteria: 5-10 units of intravenous insulin administered within 6 hours of a collected potassium level which was reported as 6 mmol/L or greater. Patients were excluded if they did not have a reported blood glucose level measured within 6 hours of insulin administration. Patient demographic data was collected including: patient's age, sex, weight, and presence of diabetes or renal dysfunction. AKI was defined as an acute rise in serum creatinine of >0.5 mg/dl within a 7-day period during hospitalization. Hypoglycemia and severe hypoglycemia were defined as blood glucose levels of <70 mg/dl and <40 mg/dl, respectively, consistent with the current medical literature. Hypoglycemic patients were grouped into hypoglycemic and severely hypoglycemic subsets based on their blood glucose levels. Information on patients' hypoglycemic symptoms was recorded when documented in the medical record. All administered doses of insulin and dextrose were documented by reviewing the medication administration record for each patient. Blood glucose levels were obtained by both point-of-care finger stick bedside measurements and blood draws taken for laboratory analysis. The incidence of patients who became hypoglycemic following a hyperkalemic treatment was then assessed.

RESULTS

Our retrospective computer data search identified 250 hyperkalemic patients (with potassium levels ≥6 mmol/L) who received intravenous regular insulin within 6 hours of the potassium level measurement during the 6-month study period. Thirty patients (12%) met study criteria but were excluded because they did not have a blood glucose level documented within 6 hours of insulin administration. One patient, who qualified for the study from the electronic data, was excluded because of an erroneous potassium level secondary to a hemolyzed blood sample. Nineteen (8.7%) of the remaining 219 study patients were identified as hypoglycemic (blood glucose <70 mg/dl). Five patients (2.3%) were classified as having severe hypoglycemia (blood glucose <40 mg/dl). The distribution of hypoglycemic events among the various insulin/dextrose regimens are shown in Table 1. Fifty-eight percent and 40% of the blood glucose <70 mg/dl and <40 mg/dl events, respectively, occurred following the commonly employed 10 units of regular insulin by intravenous push (IVP) and 25 gm of dextrose 50% IVP treatment regimen.

TABLE 2. Patient Characteristics Group in Blood Glucose Cohorts

Patient Characteristics per Cohort	<40 mg/dl Cohort (5 Patients)	41-69 mg/dl Cohort (14 Patients)	>70 mg/dl Cohort (70 Patient Subset)
Age, yr	49	56	57
Male sex, no. (%)	3 (60%)	12 (86%)	40 (57%)
Weight, kg	55.8	92	87.4
Weight <50 kg (%)	60%	7.5%	6%
Weight 51-70 kg (%)	20%	7.5%	26%
Weight >70 kg (%)	20%	85%	68%
Diabetic, no. (%)	1 (20%)	4 (28%)	22 (31%)
AKI or ESRD, no. (%)	4 (80%)	11 (78%)	46 (66%)
Average BG pretreatment	148 mg/dl*	120 mg/dl	155 mg/dl
Potassium level			
6.0-6.4 mmol/L, no. (%)	4 (80%)	8 (57%)	47 (67%)
6.5-6.9 mmol/L, no. (%)	0	1 (7%)	13 (19%)
>7 mmol/L, no. (%)	1 (20%)	5 (36%)	10 (14%)
Hospitalization in ICU	60%	36%	23%
Mortality during admission†	40%	7%	13%

Abbreviations: AKI, acute kidney injury; BG, blood glucose; ESRD, end-stage renal disease; ICU, intensive care unit. *110 mg/dl excluding 1 patient with BG of 298 mg/dl. †Patient mortality was limited to ICU patients in all but 1 patient and was not attributed to any hyperkalemia events.

The average body weight of patients with a blood glucose <40 mg/dl was significantly less than those patients having blood sugars in the 41-69 mg/dl range (55.8 kg vs 92.0 kg, P <0.05) or patients with blood sugars >70 mg/dl (55.8 kg vs 87.4 kg, P <0.05). Table 2 lists patient characteristics by blood glucose cohort, with the 200 patient >70 mg/dl group represented by a random subset of 70 patients.

The average pretreatment blood glucose level for this cohort of 19 patients was 127 mg/dl with a blood glucose range of 59-298 mg/dl. One patient was identified as hypoglycemic prior to treatment. Five hypoglycemic patients were identified as diabetic. One of these patients had an A1C level >13%, and 3 patients had levels <7%. Distribution of the potassium levels within the cohort were as follows: 6.0-6.4 mmol/L: 12

patients (67%); 6.5-6.9 mmol/L: 1 patient (5%); and 7 mmol/L or greater: 6 patients (28%). Seven patients had stat electrocardiograms ordered at the time of their hyperkalemia, and 3 patients had repeat potassium levels which verified their hyperkalemia. Fifteen (79%) of the hypoglycemic patients had acute kidney injury or were end-stage renal disease patients on hemodialysis at the time of treatment.

Hypoglycemia was demonstrated at a median time of 3 hours post-insulin administration. Documentation of the patients' hypoglycemia symptoms and the treatment of the hypoglycemic events were very poor. Only 3 patients had documentation of their hypoglycemia in the notes section of the electronic chart. The documentation included common symptoms of hypoglycemia in 2 patients, and was limited to the type of hypoglycemic treatment in the third patient. Seven patients had dextrose IV documented in the medication administration record, and 1 patient was treated with cranberry juice. No documentation of treatment was found in the remaining 58% of patients.

Eight of the 19 hypoglycemic patients were treated in an intensive care unit while receiving treatment for hyperkalemia. Of the 5 patients with severe hypoglycemia, 3 were treated in an intensive care unit and 2 of these patients died the day following treatment. One of the deaths resulted from a cardiac arrest with pulseless electrical activity while the patient was on dialysis. One patient with severe hypoglycemia was transferred to the medical intensive care unit but was discharged to home 4 days later. One additional patient, with chronic myeloid leukemia and a blood glucose level between 40 and 70 mg/dl died on the day of his admission.

DISCUSSION

Studies often do not agree on whether hypoglycemia is a complication resulting from standard insulin/glucose treatments for hyperkalemia. A previous study by Kim[12] evaluated a combination regimen of insulin/glucose with bicarbonate for the treatment of hyperkalemia in 8 end-stage renal disease patients. In this study, a solution of 8.4% bicarbonate (120 cc of bicarbonate and 80 ml of normal saline) was infused at a rate of 2 mmol/min. In addition, patients simultaneously received 550 ml of 20% glucose containing 50 units of regular insulin infused at a rate of 5 mU/kg/min. The study reported that the potassium level was lowered from 6.2 to 5.2 mEq/L in 1 hour without any patients experiencing hypoglycemia. The ratio of insulin to glucose was approximately 11 units/25 gm. However, in a similar study by Allon and Copkney,[9] asymptomatic hypoglycemia was reported in 75% of patients following the administration of 10 units of regular insulin and 25 gm of dextrose for hyperkalemia in patients with renal failure. The study demonstrated baseline plasma glucose levels of 85-92 mg/dl in patients prior to the insulin and dextrose therapy. Transient hyperglycemia developed 15 minutes post-therapy, resolved within 30 minutes, and then progressed toward significant hypoglycemia at 60 minutes with blood glucose levels declining into the 45-56 mg/dl range. The study also demonstrated that the hypoglycemia secondary to the insulin/dextrose regimen was attenuated by the concomitant use of inhaled albuterol.

Management of acute hyperkalemia stabilization lacks a standardized treatment regimen. Often a ''shot-gun'' approach employing multiple therapeutic modalities is prescribed concomitantly, and intravenous insulin and dextrose are commonly included in these treatment regimens. Hyperkalemia treatment regimens are often prescribed based on local treatment patterns or from online references including *Pepid*[6] and *UpToDate*.[7] In addition, reference manuals such as the *Washington Manual of Medical Therapeutics*[13] also provide therapeutic guidelines. However, these sources often do not agree on a standard treatment. In terms of a combined insulin and glucose therapy for hyperkalemia, the practice at our hospital is to administer, 10 units of regular insulin IVP with 50 ml (25 gm) of dextrose 50% IVP. *UpToDate*[7] suggests 10 units of regular insulin IVP with 25 gm of dextrose 50% IVP, followed by dextrose 10% infusion by intravenous piggyback (IVPB) at 50-75 ml/hr with careful monitoring. *Pepid*[6] recommends 10 units of regular insulin IVP and 25 gm of dextrose 50% IVP, whereas the *Washington Manual of Medical Therapeutics*[13] suggests 10-20 units of regular insulin and 25-50 gm of glucose administered intravenously.

Our study demonstrated a hypoglycemia frequency of 8.7% (<70 mg/dl) which occurred over a range of 5-10 units of regular insulin and 0-50 gm of dextrose 50%. However, this frequency may underestimate the true hypoglycemic incidence, as our study excluded patients without posttreatment blood glucose levels, and we were unable to control for patient self-treatment or nurse-assisted treatment of hypoglycemia with dietary sources of glucose (juice, crackers, etc). Despite these limitations, a hypoglycemic incidence of 8.7% is extremely high and constitutes an unacceptably high iatrogenic risk for complications. Data from the critical care literature suggests that hypoglycemia is an independent marker of mortality.[14] Fifty-eight percent of our total hypoglycemic events developed after patients received the commonly cited regimen of 10 units of regular insulin IVP and 25 gm of 50% dextrose IVP. One of our patients developed hypoglycemia despite a regimen of 10 units of regular insulin with 50 gm of 50% dextrose. This variability of patient response suggests that no single algorithm will prevent all hypoglycemic events, therefore, careful patient assessment and blood glucose monitoring should be routinely employed.

The decision regarding the order of dextrose and insulin administration can be influenced by clinical

factors. Dextrose administration should generally precede insulin administration.[15] In the setting of insulin and aldosterone deficiency (ie, a patient with type 1 diabetes and type IV renal tubular acidosis), dextrose administration prior to insulin administration could exacerbate the patient's hyperkalemia. In this circumstance, insulin administration should precede dextrose administration, with dextrose dosing predicated on the patient's estimated glycemic requirements and glucose monitoring. However, in patients with isolated insulin or aldosterone deficiency, the initial administration of dextrose does not predispose to further hyperkalemia.[16]

Hypoglycemia risk can be minimized by increasing the dextrose component in most insulin/dextrose hyperkalemia treatment regimens. The dextrose may be administered as 100 ml of 50% dextrose IVP or 50 ml of 50% dextrose IVPB, followed by 250 ml of D10 IVPB over 1 hour. The latter regimen may be preferred for patients at higher risk of hypoglycemia, although the added volume of fluid may not be appropriate for all patients. It must be recognized that this regimen may result in short-term hyperglycemia, and patients should be closely monitored. It is reasonable, prior to treatment, to obtain a baseline blood glucose level and to obtain a 1-hour and 3-hour posttreatment blood glucose level.

While an electronic hospital record provides convenient access to a large number of patients and allows cross-referencing of various laboratory values and prescribed medications, the ability to develop persuasive conclusions from the generated data may be significantly limited by inadequate or missing documentation of patient's pretreatment symptoms and response to therapy. The documentation of treatment response in the acute stabilization of hyperkalemia of our patients lacked specificity and standardization. Similarly, documentation of hypoglycemia and subsequent treatment response is not standardized at our institution. This lack of patient data limits our ability to gauge the level of harm experienced by our patients or evaluate the timeliness and appropriateness of their hypoglycemic treatment. Therefore, documentation of hypoglycemic symptoms and treatment will be the subject of future performance improvement initiatives and study at our institution. Further, studies need to be pursued utilizing standardized charting templates to facilitate and guide appropriate treatment assessment and follow-up documentation. This will also assist in evaluating the treatment options addressed in this article. In addition, evaluation of bolus therapy with 50% dextrose versus therapies using D10 infusions in combination with insulin for hyperkalemia treatment in emergency room patients will be pursued. Despite these limitations, any policy which can limit harm from potential hypoglycemia deserves institutional attention and study.

Iatrogenic hypoglycemia as a result of treatment for hyperkalemia is a common occurrence, is largely unrecognized, and can have adverse outcomes. In our present study, 8.7% of patients became hypoglycemic following insulin treatment for hyperkalemia. Hyperkalemia occurs disproportionately in patients with acute kidney injury or end-stage renal function. Moreover, the risk of severe hypoglycemia escalates in patients with lower body weight, and careful surveillance is needed in these cases.

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References

1. Stevens MS, Dunlay RW. Hyperkalemia in hospitalized patients. *Int Urol Nephrol*. 2000;32:177–180.
2. Acker CG, Johnson JP, Palevsky P, Greenberg A. Hyperkalemia in hospitalized patients: causes, adequacy of treatment, and results of an attempt to improve physician compliance with published therapy guidelines. *Arch Intern Med*. 1998;158:917–924.
3. Fisch C. Relation of electrolyte disturbances to cardiac arrhythmias. *Circulation*. 1973;47:408–419.
4. Surawicz B. Electrolytes and the electrocardiogram. *Postgrad Med*. 1974;55:123–129.
5. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 10.1: Life-threatening electrolyte abnormalities. *Circulation*. 2005;112: IC-121-IV121–IC-125.
6. Bibbs MA, Werfson AB. *Electrolyte disturbances*. In: Marx J, Hockberger R, Walls R, eds. Rosen's Emergency Medicine. 5th ed. New York, NY: Mosby; 2002:1722–1731. Accessed via *Pepid* 1/15/11.
7. Mount DB. Treatment and prevention of hyperkalemia. In: Basow DS, ed. UpToDate. Waltham, MA: UpToDate; 2011.
8. Williams PS, Davenport A, Bone JM. Hypoglycaemia following treatment of hyperkalemia with insulin and dextrose. *Postgrad Med*. 1988;64:30–32.
9. Allon M, Copkney C. Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. *Kidney Int*. 1990;38:869–872.
10. Blumberg A, Weidmann P, Shaw S, Gnadinger M. Effect of various therapeutic approaches on plasma potassium and major regulating factors in terminal renal failure. *Am J Med*. 1988;85:507–512.
11. Haviv YS, Sharkia M, Safadi R. Hypoglycemia in patients with renal failure. *Renal Failure*. 2000;22(2):219–223.
12. Kim HF. Combined effect of bicarbonate and insulin with glucose in acute therapy of hyperkalemia in end stage renal disease patients. *Nephron*. 1996;72(3):476–482.
13. Sankarpandian B, Cheng S. *Fluid and electrolyte management*. In: Foster C, Mistry N, Peddi P, Sharma S, eds. Washington Manual of Medical Therapeutics. 33rd ed. Philadelphia, PA: Wolters Kluwer; 2010:390.
14. Van Den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Eng J Med*. 2006;354:449–461.
15. Ljutic D, Rumboldt Z. Should glucose be administered before, with, or after insulin in the management of hyperkalemia? *Renal Failure*. 1993;15(1):73–76.
16. Goldfarb S, Cox M, Singer I, Goldberg M. Acute hyperkalemia induced by hyperglycemia: hormonal mechanisms. *Ann Int Med*. 1976;84:426–432.