Salbutamol Metered-Dose Inhaler With Spacer for Hyperkalemia*

How Fast? How Safe?

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Objective: To determine the efficacy of inhaled salbutamol (rapidly delivered, using a metered-dose inhaler with a spacer device [MDI-S]) in lowering the serum potassium levels in patients with hyperkalemia.

Design: A randomized, double-blind, placebo-controlled trial.

Patients: Seventeen chronic renal failure patients referred to the Nephrology Unit between October 1, 1997 and March 31, 1998 for hemodialysis were randomized.

Intervention and results: Group 1 received salbutamol followed by a placebo. Group 2 received a placebo followed by salbutamol. Each patient inhaled 1,200 mg salbutamol or a placebo through an MDI-S within 2 min. Blood samples were obtained repeatedly before inhalation and after 1, 3, 5, 10, and 60 min. The pulse rate and blood pressure were repeatedly measured. Insulin levels were examined in a subset of patients (n = 10) before, and 1 and 5 min following inhalation. Salbutamol's known side effects, palpitation, tachycardia tremor, and headache, were recorded. Potassium levels rose after 1 min following the completion of treatment and then decreased steadily thereafter. A rise of ≥ 0.1 mEq/L was seen in 10 of 17 patients (59%) during the treatment period and there was no change (0%) seen during the placebo period (p < 0.0001). Within 3 min after inhalation of salbutamol, potassium levels declined as a function of time. Potassium levels in those patients taking the placebo did not change as a function of time (p < 0.001).

The difference between the placebo and the salbutamol-treated periods reached significance after 5 min (p < 0.05). The serum glucose levels rose following inhalation of salbutamol, with a significant rise after 3 min. The heart rate rose significantly within the first 5 min following inhalation. Serum insulin levels remained unchanged 1 min after inhalation; however, after 5 min, a significant elevation was detected.

Conclusion: Salbutamol inhalation of 1,200 mg, using an MDI-S, has a relatively rapid onset of action that induces a consistent reduction in serum potassium levels, starting 3 to 5 min following delivery. Unexpectedly, a paradoxical elevation was detected in serum potassium levels in the first minutes following inhalation. This effect, although minor (0.15 mEq/L above baseline), may cast some doubt on the role of salbutamol inhalation as the first treatment for excessive hyperkalemia.

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Key words: β2-agonist; chronic renal failure; hyperkalemia; hypokalemia; MDI; potassium; salbutamol; spacer device

Abbreviation: MDI-S = metered-dose inhaler with spacer device

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Hyperkalemia is considered to be a common cause for sudden death. To deal effectively with this life-threatening condition, one needs a safe and dependable drug with a fast onset of action to lower elevated serum potassium levels. Calcium acts within 1 min, elevating the membrane threshold level; however, it does not lower the serum potassium level and, therefore, may not be sufficient alone. Furthermore, there is some doubt about the efficacy of a second dose of calcium. Insulin with glucose and sodium bicarbonate lowers the serum potassium.
level by moving the potassium into the cells. However, these medications are effective only after 30 min or more. Adrenaline has a double effect; initially, the serum potassium level is elevated, and only in the second phase is it lowered, possibly due to the initial $\alpha$-activity followed by the stimulation of $\beta$-agonists. Salbutamol, a selective $\beta_2$-agonist, lowers serum potassium levels on IV administration. Inhalation therapy with salbutamol for hyperkalemia requires a dose of $\geq 10$ mg, delivered over a period of 10 to 30 min. The consequences of losing precious time in a life-threatening situation with a patient having severe hyperkalemia is obvious, however, no data exist in the literature about the effect of salbutamol on potassium levels within the first 10 to 20 min after the initiation of therapy. Two questions remain unanswered: What happens within those first 10 to 20 min after the initiation of therapy? and is there a faster way to deliver the drug effectively, to allow for an earlier onset of action?

Recently, we demonstrated the efficacy of using a metered-dose inhaler with a spacer device (MDI-S) to deliver salbutamol to a patient with severe airflow obstruction, which is fast, convenient, and cheap way to deliver salbutamol that is at least as effective as wet aerosol inhalation. We designed the study to test the hypothesis that a fast delivery (2 min) of inhaled salbutamol through an MDI-S with a dose of 1,200 $\mu$g will lower serum potassium levels within the first minutes after delivery, compared to the placebo, without compromising patient safety.

**Materials and Methods**

**Patients**

The patients were studied with the approval of our institution’s ethics committee. They were personally interviewed by the investigator, and each patient gave informed and signed consent to participate in the study.

**Inclusion criteria:** Patients with severe renal failure and elevated serum potassium levels (>5 mEq/L) who were undergoing hemodialysis were included in the study.

**Exclusion criteria:** Patients in the study were excluded from participating if they had active ischemic heart disease (angina pectoris and arrhythmias), if they were receiving therapy with $\beta$-blocker agents, if they had diabetes mellitus, or if there were technical reasons preventing the delivery of salbutamol through a spacer device.

**Results**

It was shown that serum potassium levels rise initially for 1 min following salbutamol inhalation but steadily decline thereafter; with placebo therapy, no change was observed (Fig 1, *top* and *bottom*). After 1 min, a significant difference ($p < 0.001$) was detected between the declining trend of the curve following salbutamol inhalation and the lack of change with placebo therapy (general linear model), as a function of time. In 10 patients (59%) receiving...
ing salbutamol, a rise of 0.1 mEq/L or more in serum potassium levels occurred within the first minute following inhalation, compared to 0% in the placebo period. This difference was found to be significant by Fisher’s exact test. The serum glucose levels were observed to rise following inhalation of salbutamol but remained steady following placebo therapy (Fig 2). A statistically significant difference was detected between the two curves \((p < 0.001)\). No significant change in serum insulin levels was detected 1 min following salbutamol inhalation compared to the baseline; however, after 5 min a significant rise in insulin levels was demonstrated (Fig 4).

**DISCUSSION**

Sixty-four years ago, it was found that adrenaline (a nonselective \(\alpha\)- and \(\beta\)-stimulant), may lower serum potassium levels. Nevertheless, this drug was
not accepted as a clinical remedy for hyperkalemia, perhaps due to its potentially overwhelming side effects. Recently, several publications have addressed the issue of lowering serum potassium levels using β2-agonist receptor agents.4–17,20–22 Our study indicates a significant and consistent lowering of the serum potassium levels starting 3 to 5 min after inhalation of salbutamol, and persisting during the 60 min of follow-up, whereas the lowering of potassium levels quoted in the literature started after 10 min or more.8–17,21 What is the mechanism that lowers potassium levels after the administration of salbutamol? Salbutamol directly activates pancreatic β-receptors, thus causing increased insulin secretion.

Intriguingly, we observed a rise in serum insulin levels following salbutamol inhalation (Fig 4). Insulin may lower serum potassium levels directly through the sodium-potassium pump.11,23 However, this is probably not the principal mechanism because the salbutamol effect has been demonstrated in patients with insulin-dependent diabetes (in whom insulin levels normally are low).11,24 Conceivably, the main effect of potassium lowering following salbutamol inhalation results from selective activation of β2-receptors through activation of the ADP-AMP and the sodium-potassium pump.8,25 The result of this action is a net movement of extracellular potassium into the cells.5 This effect has been demonstrated in animal models following pancreatectomy and bilateral nephrectomy; therefore, the effect is independent of the influences of insulin and aldosterone on renal potassium secretion.5 Several authors have suggested an additive effect of insulin and β-agonists.23,26

Another possibility is that the mechanism of potassium lowering is mediated by glucose. Salbutamol causes an elevation of serum glucose levels (Fig 2) through its effect on gluconeogenesis and glycogenolysis in the liver.9,24 Elevated glucose levels may have a dual effect: the lowering of serum potassium through stimulation of insulin secretion; and the elevation of serum potassium levels as seen in diabetic patients lacking endogenous insulin.19

To the best of our knowledge, this is the first study looking at the effect of salbutamol delivery through an MDI-S on hyperkalemia during the first few minutes after initiation of delivery. This method of administration is considerably faster than delivery through a wet nebulizer.17 Our patients received the full dosage within 2 min compared to delivery of a high-dose nebulization of a wet aerosol, which may take 10 to 20 min to receive.6,7,11 The faster delivery enabled us to follow alterations in serum potassium levels within the very first minutes following the beginning of salbutamol administration, whereas in most articles from the literature the first data were obtained 15 to 30 min following the beginning of salbutamol administration.8–17 Although we found only two papers that examined serum potassium levels at earlier times, those papers showed that the first data were obtained 10 to 15 min following the beginning of salbutamol administration.6,12 We have demonstrated that a decrease in serum potassium levels occurs earlier than previously reported, 5 min following salbutamol inhalation, and that the decrease is significant (Fig 1). However, this fast delivery method, which allowed a close examination of early time-related changes in serum potassium levels, revealed a surprising finding: a rise in serum potassium levels that was detected after the first minute following delivery. This early rise was followed later by the expected decline in serum potassium levels. The initial rise in serum potassium levels following the administration of salbutamol has not been previously reported in humans.25 This omission probably is due to blood sampling at a later time, which is a consequence of relatively slow delivery methods.7–11 Perhaps the initial rise was missed because the earliest sample was drawn after the effect had disappeared. We demonstrated a significant rise in serum potassium levels averaging 0.15 mEq/L, a rise of > 0.1 mEq/L in the majority of patients (59%) (Fig 1, top and bottom). In two patients, the change was > 0.4 mEq/L.

It would be difficult to explain our findings indicating an initial rise in serum potassium levels following the administration of salbutamol while assuming that salbutamol is 100% β-selective. However, this is obviously not the case. In high doses, salbutamol may activate β1-receptors, thus causing tachycardia. In very high doses, salbutamol may even
stimulate α-receptors. Catecholamines have a dual effect: through β-receptor stimulation, they may lower serum potassium levels, but through α-receptor activation, they may elevate serum potassium levels. The rapid rise in serum potassium levels is attributed to the release of potassium from the liver. The α-effect occurs first, but is of short duration and appears more quickly. It has been demonstrated that following IV injection of adrenaline, a rise in serum potassium levels may be detected within 1 min. This rise will continue for 6 min and then will gradually decline, while adrenaline infusion is kept at a constant rate. Fourteen minutes after the beginning of adrenaline infusion, serum potassium levels decline below baseline levels. Many articles in the literature indicate a reduction in serum potassium levels 30 min following delivery. To the best of our knowledge, the only article addressing the issue of early changes in serum potassium levels following the delivery of IV salbutamol was published by Du Plooy et al. This article demonstrated in baboons that 3 min following the delivery of an IV bolus of salbutamol (10 µg/kg) there was a significant rise in serum potassium levels (0.65 mEq/L). In the tenth minute, a significant decrease was noted. It is interesting that these authors describe a widening of the T waves, reaching maximal effect after 30 s, and conclude that the rise in serum potassium levels may start in the very first minute. This effect was documented 3 min following the delivery of salbutamol, when the first blood sample was drawn. We conclude that salbutamol, when delivered in the doses described above, is not entirely β₂-selective (a rise in pulse rate indicates β₁-activity). The detection of the initial rise in serum potassium levels, supported also by the work of Du Plooy et al., may point to an α-stimulating effect by this agent. Further studies are required to clarify this issue. In our patients, no adverse effects were detected that could be clinically related to the elevation in serum potassium levels (ie, ECG changes and arrhythmias) because these elevations were mild. Nevertheless, this finding has to be addressed in view of the potential life-threatening hazards of hyperkalemia. The described patient population (patient with chronic renal failure) may have an elevated potassium level to start with and may face, at least theoretically, the risk of refractory arrhythmias due to further increases in serum potassium levels as a paradoxical effect. Life-threatening hyperkalemia may occur for reasons other than chronic renal failure (eg, iatrogenic disease, overdose, rhabdomyolysis, etc); it frequently occurs in patients in critical care units. The overall frequency of fatal hyperkalemia in hospitalized patients receiving KCL supplements was estimated as 1:1,000.2 We wondered whether the slight initial and transient elevations in serum potassium levels have any clinical significance in medical emergencies. An already existing high adrenergic tone is expected in some of these situations and may neutralize the drug-induced hyperkalemia, but this remains pure speculation. We conclude, therefore, that although salbutamol inhalation is probably beneficial as part of the therapeutic armamentarium in the treatment of hyperkalemia, because of patients’ rapid response to it, salbutamol administration should not be the first action taken when hyperkalemia is excessive. We recommend the administration of calcium, before salbutamol, for its rapid onset of action and to avoid the potential deleterious side effects due to the initial rise in potassium following salbutamol inhalation. Calcium, as is well known, does not affect serum potassium levels; however, it takes effect immediately, protecting against arrhythmias by elevating the threshold potential.

We conclude that the inhalation of salbutamol, 1,200 µg, with an MDI-S has a rapid onset of action, which induces a consistent reduction in serum potassium levels starting 3 to 5 min following delivery. Surprisingly, a paradoxical elevation was detected in serum potassium levels in the first minutes following inhalation. This effect, although minor (0.15 mEq/L above baseline) and of questionable significance, may cast doubt on the role of salbutamol inhalation as a sole treatment for excessive hyperkalemia.

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