Treatment of Hyperkalemia With a Low-Dose Insulin Protocol Is Effective and Results in Reduced Hypoglycemia

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Introduction: Complications associated with insulin treatment for hyperkalemia are serious and common. We hypothesize that, in chronic kidney disease (CKD) and end-stage renal disease (ESRD), giving 5 units instead of 10 units of i.v. regular insulin may reduce the risk of causing hypoglycemia when treating hyperkalemia.

Methods: A retrospective quality improvement study on hyperkalemia management (K+ ≥ 6 mEq/l) from June 2013 through December 2013 was conducted at an urban emergency department center. Electronic medical records were reviewed, and data were extracted on presentation, management of hyperkalemia, incidence and timing of hypoglycemia, and whether treatment was ordered as a protocol through computerized physician order entry (CPOE). We evaluated whether an educational effort to encourage the use of a protocol through CPOE that suggests the use of 5 units might be beneficial for CKD/ESRD patients. A second audit of hyperkalemia management from July 2015 through January 2016 was conducted to assess the effects of intervention on hypoglycemia incidence.

Results: Treatments ordered using a protocol for hyperkalemia increased following the educational intervention (58 of 78 patients [74%] vs. 62 of 99 patients [62%]), and the number of CKD/ESRD patients prescribed 5 units of insulin as per protocol increased (30 of 32 patients [93%] vs. 32 of 43 [75%], P = .03). Associated with this, the incidence of hypoglycemia associated with insulin treatment was lower (7 of 63 patients [11%] vs. 22 of 76 patients [28%], P = .03), and there were no cases of severe hypoglycemia compared to the 3 cases before the intervention.

Conclusion: Education on the use of a protocol for hyperkalemia resulted in a reduction in the number of patients with severe hypoglycemia associated with insulin treatment.

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adverse effect of insulin treatment. The incidence of hypoglycemia ranges from 0% to 50%, depending on the amount and timing of insulin.\textsuperscript{2,17–20} In the hospital setting, 1 study showed that hypoglycemia occurred a median of 3 hours after insulin treatment\textsuperscript{19} and occurred up to 6 hours in another study.\textsuperscript{17} Risk factors for hypoglycemia following insulin treatment of hyperkalemia in ESRD patients include lack of diabetes, use of diuretic medication, and a lower pretreatment glucose.\textsuperscript{14} The risks of serious adverse events related to hypoglycemia associated with insulin treatment for hyperkalemia were highlighted in a survey of 142 trusts in the United Kingdom, which noted 2 deaths directly attributable to insulin–glucose use to correct hyperkalemia.\textsuperscript{21}

CPOE allows providers to electronically order laboratory tests, implement pharmacy orders, and document treatment and management.\textsuperscript{22–24} Protocol treatment plans (herein referred to as “protocols”) are available through CPOE. These protocols may reduce unnecessary variations in treatment, highlight patient-specific treatment options, and allow maintenance and improvement in quality of care.\textsuperscript{25} Protocols for the management of hyperkalemia are used in both the ED and hospital setting, aiming at effective reduction of potassium and reducing the iatrogenic risk of hypoglycemia associated with i.v. insulin use. Providers may not always use the protocols for hyperkalemia management, however, as they may not be aware of the order set within their electronic medical prescribing system. Providers may also individually prescribe each component based on what they have used previously to manage hyperkalemia. Although providers may be familiar with managing hyperkalemia, following protocol plans can highlight nuances that may be specific to the patient, for example, flagging a lower insulin dose for patients with CKD or ESRD or use of other agents for reducing potassium in addition to insulin–glucose, as well as providing order sets for monitoring and management of hypoglycemia.

In this study, we describe the presentation, laboratory values, and pharmacological management of hyperkalemia over a 6-month period in an ED. We noted variable use of the protocol for hyperkalemia treatment, with CKD and ESRD patients receiving higher than recommended doses of insulin suggested by the hospital-recommended protocol for hyperkalemia management. An educational intervention led by pharmacists and nurse specialists was instituted to increase ED providers’ awareness of the protocol for hyperkalemia management available through CPOE, and highlighted the recommended lower dose of insulin for patients with CKD and ESRD. In a second follow-up audit, we reassessed the rate of hypoglycemia following use of insulin–glucose for hyperkalemia management.

**METHODS**

**Patient Population and Ethical Approval**

Study protocol ethical approval for this study were obtained from the humans subjects division at the University of Washington, and the study is adherent to the Declaration of Helsinki.

**Study Design and Methods**

This was a retrospective, quality improvement study carried out before and after an intervention. In the initial audit, patients with hyperkalemia, defined as potassium $\geq$ 6 mEq/l without hemolysis, who presented to a large urban ED (Harborview Medical Centre [HMC], Seattle, WA) from 1 June 2013 through 31 December 2013 were assessed. Patients with a potassium $\geq$ 6 mEq/l who presented to the ED were identified through a laboratory database. After the intervention, a follow-up audit was conducted from 1 July 2015 through 31 January 2016. A flowchart of the audit is provided in Figure 1. No patients were excluded from the analysis, but reasons for non-treatment of hyperkalemia (n = 56 for audit 1 and n = 61 for audit 2) were not pursued.

Pharmacological treatment that was considered part of hyperkalemia management included a $\beta_{2}$ agonist (albuterol), regular insulin, glucose 50%, sodium polystyrene sulfonate (resin), 8.4% sodium bicarbonate, and i.v. calcium. The dosage and route of insulin administration were noted. Blood glucose levels obtained either by point-of-care finger stick measurement or blood draws taken for laboratory analysis were noted. Treatment was stratified based on whether treatment was ordered as part of a protocol available through CPOE (protocol) or were manually entered into the electronic medical record (EMR) (CPOE vs. non-CPOE). When pharmacological potassium-lowering treatment was instituted, the time and dosage of treatment was noted. Hypoglycemia was defined as blood glucose < 70 mg/dl and severe hypoglycemia as blood glucose < 40 mg/dl within 6 hours of insulin treatment.\textsuperscript{26} Acute kidney injury (AKI) was defined as a serum creatinine that was > 0.5 mg/dl higher than the last previously reported creatinine available or, in the case of patients who had no previous presentation to the ED, as oliguria or a serum creatinine > 1.5 mg/dl in patients who had no known previous history of CKD. Presence of CKD was defined as an estimated glomerular filtration rate (eGFR) rate of < 60 ml/min per 1.73 m$^2$ using the Modification of Diet in Renal Disease (MDRD) Study equation. Case records of all patients were reviewed by at least 2 of 4 authors (BM, AC, KC, MP).

The quality improvement intervention was implemented in which clinical nurse educators and
pharmacy staff delivered education to ED providers outlining the availability of a protocol for hyperkalemia through CPOE, and emphasized the appropriate dose of insulin in CKD and ESRD. This was conducted at morning education sessions and at morbidity and mortality conferences. Following this intervention, we re-audited management of hyperkalemia to determine whether improved awareness of the protocol for hyperkalemia and its components resulted in a change in adverse events associated with hyperkalemia management.

**Statistical Analysis**

Statistical analysis was performed using GraphPad software (GraphPad Software Inc., San Jose, CA). Summary statistics of continuous variables were given by mean (SD) or median (interquartile range), as appropriate, and frequencies (percentages) for categorical variables. Comparisons of proportions were performed using a $\chi^2$ test and continuous variables using the Student t test. A $P$ value of $< 0.05$ was considered significant.

**RESULTS**

From 1 June 2013 to 31 December 2013 (audit 1), we identified 125 patients (86 male and 69 female) who had 155 consecutive presentations of potassium ≥ 6 mEq/l without hemolysis. Of the 155 presentations, AKI or CKD was present in 56 (36%), ESRD was present in 74 (48%), and hyperosmolar hyperglycemia was present in 10 (6%). Eleven patients (7%) were treated as part of cardiopulmonary resuscitation. Three patients (2.4%) left without treatment, and 2 patients (1.2%) underwent dialysis before treatment was instituted. Two patients (1.2%) presented with hyperkalemia because of medications (angiotensin-converting enzyme inhibitor treatment with trimethoprim [$n = 1$] or spironolactone [$n = 1$]) in the setting of normal renal function. A total of 102 cases (65%) were single presentations, 12 patients (7%) presented 2 times, 7 (4%) presented 3 times, and 2 (1.2%) had 4 separate presentations for hyperkalemia within the study period.

Table 1 outlines laboratory values for potassium, glucose, creatinine, and bicarbonate at initial presentation to the ED. Creatinine is subdivided based on whether the patient was or was not on regular hemodialysis. Electrocardiographic findings were recorded in the chart in 115 (74%) of cases; abnormal findings are outlined in Table 1. Dialysis treatment was used in 61 (39%) cases, with a mean length of time from release of potassium results to dialysis of 7.4/6.1 hours. Of note, in audit 1, 9 of 155 patients (5.8%) were both hypoglycemic and hyperkalemic on admission, all either with ESRD (6 of 9 patients [55%]) or a glomerular filtration rate (GFR) < 30 ml/min (1 of 9 patients

| Laboratory parameter | Mean ± SD | ECG rhythm** | n (%) |
|----------------------|----------|--------------|-------|
| Potassium (mEq/l)    | 6.73 ± 0.78 | Normal or unchanged ECG | 47 (40) |
| Glucose (mg/dl)      | 186 ± 227 | PTW          | 50 (43) |
| Creatinine (mg/dl)   | 3.1 ± 3.3 | Widening of QRS | 9 (7) |
| (non-ESRD)           |          |              |       |
| Creatinine (mg/dl)   | 11.7 ± 4.1 | Sinus bradycardia with PTW | 2 (1.7) |
| (ESRD)               |          |              |       |
| Bicarbonate (mEq/l)  | 20.1 ± 7.6 | Ventricular fibrillation | 1 (0.8) |
|                      |          | Junctional rhythm | 5 (4) |
|                      |          | Sine wave     | 1 (0.8) |

ECG, electroencephalographic; ED, emergency department; ESRD, end-stage renal disease; PTW, peaked T wave.

*Of 155 cases, 115 had ECG or telemetry findings recorded in the chart for review.
was initiated. Clinical nurse educators and pharmacy staff delivered education to nursing staff and ED providers within the department, regarding the treatment plan recommended at HMC for hyperkalemia management. Emphasis was placed on using a lower dose of insulin in CKD and ESRD, as recommended in the protocol. Cases in which hypoglycemia occurred following insulin-glucose treatment were discussed in morbidity and mortality conferences.

Following this, a follow-up audit (audit 2) was carried out from 1 July 2015 to 31 January 2016, in which 98 patients (69 male and 29 female) with 116 cases of hyperkalemia presented to the HMC ED. Pharmacological treatment was used in 78 patients (67%), and in 58 cases (74%) this was ordered using the protocol. There was a greater use of the protocol in audit 2 (58 of 78 patients [74%] vs. 62 of 99 [62%]). Medications used for the management of hyperkalemia are listed in Table 2. Fewer patients with ESRD were exposed to 10 units of insulin in audit 2 compared to audit 1 (2 of 32 patients [6%] vs. 11 of 43 [25%], respectively, \( P = .03 \)). The number of cases of hypoglycemia associated with insulin treatment was reduced in audit 2 compared to audit 1 (7 of 63 patients [11%] vs. 22 of 76 [28%], respectively, \( P = .01 \)), and there were no cases of severe hypoglycemia (blood glucose < 40 mg/dl), compared to 3 cases in audit 1. Time to first check of glucose improved from 2.37 ± 2.2 hours in audit 1 to 1.33 ± 1.19 hours in audit 2. In audit 2, of 63 patients treated with insulin, 52 (82%) had a glucose recheck within 2 hours and 53 (82%) within 6 hours of insulin administration. Despite better adherence to the protocol, 5 of 7 cases of hypoglycemia occurred in dialysis patients who were appropriately given 5 units of insulin and 50% glucose using the protocol for hyperkalemia through CPOE (Table 3).

### DISCUSSION

This study shows that in a cohort of patients presenting to the ED, hypoglycemia is common following the use of i.v. insulin for management of hyperkalemia despite concurrent use of glucose. We implemented education within the ED to increase the use of a protocol for hyperkalemia through CPOE, with the aim of reducing hypoglycemia associated with insulin–glucose treatment of hyperkalemia. With this intervention, the number of ESRD patients receiving appropriate insulin therapy was increased, and there was a reduction in hypoglycemia, including no cases of severe hypoglycemia in the follow-up audit.

A notable finding from the initial audit was the high incidence of hypoglycemia (28% of cases) following insulin administration. In the experimental or hospital
setting, the incidence of hypoglycemia associated with the use of insulin ranges from 0% to 50% depending on the amount of glucose and insulin administered.\textsuperscript{12,18,19,27–30} Hypoglycemia is an expected outcome of insulin therapy, based on the expected pharmacokinetics of its glucose-lowering effects.\textsuperscript{9} Glucose without insulin treatment is not recommended, as the high osmolarity of 50% glucose can increase serum potassium concentrations because of solute drag.\textsuperscript{11} In CKD and ESRD, due to the loss of the

Figure 2. Outline of management protocol for hyperkalemia available for emergency department (ED) providers to use as part of computerized provider order entry (CPOE) system. This is a summary of the comprehensive protocol for hyperkalemia management available through the CPOE system in the ED. The protocol stipulates monitoring of patients, including a facilitating telemetry order and potassium recheck. The protocol indicates a different treatment algorithm based on whether the patient had end-stage renal disease (ESRD) and whether hyperkalemia was emergent (K > 6.5 or K ≥ 5.3 with electrocardiographic [ECG] changes). Treatment is stratified according to insulin and non–insulin-based therapy with information on the rationale for treatment. Blood glucose (BG) monitoring guidelines after insulin treatment are also provided, with a link to a hypoglycemia management protocol. amps, Ampules; CKD, chronic kidney disease; HD, hemodialysis; POC, point of care; Rx, prescription.
It also reflects the considerable medical complexity present in ESRD patients presenting to the ED, who often have multiple comorbidities in addition to hyperkalemia. Despite more consistent use of a protocol for hyperkalemia through CPOE, all cases of hypoglycemia occurring in audit 2 were in hemodialysis patients who received 5 units of insulin. This suggests that ESRD patients receiving insulin therapy need to be carefully monitored for hypoglycemia up to 6 hours after treatment, as hypoglycemia was recorded in the cohort as late as 6 hours after treatment, and this has been noted in other studies of CKD patients who received an i.v. infusion of insulin plus glucose to treat hyperkalemia. Most of the patients developing hypoglycemia were not diabetic. Alternative treatments should be considered when possible, including performing dialysis in a timely fashion in ESRD patients as well as using non—insulin-based therapies. With the advent of new resins for the management of hyperkalemia, the dependence on acute reduction of hyperkalemia in this patient population may be reduced. Our study also highlights the logistical difficulty complying with glucose checks required for hyperkalemia management, which may be more accentuated in an ED environment.

Many patients in the study had ESRD and several patients presenting multiple times, reflecting the high burden of use on the ED for managing hemodialysis patients. The high rate of hypoglycemia may be due to nutritional deficiencies known to occur in ESRD. Many of the cases of hypoglycemia occurred in ESRD patients, and several ESRD patients presented with both hypoglycemia and hyperkalemia. Despite this, there was no significant difference in the number of hemodialysis patients treated between the time periods studied that would explain the difference in rates of hypoglycemia. Hypoglycemia is a potentially fatal disorder, with mortality rates for type 1 diabetic individuals ranging from 4% to 10% of deaths. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, type 2 diabetic patients in the intensive treatment arm, which was associated with hypoglycemia, had a 3-fold higher mortality. Although hypoglycemia can lead to brain death, most deaths are likely related to ventricular arrhythmias. ESRD patients have a high mortality rate, and ventricular

Table 2. Summary of pharmacological treatment used in patients presenting with hyperkalemia

| Pharmacological management     | Audit 1, n = 99 | Audit 2, n = 78 |
|-------------------------------|----------------|----------------|
|                               | CPOE/Non-CPOE  | CPOE/Non-CPOE  |
| Calcium gluconate             | 78 (50.3)      | 50/28          |
| Sodium bicarbonate (8.4%)     | 40 (25.8)      | 29/11          |
| β₂ agonist (albuterol)        | 26 (16.7)      | 20/6           |
| Kayexalate resin              | 64 (41.2)      | 35/29          |
| Regular insulin               | 76 (76)        | 48/27          |

*CPOE (computerized physician order entry) refers to orders being placed through protocol treatment plans available through the electronic medical record; Non-CPOE refers to orders individually entered into the electronic medical record.

Table 3. Clinical features of patients with hypoglycemia compared with no hypoglycemia and patients not treated with insulin

| Blood glucose | < 40 mg/dl | 40—69 mg/dl | > 70 mg/dl | Not treated with insulin |
|---------------|------------|-------------|------------|--------------------------|
|               |Audit 1     |Audit 2      |Audit 1     |Audit 2      |Audit 1     |Audit 2      |
| Male/female   | 0/3        | 11/8        | 5/2        | 42/12       | 36/20      | 56/23       | 37/14       |
| Age (yr)      | 62.6 ± 18.1| 50.1 ± 12.4 | 41.6 ± 14.5| 55.8 ± 14.8 | 58.1 ± 15.7| 52.2 ± 15.3 | 54.6 ± 13.8 |
| ESRD (yes/no) | 3/0        | 12/7        | 5/2        | 28/26       | 27/29      | 31/48       | 20/31       |
| Diabetes (yes/no) | 1/2      | 2/17        | 2/5        | 17/37       | 35/21      | 22/57       | 20/31       |
| Insulin dose (< 5 / > 5 units) | 1/2      | 8/11        | 6/1        | 42/12       | 43/13      | NA          | NA          |
| K⁺ (mEq/l)    | 7.3 ± 0.6  | 7.3 ± 1.2   | 6.7 ± 0.7  | 6.6 ± 0.7   | 6.6 ± 0.6  | 6.4 ± 0.6   | 6.4 ± 0.5   |
| Creatinine (mg/dl) (ESRD) | 9.8 ± 1.8 | 13.5 ± 4.4  | 11.0 ± 1.6 | 11.3 ± 3.9  | 10.7 ± 3.5 | 6.2 ± 5.4   | 11.7 ± 3.3  |
| Creatinine (mg/dl) (non-ESRD) | NA        | 4.3 ± 2.5   | 4.8 ± 2.7  | 3.7 ± 3.8   | 3.3 ± 3.7  | 6.2 ± 5.4   | 2.9 ± 3.0   |
| Blood glucose at baseline (mg/dl) | 122 ± 70  | 99 ± 24     | 109 ± 32   | 155 ± 98    | 266 ± 289  | 231 ± 308   | 247 ± 283   |

ESRD, end-stage renal disease; NA, not applicable.
arrhythmias have been strongly implicated as a cause of death. It is possible that the metabolic stress associated with hypoglycemia is a risk factor for inducing arrhythmias. Hypoglycemia can have deleterious effects on neurocognitive function. Cognitive dysfunction is common in ESRD patients, and their ability to respond to hypoglycemia may be reduced because of autonomic dysfunction. Although studies from the Diabetes Control and Complications Trial (DCCT) showed that there was no difference in neurocognitive outcomes among adults experiencing severe hypoglycemia compared to those without a history of severe hypoglycemia, this may not be same in ESRD patients.

Our next finding was that in the follow-up audit, management of hyperkalemia could be standardized to reduce hypoglycemia associated with the use of i.v. insulin, but that protocol use needed to be reinforced to ensure safety. Before educational interventions regarding the protocol were instituted within the ED, many providers prescribed various types of treatment plans, likely based on their previous clinical experience. After the educational program, more patients were treated according to the protocol. There was lower use of 10 units of insulin for patients with ESRD. Despite providers accessing the protocol to manage treatment of hyperkalemia, we noted that the use of ß3 agonists increased, whereas the use of potassium-binding resin decreased.

Our study adds to findings of previous work examining adherence of physicians to hyperkalemia treatment guidelines albeit in a pre—electronic medical record era. Ackers et al. carried out a prospective study on physician adherence to treatment recommendation for hyperkalemia management in a medical—surgical unit in which treatment recommendations for hyperkalemia management were sent when hyperkalemia was noted. The study found no improvement in adherence to treatment recommendations (38% observation phase, 42% notification phase, P < .05). The authors also noted that treatment adherence was higher in the intensive care unit, likely reflecting lower patient-to—provider and nurse number. This indicates that although guidelines may be at physicians’ and other health care providers’ disposal, direct education about their use is an important component in ensuring that these guidelines are appropriately used.

There are several limitations to this study. We focused on patients treated for hyperkalemia and did not explore data on the patients who were not treated or how they fared. In addition, this study examined patients presenting to an ED in which a CPOE and electronic prescribing system is available, and therefore may not apply to hospitals in which this is not available. Moreover, improved knowledge on hyperkalemia management may not fully explain the fall in incidence of hypoglycemia between the 2 study periods; another factor or factors may be involved that we have not identified. There was only a modest improvement in the use of the protocol between the 2 audit periods. Although use of the protocol could have been improved by making it mandatory, this was not pursued, because treatment of hyperkalemia is complex and there is a risk that reducing physician autonomy to tailor treatments based on patient’s clinical status may be deleterious in the long term. Finally, given the increased use of CPOE in hospitals, a randomized controlled trial in which mandatory implementation of order entry is compared with physician entry may be necessary, but was not within the scope of this project.

It is also unclear what contributed to fewer patients requiring treatment between the audit periods. In the initial audit, there were multiple admissions of some individuals, which may have contributed to a higher number of cases in the initial audit that were not present in the follow-up audit (audit 1: 122 individuals with 155 presentations, vs. audit 2: 98 individuals with 112 presentations). HMC is a county hospital that provides care to a socially deprived population, including patients with drug addiction. We can only hypothesize that the reason for fewer patients being treated for hyperkalemia between the 2 audit periods was a reduction in the number of patients with marginal social circumstances presenting for emergent dialysis. We focused mainly on the use of insulin therapies and their safety in the ED, and did not critique the uptake of other treatment modalities. Of concern, despite standardized management of hyperkalemia, hypoglycemia still occurs, which suggests that further studies of the appropriate dose of insulin and glucose for CKD and ESRD patients is necessary. Finally, glucose checks in the study did not comply with that recommended by the protocol. Given that not all patients had blood glucose checked after insulin administration, it is possible that episodes of hypoglycemia were missed.

In summary, improving ED providers’ awareness of a protocol for hyperkalemia via CPOE was associated with an increase in appropriate prescribing of a lower dose of insulin in ESRD, and, as a result, fewer patients experienced hypoglycemia. The study also highlights the difficulty in achieving the recommended blood glucose and potassium checks following insulin—glucose treatment for hyperkalemia. Our study suggests that even with a treatment protocol easily available via CPOE, continued education is needed to ensure optimal management and to improve clinical outcomes.
DISCLOSURE

All the authors declared no competing interests.

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