Continuous infusion of a standard combination solution in the management of hyperkalemia

Halima S. Janjua, John D. Mahan, Hiren P. Patel, Mark Mentser and Andrew L. Schwaderer

Division of Nephrology, Department of Pediatrics, Nationwide Children’s Hospital, The Ohio State University, Columbus, OH, USA

Correspondence and offprint requests to: Andrew L. Schwaderer; E-mail: schwaderer.5@osu.edu

Original Articles

Abstract

Background. Hyperkalemia, due to its effect on cardiac conductivity, is a potentially life-threatening electrolyte abnormality. Multiple therapeutic agents may be used alone or in combination for its prompt management.

Methods. We report on the safety and efficacy of continuous infusion of a solution containing fixed concentrations of calcium gluconate, insulin, dextrose and sodium acetate (HyperK-Cocktail) for the treatment of hyperkalemia. This solution is prepared at our institution and is infused parenterally until the plasma potassium level stabilizes. Twenty-one consecutive hyperkalemic patients managed with HyperK-Cocktail on 23 occasions are reported.

Results. None of the subjects had intravenous extravasation injuries, hypernatremia, hypocalemia, hypercalcemia or alkalosis during HyperK-Cocktail infusion. Transient hyperglycemia developed in nine subjects and hypoglycemia in one subject. The decrease in serum potassium was similar in the initial hour when compared to prior studies using a beta-agonist and/or insulin and glucose; a larger decrease was present from 2 to 8 h with the HyperK-Cocktail. The plasma potassium decreased by a mean of 1.0, 1.7, 2.1 and 2.1 mmol/L at 1, 2, 4 and 8 h, respectively. The mean serum potassium at hours 1–8 was significantly lower than the initial level.

Conclusion. The results of our study demonstrated that HyperK-Cocktail is a safe and effective combination therapy for children with hyperkalemia.

Keywords: acetate; bicarbonate; calcium; children; insulin

Introduction

Hyperkalemia is a potentially lethal condition that occurs in between 1 to 10% of hospitalized patients [1, 2]. Hyperkalemia can lead to significant morbidity and mortality from ventricular arrhythmias if not treated promptly [3]. Primary goals of management of severe hyperkalemia are to (i) prevent or diminish its electrophysiologic effects on myocardium, (ii) redistribute potassium from extracellular to intracellular compartment and (iii) increase removal of potassium from the body. Intravenous (i.v.) calcium is used to stabilize the myocardial membrane effects of hyperkalemia. Calcium is infused over 2–3 min but, as its effects are short lived and may need to be redosed every 30–60 min [4], a continuous infusion of calcium has been suggested as a more efficacious dosing strategy [5]. Potassium is redistributed to the intracellular compartment by insulin, beta-adrenergic agonists and sodium bicarbonate. Prior publications have suggested that different combinations of the aforementioned medications might be more effective than monotherapy in lowering plasma potassium level [6, 7]. Elimination of potassium from the body is facilitated by diuretics, such as furosemide, ion-exchange resins, such as sodium polystyrene, or dialysis. Despite the frequency and potential severe sequelae of hyperkalemia, treatment is often delayed even in an intensive care unit (ICU) setting [2]. Most treatment studies have involved limited numbers of patients and adverse events of treatment have been rarely reported. Timely treatment is often more difficult to initiate in children secondary to the need to calculate doses and prepare medications based on body size. A continuous infusion of standard solution of effective medications used in the management of hyperkalemia might expedite timely treatment, limit dosing errors and prevent inadequate redosing.

A combination solution, HyperK-Cocktail, has been used at our institution for treatment of hyperkalemia for over 20 years. This solution is prepared in our institution’s pharmacy by compounding 30% dextrose, regular insulin, 10% calcium gluconate and sodium acetate to give final dextrose concentration of 27%. Specific amounts of all constituents are detailed in Table 1. It can be prepared as quickly as 15 min of receiving an order through use of an Exacta-Mix 2400 Compounder (BAXA Corporation, Englewood, CO). Each bag is labeled with 30 h expiration time to maintain sterility despite longer stability of this preparation in solution. The solution is infused continuously through a central or peripheral i.v. access at a recommended rate of 2 mL/kg/h for the first hour and then 1 mL/kg/h until potassium stabilizes at a safe level. The decision to start and stop HyperK-Cocktail is typically made at the discretion of the managing physician. We hypothesized that HyperK-Cocktail has minimal risk for electrolyte...
obtained prior to administration of the secondary potassium lowering agent. Medicines were given mid-HyperK-cocktail infusion, only potassium levels.

Sodium acetate 100 mEq
10% Calcium gluconate 3 g
Regular insulin 30 U

abnormalities and is efficacious in the management of hyperkalemia for the majority of patients.

Materials and methods

Subjects
Following approval by the Institutional Review Board, we performed a retrospective chart review on all subjects with hyperkalemia who were managed with HyperK-Cocktail at Nationwide Children’s Hospital. Inclusion criteria included subjects aged 0–18 years managed with HyperK-Cocktail for hyperkalemia with a non-hemolyzed plasma potassium of >5.5 mmol/L in all ages except neonates in whom plasma potassium of >6.0 mmol/L was considered as inclusion criteria. Subjects who were concomitantly on renal replacement therapy were excluded.

Methods
All patients were included in the safety analysis of the infusion. Patients who received albuterol, furosemide or sodium polystyrene before a follow-up plasma potassium level were excluded from the efficacy analysis; if these medicines were given mid-HyperK-cocktail infusion, only potassium levels obtained prior to administration of the secondary potassium lowering agent were included in the efficacy analysis.

Twenty-one subjects met the criteria for our study with a total of 23 incidences of hyperkalemia managed with HyperK-Cocktail. These subjects were identified by review of medication orders in pharmacy database.

Salient clinical parameters were recorded and the glomerular filtration rate was estimated using the Schwartz formula [8]. The mean cumulative change in plasma potassium from the time of initiation of HyperK-Cocktail (Time 0) to hours 1 through 8 was determined by linear regression of initial potassium and levels within 30 min of each hour (30–90 min for 1 h, 91–150 min for 2 h, 151–210 min for 3 h and etc.). If more than one potassium level was obtained within 30 min of each hour, the level closest to the hour was used. The difference between the initial plasma potassium and the plasma potassium in each time group was evaluated; significance was asserted when P values were <0.05 as calculated by Student’s t-test (two-tailed two-sample equal variance, paired or unpaired). The curve representing every potassium measurement on all patients was evaluated for best fit with linear, polynomial and exponential regression with Excel (Microsoft Corporation, Redmond, WA).

Results

Patient characteristics
The characteristics of the included subjects are presented in Table 2. The subjects ranged from 6 days to 16 years with a median age of 6 months. Included were 11 (52 %) males and 10 (48%) females. Race was recorded in 19 subjects. Fourteen of nineteen (67%) were Caucasians and 5/19 (24%) were African-Americans. These subjects had a wide range of primary diagnoses. The cause for hyperkalemia was identified as acute kidney injury in nine (39%), tissue/cell breakdown in six (26%), exacerbation of chronic kidney disease in two (9%), excessive potassium administration in one (4%), acidosis in one (4%), recurrent hyperkalemia after stopping HyperK-Cocktail in two (9%) and multifactorial causes in two (9%).

Efficacy
Mean plasma potassium level at the start of HyperK-Cocktail was 7.6 mmol/L with range from 5.8 to 11.1 mmol/L. Mean potassium levels at hours 1 through 8 were determined by linear regression (Figure 1). The differences between the
initial plasma potassium level and the levels at hours 1 through 8 were all statistically significant ($P < 0.05$). Compared to published outcome studies of patients treated for hyperkalemia, the mean plasma potassium of our patients treated with the HyperK-Cocktail was comparable at hour 1 and trended lower for hours 2–8 (Table 4). None of the
subjects had rebound hyperkalemia during HyperK-Cocktail infusion, but two did have rebound hyperkalemia after the infusion was stopped. XY scatter graph (Figure 2) of all potassium levels on all patients included in the efficacy analysis demonstrates maintenance of the lower potassium levels past hour 8 of infusion.

The HyperK-Cocktail was stopped due to improvement in plasma potassium level in 16 cases. In three cases, HyperK-Cocktail was stopped at the initiation of dialysis. Dialysis was started due to acute renal failure and hypertension in Subject 3, tumor lysis syndrome in Subject 5 and fluid overload and uremia in Subject 22. In these subjects, plasma potassium levels before starting dialysis were 6.4, 7.1 and 4.5, respectively.

Discussion

Hyperkalemia has a significant impact on both conduction and automaticity of cardiac cells. Calcium acts intracellularly to antagonize the myocardial effects of hyperkalemia. The duration of action for i.v. 10% calcium gluconate is 30–60 min that warrants repeated doses or a continuous infusion. The efficacy of calcium in preventing the cardiac complications of hyperkalemia has not been directly studied in humans [15]. In our study, serial follow-up EKGs were not obtained, so we were not able to determine the time between initiation of therapy and stabilization of the EKG.

If EKG changes are more severe than peaked T waves, a traditional bolus dose of calcium gluconate or calcium chloride prior to starting HyperK-Cocktail should be considered. Bradycardia can occur with rapid calcium gluconate infusion. In our study, four patients died. Two patients died from withdrawal of care secondary to worsening multi-organ failure. Both the subjects with asystole (Subjects 10 and 14) had initial cardiac arrhythmias preceding the initiation of the HyperK-Cocktail by over an hour and their plasma potassium decreased to <6.5 at the time of death. The patients who died did not have onset of other electrolyte disturbances, such as sodium, calcium, magnesium and chloride imbalances following the initiation of the HyperK-Cocktail. Therefore, it is unlikely that lack of efficacy of the HyperK-Cocktail was responsible for the cardiac arrest.

Insulin lowers plasma potassium level by shifting potassium into the cells. Its onset of action is within 15 min and its effect lasts ~60 min [7]. It is usually given with dextrose to avoid hypoglycemia that remains a common adverse effect and is reported in up to 75% of the cases [12]. Hypoglycemia was seen only in one subject (5.5%) in our study, but hyperglycemia was more prominent with HyperK-Cocktail and was seen in 10 (50%) cases. This hyperglycemia is likely due to the lower insulin/dextrose ratio in the infusion versus traditional therapy (0.22 U/gm versus 0.4 U/gm). The one subject with hypoglycemia (Subject 2) had concurrent gram-negative sepsis that can explain his transient hypoglycemia. We believe that HyperK-Cocktail should be used with caution in subjects with baseline hyperglycemia with frequent blood glucose monitoring. Of note, blood glucose level was not recorded during five of the HyperK-Cocktail infusions; therefore, the risk of hypoglycemia or hyperglycemia may be different than recognized in this series.

The role of i.v. sodium bicarbonate in hyperkalemia is controversial and studies evaluating its efficacy have yielded inconsistent results. It does not affect plasma potassium levels significantly in the first 60 min after administration [16–18] though it might be of some value after 4–6 h of continuous infusion [14]. Kim [16, 18] showed a synergistic effect of sodium bicarbonate with insulin and salbutamol; another study reported no such synergy with insulin or albuterol however, patients in this study were not hyperkalemic [17]. Since acetate and gluconate are metabolized in the liver to generate bicarbonate, caution is needed when using HyperK-Cocktail in patients with liver disease. None of our subjects experienced hypernatremia, metabolic alkalosis or hypocalcemia.

Despite the calcium and the hypertonicity of the HyperK-Cocktail, we observed no problems with tissue damage secondary to i.v. infiltration in our subjects. The HyperK-Cocktail is preferably given through a central access since tissue damage with peripheral infusion is possible. If HyperK-Cocktail is initiated in a peripheral i.v., we suggest that central access is considered as soon as possible and that the i.v. site is closely monitored and quickly stopped if extravasation occurs.
Continuous infusion of a standard combination solution

Table 4. Comparison of HyperK-Cocktail therapy to published outcome studies of hyperkalemia therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Start K⁺</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo [9]</td>
<td>9</td>
<td>5.7</td>
<td>*0.3</td>
<td>*0.3</td>
<td>0.0</td>
<td>–0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo [10]</td>
<td>11</td>
<td>6.9</td>
<td>0.7</td>
<td>–0.7</td>
<td>–1.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol 400 μg, nebulized [a]</td>
<td>8</td>
<td>7.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol 10 mg, nebulized [9]</td>
<td>10</td>
<td>5.9</td>
<td>–0.5</td>
<td>–0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol 20 mg, nebulized [7]</td>
<td>10</td>
<td>5.6</td>
<td>–0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol 20 mg, nebulized [9]</td>
<td>8</td>
<td>5.8</td>
<td>–0.9</td>
<td>–1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol 0.5 mg i.v. [11]</td>
<td>24</td>
<td>7.0</td>
<td>–1.4</td>
<td>–1.0</td>
<td>–0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose 40 gm i.v., insulin 10 U i.v. 15 min later [12]</td>
<td>10</td>
<td>&gt;6</td>
<td>–1.0</td>
<td>–0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin 10 U i.v. bolus, 50 ml of 50% glucose over 5 min [7]</td>
<td>12</td>
<td>5.5</td>
<td>–0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin 0.05–0.1 U/kg/h, glucose ('existing i.v. fluid') [13]</td>
<td>7</td>
<td>8.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–0.8</td>
</tr>
<tr>
<td>Insulin 10 U i.v. bolus, 50 ml of 50% glucose over 5 min, albuterol 20 mg, nebulized [7]</td>
<td>10</td>
<td>5.9</td>
<td>–1.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose 40 gm i.v., insulin 10 U i.v. 15 min later, salbutamol 0.5 mg i.v. [12]</td>
<td>10</td>
<td>&gt;6</td>
<td>–1.5</td>
<td>–1.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.4% NaHCO₃ 4 mmol/min × 1 h then 0.5 mmol/min/h 2–6 [14]</td>
<td>12</td>
<td>6.0</td>
<td>–0.1</td>
<td>–0.2</td>
<td>–0.6</td>
<td>–0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HyperK-Cocktail</td>
<td>21</td>
<td>7.7</td>
<td>–1.0</td>
<td>–1.7</td>
<td>–1.6</td>
<td>–2.1</td>
<td>–1.7</td>
<td>–2.0</td>
<td>–2.2</td>
<td>–2.1</td>
</tr>
</tbody>
</table>

*a*All plasma potassium (K⁺) levels and cumulative change in K⁺ are listed in millimoles(milliequivalent)/liter.

*b*Dose repeated every 2 h until the plasma K⁺ was <5.

*c*Neonatal study.

*d*Twenty-one occurrences of hyperkalemia in 19 patients were included, not every patient had an occurrence in every time period resulting in some variation of the n and mean initial K⁺ (hour/initial K⁺; 1/10/7.9; 2/11/8.1; 3/11/7.9; 4/10/7.6; 5/7/8.4; 6/8/7.9; 7/8/7.8; 8/4/8.0.

Compared to published studies of patients treated for hyperkalemia, the HyperK-Cocktail appears to lower the plasma potassium by a comparable amount at 1 h. Following 1 h, the HyperK-Cocktail appears to be more efficacious at lowering the plasma K level and sustaining these lower levels than insulin and glucose, beta agonist or a combination thereof (Table 4). One of the benefits of HyperK-Cocktail, in our experience, was a lack of rebound hyperkalemia during infusion. Some studies did not report the plasma potassium level after 60 min of a bolus of insulin and dextrose, whereas in others, rebound hyperkalemia has been a problem [7, 16]. Recurrent hyperkalemia is still possible once HyperK-Cocktail is stopped as it was seen in subjects. It should be noted that the HyperK-Cocktail results in a shift of potassium from the extracellular to intracellular space and removal of potassium from the body with dialysis, furosemide and/or sodium polystyrene is a critical component of ongoing hyperkalemia management.

In conclusion, the combination of dextrose, insulin, calcium gluconate and sodium acetate in one solution at fixed concentrations provides several potential benefits compared to intermittent dosing of the individual components. The need for multiple time-consuming dosing calculations in an urgent situation like hyperkalemia is avoided, titration to clinical effect is simplified, and the potential for dosing error is reduced as well as the risk of inadequate redosing and rebound hyperkalemia. Potential error in pharmacy compounding of the solution still exists although it was not observed in this study. Our results demonstrate that the HyperK-Cocktail is effective at lowering the plasma potas-

Fig. 2. After 8 h, the potassium continued to slowly decrease as represented by the scatter graph of all plasma potassium levels (n = 120) on all events of hyperkalemia (n = 21). The ‘best fit’ curve was obtained by polynomial regression to the third order and represented by the equation:

\[
Y = -0.0005X^3 + 0.0247X^2 - 0.402X + 7.2862.
\]

While this trendline demonstrates maintenance of stable potassium levels several hours following initiation of the HyperK-Cocktail infusion, it underrepresents the decrease in potassium in the initial few hours since patients with multiple readings have disproportionate influence and the large number of readings after the initial 8 h decreases the initial slope.
monitored. This study was limited by its retrospective nature, a limited number of subjects, variability of dosing, absence of follow-up EKGs and lack of a control group treated with intermittent calcium, glucose, insulin and bicarbonate. This analysis focused on children ≤18 years of age, and therefore, the safety, efficacy and dosing of the HyperK-ccktail for adults remains to be determined. Further prospective studies are needed to study adult patients, determine the most efficacious concentrations of insulin, directly compare a continuous infusion of HyperK-Cocktail to intermittent treatment dosing.

Conflict of interest statement. None declared.

References


Received for publication: 8.6.10; Accepted in revised form: 9.11.10