

Albuterol for the Treatment of Hyperkalemia

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REQUEST

What is the role of albuterol in the treatment of hyperkalemia?

RESPONSE

BACKGROUND

Hyperkalemia, defined as serum potassium >5.5 mEq/L, is a life-threatening complication that can occur with renal insufficiency, metabolic acidosis, muscle breakdown, stress, increased administration of exogenous potassium through salt substitutes, and hemolysis with blood transfusions. Various drugs have been implicated in elevating serum potassium concentrations. Included are penicillin V potassium, angiotensin converting-enzyme inhibitors, angiotensin II antagonists, potassium-sparing diuretics, digoxin, and β -antagonists. These medications can cause hyperkalemia even at their normal therapeutic dosages.¹

Since potassium is primarily an intracellular cation, with 98% found inside cells, small shifts between the intracellular and extracellular spaces can result in dramatic physiologic effects.² Hyperkalemia is a medical emergency because of its potential to cause arrhythmogenic effects on cardiac tissue, which can ultimately result in asystole.³ The goals in the treatment of hyperkalemia are to (1) block the adverse effects of potassium on the heart muscle, (2) redistribute potassium from outside to inside cells, and (3) enhance the excretion of potassium from the body. Potassium is sequestered within cells and intracellular potassium cannot be measured easily. Therefore, serum potassium concentrations may not represent the true status of total body potassium. Patients should be clinically assessed and treated based on the manifestations they exhibit as well as risk factors such as electrolyte imbalance and comorbid cardiovascular disease. Patients with acute changes in potassium may develop more critical complications than patients who experience a more gradual shift. Furthermore, not all hyperkalemic situations should be treated.

For example, the hyperkalemia that occurs during diabetic ketoacidosis may resolve with the correction of the glucose status and even reveal a hypokalemic state. In vitro hemolysis will also raise measured potassium concentration, but does not represent a clinical situation in the patient. Therefore, it should not be treated.

As a general guide, changes in the electrocardiogram often parallel rises in potassium concentration; however, interpatient variations do occur. When potassium concentrations reach 5.5–6.0 mEq/L, the electrocardiogram often shows peaked T waves and QRS shortening. At this point, if the patient is otherwise hemodynamically stable, administration of diuretics, like furosemide, or ion-exchange resins, like sodium polystyrene sulfonate, is effective. Furosemide enhances the renal excretion of potassium by altering its reabsorption in the kidney. Sodium polystyrene sulfonate works by exchanging 1–2 mEq of sodium for each mEq of potassium that is bound in the gastrointestinal tract. The potassium is then eliminated from the body.²

When potassium concentrations rise to between 6 and 7 mEq/L, PR and QRS complex prolongation are common. When these cardiac complications exist, glucose, insulin, and probably sodium bicarbonate should be administered to quickly remove potassium from circulation by shifting it into the intracellular fluid where it is relatively harmless. The intracellular and extracellular potassium concentrations are maintained by Na^+/K^+ adenosine triphosphatase (ATPase) in cell membranes, which exchanges sodium for potassium in a 3:2 ratio. This “pump” uses ATP hydrolysis as its energy source.^{4,5} Activation of this pump enhances the movement of potassium into cells. This effect is accomplished with the use of insulin and glucose. The proposed mechanism is that insulin can increase the ATP hydrolysis rate.⁴ Glucose is administered to counteract the hypoglycemic effect of insulin. Another method used to shift potassium intracellularly is the administration of sodium bicarbonate. The reasoning behind this is that metabolic acidosis can cause an extracellular potassium shift. Correcting acidosis with bicarbonate can reverse this shift and lower potassium concentrations. However, the efficacy of bicarbonate treatment is often inconsistent.⁶ Using bicarbonate or insulin and glucose only shifts potassium into cells temporarily. Therefore, these methods should always be coupled with ion-exchange resins or hemodialysis as a definitive means to correct severe hyperkalemia.

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If potassium concentrations exceed 7 mEq/L, the risk for cardiac complications increases. There can be widening and flattening of the QRS complex, which can quickly progress to asystole. In any setting of severe cardiac decompensation in the presence of elevated potassium concentrations, calcium gluconate (10–20 mL of 10% solution) or calcium chloride should be given to counteract these adverse cardiac effects. It is vital to understand that calcium administration has no effect on reducing the total body potassium concentration.² Other modalities should be initiated simultaneously.

Recently, there has been increasing investigation on the use of albuterol as an alternative approach for shifting potassium intracellularly. Albuterol is a β_2 -agonist that is believed to exert a hypokalemic effect by binding to a β_2 -adrenoreceptor, resulting in adenylate cyclase activation. Adenylate cyclase stimulates the production of cyclic adenosine monophosphate, which is then used by the Na^+/K^+ ATPase pump to transfer potassium into the intracellular space. Because β_2 -agonists and insulin work on separate aspects of the pump, the effects of these two agents are additive.^{7,8}

CLINICAL TRIALS

Several small studies have been conducted to evaluate the efficacy of albuterol use in the treatment of hyperkalemia, generally in patients with renal failure. The following are some examples of these studies.

Montoliu et al.⁹ conducted a two-part study to evaluate the effect of albuterol on serum potassium in patients with chronic renal failure. In part 1, the investigators evaluated 20 patients with glomerular filtration rates <5 mL/min who were receiving maintenance hemodialysis. All patients were clinically stable with a mean pretreatment serum potassium concentration of 5.6 ± 0.2 mEq/L. Albuterol sulfate 0.5 mg, in 1 dL of dextrose 5% in water, was administered intravenously over 10–15 minutes. The mean potassium concentration fell to 4.5 ± 0.2 mEq/L ($p < 0.001$) within 30 minutes. This concentration was maintained even 60 minutes after albuterol administration. In part 2, 24 patients with acute or chronic renal failure and hyperkalemia were given the same treatment (mean serum urea nitrogen concentration 117.5 ± 9.5 mg/dL, mean serum creatinine concentration 9.8 ± 0.8 mg/dL, mean pretreatment potassium concentration 7 ± 0.2 mEq/L). Within 30 minutes, the potassium concentration fell to 5.6 ± 0.2 mEq/L (p value not stated) which was maintained until the 60-minute mark. Even at 360 minutes, the potassium concentrations were significantly (p value not stated) below the initial concentrations. This is consistent with the 4- to 6-hour half-life of albuterol. However, some patients showed a relative resistance to the hypokalemic effect of albuterol, showing a maximal reduction in potassium of only 0.5–0.6 mEq/L.

In both groups of patients, the albuterol infusion was associated with a significant rise in insulin and glucose concentrations, as well as in heart rate. The authors believed that the drop in potassium was due to the albuterol and not the increase in endogenous insulin since three diabetic patients included in this study experienced the same reduction in potassium while their subnormal or undetectable unbound C-peptide concentrations remained constant. This infers that the reduction in potassium can occur without insulin. There was no change in serum sodium concentration, arterial pH, pCO_2 ,

aldosterone concentration, or arterial blood pressure. Eight patients in part 1 (40%) and 9 patients in part 2 (38%) had tremor; six patients in part 1 (30%) and four patients in part 2 (17%) had generalized, ill-defined discomfort. These adverse effects resolved without treatment. The authors concluded that intravenous albuterol is safe and effective for the treatment of hyperkalemia in patients with acute or chronic renal failure.⁹

Allon and Copkney⁸ demonstrated the additive effect of the coadministration of albuterol with insulin and glucose. In this study, 10 patients with persistent hyperkalemia were treated with three different regimens: intravenous administration of regular insulin 10 units with 50 mL of glucose 50%, albuterol 20 mg nebulized over 10 minutes, and a combination of the first two treatments. Each treatment regimen was separated from the next by at least one week. Potassium reductions of 0.65 mEq/L were seen with both albuterol and insulin plus glucose. When patients received combination therapy, their mean potassium concentration fell by 1.21 mEq/L ($p < 0.001$ vs. baseline; $p < 0.05$ vs. the other two treatment regimens). About 75% of the patients experienced hypoglycemia (plasma glucose 50.7 ± 5.4 mg/dL) when treated with insulin and glucose. Patients receiving albuterol alone had an elevation in serum glucose concentrations (plasma glucose 123.1 ± 9.0 mg/dL; baseline glucose 84.6 ± 5.4 mg/dL). This is consistent with β_2 -agonistic activity on the liver where stimulation of gluconeogenesis and glycogenolysis occurs.^{6,10–12} In patients who received the combination therapy, albuterol seemed to offset the expected hypoglycemia from insulin therapy. There was no change in blood pressure in any of the treatment regimens. Heart rate was mildly elevated in patients when they were treated with insulin or albuterol ($+6.6 \pm 2.3$ and $+6.9 \pm 3.0$ min^{-1} , respectively). When the subjects were treated with the combined regimen, heart rate increased substantially ($+15.1 \pm 6.0$ min^{-1} ; $p < 0.002$). Four patients (40%) were resistant to albuterol treatment, with a maximal decrease in serum potassium concentration following albuterol therapy of <0.5 mEq/L. The authors concluded that nebulized albuterol 20 mg and intravenous regular insulin 10 units produced similar hypokalemic effects in maintenance hemodialysis patients. Coadministration of the drugs resulted in a greater decrease in plasma potassium than that observed with either drug alone.⁸

Another study¹² showed that the incidence of adverse effects with albuterol use can be minimized by nebulizing the drug instead of administering it intravenously, while maintaining equivalent efficacy. A total of 15 patients with chronic renal failure (blood urea nitrogen >80 mg/dL, creatinine >8.0 mg/dL) were enrolled in the study. Five were excluded due to lack of response to intravenous albuterol (maximal decrease in plasma potassium <0.5 mEq/L). Ten patients received albuterol 0.5 mg intravenously for one episode of hyperkalemia and 10 mg nebulized albuterol for a second episode. Baseline potassium concentrations were 5.53 ± 0.12 and 5.66 ± 0.14 mEq/L before intravenous and nebulized therapies, respectively. The intravenous therapy resulted in a maximal reduction in potassium of 0.92 mEq/L ($p < 0.05$) after 30 minutes, while a similar reduction of 0.85 mEq/L ($p < 0.05$) occurred after 90 minutes of nebulized treatment. The nebulized treatment caused less tachycardia than the intravenous therapy.

There was no change in blood pH, pCO₂, plasma sodium, osmolality, or blood pressure with either treatment protocol. Transient palpitations and mild chest tightness occurred in two patients while receiving intravenous therapy. One patient had mild dizziness during nebulization. The investigators demonstrated that both intravenous infusion and nebulized albuterol were safe and effective. Intravenous albuterol produced a faster onset of action and was more appropriate in patients with life-threatening hyperkalemia, whereas nebulized albuterol had fewer systemic adverse effects and is preferred for patients with cardiac disease.

In a study conducted by McClure et al.,⁷ 10 children received intravenous albuterol 4 µg/kg and nebulized albuterol 2.5 mg for those weighing <25 kg and 5 mg for those >25 kg. Eleven children were originally recruited, but 1 child could not tolerate a mask on her face and was withdrawn from the study. The two treatments were given on separate dates. Each dose was then repeated in two hours. Both treatments provided a reduction in potassium within the first 30 minutes (pretreatment concentrations of 5.6 and 5.9 mEq/L for intravenous and nebulized therapies, respectively; reductions in potassium of 0.87 and 0.61 mEq/L for intravenous and nebulized therapies, respectively; *p* values not stated). Sixty minutes after the second dose, the concentrations dropped by an additional 0.28 and 0.53 mEq/L, respectively (*p* values not stated). The difference in onset of activity was not significant but did favor intravenous treatment. However, a marked difference was seen at 300 minutes when the nebulized group maintained a reduction of 1.19 mEq/L versus a reduction of only 0.7 mEq/L in the intravenous group. When albuterol was given intravenously, six children (60%) experienced mild tremor, one (10%) had mild vasomotor flushing, and three (30%) had no adverse effects. When the drug was nebulized, four children (40%) experienced tremor alone, two (20%) had tremor with nausea, one (10%) had only mild vasomotor flushing, one (10%) had tremor with vasomotor flushing, and two (20%) had no adverse effects. The authors concluded that since there was a major difference in potassium reduction between the two routes of administration at 300 minutes, nebulized albuterol is preferable over intravenous albuterol in the treatment of emergency hyperkalemia in children.

Allon and Shanklin¹³ studied the effect of albuterol administration on potassium removal by subsequent hemodialysis. Seven patients underwent dialysis 30 minutes after receiving nebulized albuterol 20 mg. One or two weeks later, as a control, they received hemodialysis with no albuterol treatment. The mean pretreatment potassium concentrations were 4.54 ± 0.18 and 4.50 ± 0.10 mEq/L, respectively. When treated with albuterol, potassium concentrations fell within 30 minutes by 0.84 ± 0.06 mEq/L (*p* < 0.001); no change was seen with the control group. During dialysis, serum potassium concentrations remained consistently lower with albuterol treatment (*p* < 0.01). However, the cumulative amount of potassium removed by dialysis was 31–68% lower with albuterol (29.0 ± 5.7 vs. 49.6 ± 7.0 mEq; *p* < 0.001). With albuterol treatment, plasma glucose, insulin concentrations, and heart rate rose significantly. The authors concluded that albuterol administration significantly reduces the potassium removal during dialysis, which may result in rebound hyperkalemia several hours later.

CONCLUSIONS

Hyperkalemia is a medical emergency because of its potentially life-threatening consequences in patients with chronic renal failure. Treatment for emergency situations should not only be effective, predictable, and fast, it must also be safe and have minimal adverse reactions. Albuterol is a β₂-adrenergic agonist that has a stimulatory effect on Na⁺–K⁺ ATPase and the resultant intracellular shift of potassium. Therefore, it is a logical choice for use in the treatment of hyperkalemia.

Clinical trials support the hypokalemic efficacy of albuterol in patients with chronic renal failure. It is effective when used by either the intravenous (adult dose 0.5 mg) or nebulized (adult dose 20 mg) routes. Potassium concentrations begin to fall within 30 minutes of administration, are maintained at a constant reduced concentration for approximately 60 minutes, and are still depressed at 300 minutes when albuterol is nebulized.

As parenteral forms of albuterol are not commercially available in the US, the nebulized route remains a more viable option. Most medical professionals are familiar and comfortable with this convenient route of administration as well. The use of a metered-dose inhaler (MDI) may offer an easy and rapid means of albuterol administration in this situation. However, it may be difficult to coordinate inhaler use in an emergency setting in patients who are unfamiliar with the proper technique for MDI use. Furthermore, the efficacy of MDI use in this situation has not yet been evaluated.

There are some problems associated with the use of albuterol for the treatment of hyperkalemia. As mentioned earlier, albuterol, like insulin and glucose, results only in a temporary intracellular shift of potassium and does not actually remove potassium from the body. Therefore, its use must still be followed by the administration of ion-exchange resins or the institution of hemodialysis. The efficacy of hemodialysis in removing serum potassium depends on the concentration gradient between the potassium in the blood and the dialysate. Intracellular shifts of potassium with albuterol treatment that decrease the serum potassium concentration should also limit the ability of hemodialysis to remove potassium. If hemodialysis is instituted while the albuterol effects are still significant (within 3–4 h), it may be necessary to redialyze patients to prevent possible rebound hyperkalemia as the albuterol wears off and potassium reequilibrates.¹³

Another concern is resistance to the effects of albuterol observed in patients in various studies.^{7,9,12,14} Resistance to β-receptor stimulation has been shown to develop with advancing age.¹⁵ This may be related to elevated circulating concentrations of endogenous catecholamines often found in the elderly.^{9,14,15} It has also been suggested that uremic patients may be less responsive to β-agonists due to a hypersensitivity of their α-receptors.¹² Certain other populations have been shown to be more resistant to albuterol. These include patients with hypertension, patients with volume overload, and African-Americans.¹⁴ The efficacy of albuterol is also questionable in patients using digoxin, which inhibits the Na⁺–K⁺ ATPase, or β-blockers.^{7,14} Because of the possibility of encountering resistance, albuterol should be used with insulin and glucose to ensure a sufficient response in emergency situations.

Albuterol treatment is associated with various adverse reactions. These include slight tachycardia, tremor, elevation in

blood glucose and insulin concentrations, and vasomotor flushing. These effects are generally mild and self-limiting.

In conclusion, hyperkalemia with electrocardiographic changes is a medical emergency requiring hemodialysis. Because of the inevitable delay in initiating dialysis, temporary measures are required. Intravenous calcium should be administered immediately to counteract the adverse cardiac effects. A method to remove the potassium from the body, such as resin administration, should be instituted. However, since results of resin administration are not immediate, insulin with glucose should be administered to rapidly shift potassium intracellularly. Nebulized albuterol has been shown to be effective for the temporary treatment of hyperkalemia in adults and children with renal failure, and it can be added to insulin and glucose therapy to provide an additive reduction in potassium concentrations while minimizing the risk of hypoglycemia from insulin. Its mild adverse effect profile and effectiveness via nebulization make it safe and easy to administer. Albuterol alone, however, should be used with caution because of the inconsistent response seen in some individuals. Although further study is warranted, nebulized albuterol can be added to insulin and glucose in the emergency treatment of hyperkalemia in patients with end-stage renal disease undergoing hemodialysis.

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