The Effects of Enalapril and Spironolactone on Terbutaline-Induced Hypokalemia*

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Objective: To investigate whether enalapril (E) 10 mg and spironolactone (S) 100 mg attenuate the hypokalemic effect of inhaled terbutaline (T).

Design: Randomized single-blind crossover. Subjects received the following treatment combinations: (a) placebo (P), (b) T alone, (c) T + S, (d) T + S.

Setting: University Department of Clinical Pharmacology.

Participants: Twenty healthy volunteers (ten male, ten female) of mean age 22.8 ± 3.1 years.

Main Outcome Measures: Serum potassium, magnesium, ECG changes (R-R interval, T wave, and QTc interval) for 4 h after terbutaline inhalation.

Main Results: Baseline serum potassium levels were higher following prior treatment with E and S; P, 3.75 mmol/L (3.67 to 3.85); T + E, 3.93 mmol/L (3.82 to 4.03); and T + S, 4.03 mmol/L (3.93 to 4.14) (p < 0.05). Mean potassium concentrations over 4 h were also higher following prior treatment with E and S; T, 3.58 mmol/L (3.54 to 3.63); T + E, 3.68 mmol/L (3.64 to 3.72) (p < 0.05); and T + S, 3.75 mmol/L (3.68 to 3.78) (p < 0.01).

Conclusions: Enalapril and spironolactone protect against the fall in serum potassium over 4 h by elevating baseline potassium concentration. These potassium-sparing drugs, however, should not be used to prevent the hypokalemic and electrocardiographic sequelae of inhaled β₂-agonists.

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Inhaled β₂-agonists, beside having bronchodilator properties, have been shown to cause systemic effects.¹² These, their hypokalemic and electrocardiographic effects have aroused considerable interest recently. The extracellular potassium ion concentration is the single most important determinant of myocardial membrane stability.³⁴ In susceptible individuals with the underlying substrate of ischemic heart disease,⁶⁷ hypokalemia may predispose to cardiac arrhythmias. We have shown previously that the concurrent administration of potassium-losing diuretics augments β₂-agonist-induced hypokalemia.⁵ Furthermore, potassium-sparing drugs such as spironolactone and triamterene attenuate the hypokalemic effect of combined diuretic/β₂-agonist therapy.⁶ We have now investigated whether the use of potassium-sparing drugs on their own or blocking the renin angiotensin aldosterone system with an angiotensin-converting enzyme (ACE) inhibitor might confer protection against β₂-agonist-induced hypokalemia.

METHODS

Twenty healthy volunteers were recruited (ten male, ten female) with a mean age of 22.8 ± 3.1 years. The protocol was approved by the hospital ethical committee. All volunteers gave informed written consent and underwent a full clinical examination, a 12-lead ECG, and a blood biochemical and hematologic screen. Volunteers were studied on four occasions. They were pretreated for a week prior to each visit with either placebo (on two occasions), enalapril (E) 10 mg daily, and spironolactone (S) 100 mg daily. There was a one-week washout period between treatments. At the end of each treatment period, volunteers reported to our clinical laboratory at 2 PM. They were asked to refrain from alcohol, caffeine-containing beverages, and cigarettes for 24 h prior to each visit. Volunteers rested supine for the first 30 min when an intravenous cannula was inserted in the antecubital fossa under local anesthesia. A semiautomatic sphygmomanometer (Dinamap, Critikon, Tampa, Fl) was used to measure blood pressure at set intervals every minute. Once baseline was achieved (as assessed by the lowest five consecutive heart rates), blood samples, an ECG strip (lead 2) of five complexes, and blood pressure were recorded on two occasions 10 min apart (ie, two baseline measurements were taken). Volunteers were then asked to sit up and inhale terbutaline 5 mg (on three visits) and placebo (on one visit) given in a single-blind randomized crossover design. The inhaled drugs were delivered through a pear-shaped spacer device (PSS) using the method of Gleeson and Price⁶ to avoid individual differences in inhaler technique. The dose per actuation was 1 mg and five actuations were delivered separated by 1-min intervals. Therefore, in essence, volunteers received the following combinations: placebo (P), terbutaline inhalation (T), enalapril followed by terbutaline (T + E), and spironolactone followed by terbutaline (T + S).

Measurements

Volunteers were monitored for 4 h postinhalation. Measurements were made at 30 min, 60 min, and then hourly. From the ECG strips, the following measurements were made: heart rate using the R-R interval, T-wave amplitude, heart rate-corrected QT interval.
(QT) using the Bazett formula. The mean of five complexes was used for analysis. Blood pressure was also measured at each time point taking a mean of five consecutive readings. In addition to serum potassium, samples were also taken for plasma renin activity and serum magnesium. Samples were all immediately cooled and centrifuged within 10 min of collection. All samples were stored at −20°C for later analysis in batches and assayed in duplicate. Serum potassium was analyzed using a flame photometer (Instrumentation Laboratory, Warrington, United Kingdom) with an analyzer (IL843). The within- and between-assay values for analytical precision (expressed as CV) were 0.7 percent and 1.8 percent, respectively.

The normal reference range for our laboratory is 3.5 to 5.0 mmol−1. Plasma renin activity (PRA) was assayed by radioimmunoassay (CIS Ltd, High Wycombe, United Kingdom). The within-coefficient of variation CVw was 13.1 percent and the between-coefficient of variation CVb was 11.1 percent. Serum magnesium was measured by the colorimetric method (using Wako kit on Cobas-Bio centrifugal analyser, Roche, Basle, Switzerland). The CVw was 0.87 percent and CVb was 1.4 percent.

Statistical Analysis

A statgraphics software package (STSC Publishing Group, Maryland) was used to analyze data by repeated measured analysis of variance (ANOVA). In the presence of a significant overall ANOVA, multiple range testing was used to compare treatments (Brown et al, 1988). The primary end point was the serum potassium level and ECG changes were the secondary end point. The mean concentration of potassium over 4 h was calculated and reflects the area under the curve (AUC) for serum potassium concentration time profile as defined by the equation AUC = mean × time (time being a constant for all study days). A level of p<0.05 was considered as being of significance (two-tailed). The study was designed with a 10 percent β-error to detect a difference between treatments in potassium concentration of 0.3 mmol/L. All data are expressed as means and 95 percent confidence intervals.

RESULTS

Serum Potassium (Fig 1 and 2a) and Magnesium

On the placebo day, potassium level throughout the 4-h period showed a slight though not significant increase and this returned to baseline at the end of the monitoring period. Baseline potassium was 3.78 mmol/L (3.67 to 3.88). Following pretreatment with placebo, inhaled terbutaline caused a significant (p<0.0001) fall in potassium concentration maximal at 1 h after inhalation. The baseline potassium value was 3.82 mmol/L (3.71 to 3.92) and this fell to 3.37 mmol/L (3.28 to 3.49). Following pretreatment with enalapril, baseline potassium value was higher though not significantly so, 3.93 mmol/L (3.82 to 4.03). Subsequent to the terbutaline inhalation, the potassium level fell significantly (p<0.0001) and was maximal 1 h after inhalation: 3.50 mmol/L (3.39 to 3.60). Baseline potassium level after spironolactone was significantly higher (p<0.05) than after placebo: 4.03 mmol/L (3.93 to 4.14). Terbutaline (after spironolactone) caused serum potassium level to fall to 3.53 mmol/L (3.42 to 3.63) again maximal after 1 h. On all the days when inhaled terbutaline was given, potassium levels failed to return to baseline by the end of the 4-h monitoring period. There was no significant difference in the magnitude of the actual hypokalemic response to terbutaline following treatment with either placebo −0.43 mmol/L (−0.54 to −0.32), enalapril −0.42 mmol/L (−0.53 to −0.30), or spironolactone

![Figure 1](https://www.annualreviews.org/content/1988/0000/0000/fig1)

**Figure 1.** Average serum potassium concentration (mean and 95 percent CI) postinhalation over 4 h; p = placebo; T = terbutaline; T + E = terbutaline plus enalapril; and T + S = terbutaline plus spironolactone.

![Figure 2a](https://www.annualreviews.org/content/1988/0000/0000/fig2a)

**Figures 2a (upper) and b (lower).** Serum potassium and T-wave amplitude time profile; 95 percent CI shown only for baseline and maximal response. Time points shown are 0 min, 30 min, 60 min, 2 h, 3 h, and 4 h postinhalation. P = placebo; T = terbutaline; T + E = terbutaline plus enalapril; T + S = terbutaline plus spironolactone.
-0.48 mmol/L (-0.59 to -0.37). However, average potassium levels throughout the 4-h monitoring period following terbutaline inhalation showed a significantly higher level with enalapril 3.68 mmol/L (3.64 to 3.72) (p<0.01), and spironolactone 3.73 mmol/L (3.69 to 3.78) (p<0.01) compared with placebo 3.58 mmol/L (3.54 to 3.63).

Baseline serum magnesium value was not affected by enalapril or spironolactone. Inhalation of terbutaline significantly lowered serum magnesium level 1 h after inhalation. Hypomagnesemia also occurred following treatment with enalapril and spironolactone. Magnesium levels 1 h after inhalation were as follows: P; 0.89 mmol/L (0.88 to 0.91); T; 0.86 mmol/L (0.84 to 0.88); T+E; 0.86 mmol/L (0.84 to 0.87); and T+S; 0.86 mmol/L (0.85 to 0.88) (p<0.01).

**Plasma Renin Activity**

Baseline PRA was significantly higher (p<0.0001) after pretreatment with enalapril and was also higher but not significantly so following spironolactone; P; 2.5 ng/ml·h⁻¹ (0.5 to 4.5); T; 3.8 ng/ml·h⁻¹ (1.8 to 5.8); T+E; 12.7 ng/ml·h⁻¹ (10.6 to 14.8); and T+S; 4.8 ng/ml·h⁻¹ (2.7 to 6.9). Terbutaline inhalation did not affect PRA.

**Electrocardiogram (Fig 2b)**

T-wave changes followed the same pattern as potassium. T-wave amplitude showed a slight increase from baseline following placebo inhalation. After inhalation of terbutaline, there was a significant blunting of T-wave amplitude, occurring maximally between 30 to 60 min (p<0.01). Baseline T-wave amplitude showed a similar pattern to potassium in that values were higher after enalapril or spironolactone, although the difference was not significant; P; 0.57 mV (0.53 to 0.61); T; 0.56 mV (0.52 to 0.60); T+S; 0.59 mV (0.55 to 0.64); and T+E; 0.59 mV (0.55 to 0.63). T-wave amplitude after terbutaline inhalation was not significantly affected by spironolactone or enalapril. Lowest T-wave amplitudes were as follows: P; 0.58 mV (0.54 to 0.62); T; 0.37 mV (0.33 to 0.41); T+E; 0.39 mV (0.35 to 0.43); and T+S; 0.39 mV (0.34 to 0.43).

QT interval following placebo inhalation showed no significant change. Following terbutaline inhalation, there was a significant prolongation of QT interval that was not affected by prior treatment with enalapril or spironolactone. Prolongation of QTc, like T-wave blunting, was maximal between 30 to 60 min post-inhalation. Average QT interval over 4 h on the different days were as follows: P; 403 ms (399 to 407); T; 413 ms (410 to 418); T+E; 419 ms (416 to 423); and T+S; 413 ms (409 to 417).

**Hemodynamic Response (Table 1)**

Terbutaline significantly increased heart rate. The increase in heart rate was maximal 30 min after inhalation and failed to return to baseline by the end of 4 h. Maximum heart rate after terbutaline was 79 beats/min (75 to 82) from a baseline of 62 beats/min (59 to 65). Systolic blood pressure was not significantly different on any of the four study days. Mean diastolic pressure over 4 h was significantly lower on all the days volunteers received terbutaline: P; 60 mm Hg (59 to 61); T, 56 mm Hg (55 to 57); T+E, 55 mm Hg (54 to 56); and T+S, 57 mm Hg (56 to 58).

**Discussion**

This study confirms previous work that showed that inhaled β₂-agonist caused significant hypokalemia, hypomagnesemia, T-wave blunting, prolongation of QT interval, increased heart rate, and a fall in diastolic blood pressure. It also showed that prior treatment with enalapril and spironolactone raises baseline potassium but does not prevent the hypokalemic response after terbutaline. The net effect is to have a higher 4-h level of serum potassium. This effect was not seen with magnesium levels or ECG changes. Plasma renin activity was significantly elevated with enalapril treatment. This was expected in view of the fact that ACE inhibitors cause a withdrawal of the inhibitory effect on renin release by angiotensin II and demonstrates that our volunteers were complying with treatment. PRA was unaffected by terbutaline, which is consistent with the view that renin release is mediated primarily via β₁-adrenoceptors.

Several factors contribute to the hypokalemic effect of inhaled terbutaline. Besides stimulation of membrane bound β₂-adrenoceptor linked Na⁺/K⁺ ATPase, it may also reduce serum potassium by insulin-dependent potassium influx into cells. Stimulation of insulin release by β₂-agonist is thought not to be important since adrenaline, a potent β-adrenergic, despite inhibiting insulin release, also induces hypokalemia. The other possible contributory factor is via renal sodium loss through stimulation of the renin

**Table 1 — Hemodynamic Response**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (P)</th>
<th>Terbutaline (T)</th>
<th>Terbutaline Plus Enalapril (T+E)</th>
<th>Terbutaline Plus Spironolactone (T+S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>63 (61-64)</td>
<td>70* (69-72)</td>
<td>73* (71-74)</td>
<td>70* (69-71)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>114 (113-115)</td>
<td>114 (113-115)</td>
<td>112* (111-114)</td>
<td>113 (112-114)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>60 (59-61)</td>
<td>56* (55-57)</td>
<td>55* (54 + 56)</td>
<td>57* (56-58)</td>
</tr>
</tbody>
</table>

*P<0.01 vs P (ANOVA).
cascade. It had been suggested previously that \( \beta_2 \)-subtype may have a role in renin-releasing response.\(^{15}\)

Our data showed that PRA was not affected by terbutaline. It also suggests that whatever effect prior treatment with enalapril and spironolactone may have on \( \beta_2 \)-agonist-induced effects, it was not via inhibition of renin release or disruption of the renin cascade per se.

Serum magnesium does not reflect intracellular levels.\(^{10,17}\) The small magnitude of hypomagnesemia following terbutaline confirms previous findings\(^{18,19}\) and may have contributed to the QTc prolongation. The mechanism of hypomagnesemia following terbutaline is via increased renal excretion.\(^{18}\)

There are reasons for believing that spironolactone might block the hypokalemic effects of \( \beta_2 \)-agonist and reasons for thinking otherwise. Spironolactone, besides having renal effects, is also thought to cause a shift of potassium from the intracellular to the extracellular compartments.\(^{40}\) This hypothesis was based on observations that treatment with spironolactone, despite causing kaliuresis,\(^{31}\) leads to elevation of the serum potassium level. On the other hand, spironolactone has little effect on electrolytes in the absence of an activated renin-angiotensin-aldosterone system.\(^{42}\) We did, however, find significantly higher levels of mean serum potassium concentration with spironolactone and enalapril despite not activating the renin-angiotensin-aldosterone system. This was not because either drug attenuated the hypokalemic response to terbutaline but because both drugs caused a higher baseline serum potassium concentration and therefore fell to higher levels (ie, fall in K\(^+\) was the same after terbutaline on all days). Mean potassium levels over the 4-h period is a better reflection of the total hypokalemic burden and might reflect a more clinically relevant parameter. The importance of extracellular potassium concentration is highlighted by the fact that resting myocardial membrane potential is determined by the ratio of extracellular to intracellular concentration in a ratio of approximately 1:35.\(^{53}\) Changes in extracellular potassium concentration will have a much larger effect on this ratio than comparable changes in intracellular potassium.

Baseline T-wave amplitude also was higher with enalapril and spironolactone. Blunting of T-wave amplitude by terbutaline was not altered by these drugs. We have shown previously a good correlation between T-wave amplitude and serum potassium.\(^{8}\) The explanation for the failure of spironolactone and enalapril to blunt T-wave effects are twofold. In the first instance, the protective effect on serum potassium level that occurred was probably not large enough in magnitude to cause any significant corresponding T-wave effects. Secondly, it shows that T-wave amplitude is a less sensitive indicator of extracellular potassium level and should not be used as a substitute for the serum level.

Heart rate increase with terbutaline, though not remarkable, was significant. The chronotropic effect is due to a combination of direct stimulation of cardiac \( \beta_1 \)-receptors\(^{34-35}\) and reflex vagal withdrawal.\(^{37}\) However, the small fall in diastolic blood pressure suggests that reflex vagal withdrawal is not important. Systolic blood pressure, on the other hand, is mainly a \( \beta_1 \) effect\(^{36-38}\) and this explains why no significant change in systolic blood pressure occurred in response to terbutaline.

The clinical significance of \( \beta_2 \)-agonist-induced hypokalemia continues to stimulate discussion. In particular, recent case control studies with fenoterol have suggested that the use of this drug may be associated with increased mortality in patients with asthma.\(^{31,38}\) Interestingly, fenoterol also causes greater potassium and ECG effects than other \( \beta \)-agonists.\(^{32}\) Levels of serum potassium, which may have no clinical relevance in normal individuals, may assume importance in patients with ischemic heart disease,\(^{4,7}\) concurrent digitalis therapy,\(^{34}\) and hypokalemia.\(^{30}\) Patients receiving long-term \( \beta_2 \)-agonist therapy, however, have been shown to develop tachyphylaxis\(^{29}\) and are less likely to develop adverse systemic effects with inhaled \( \beta_2 \)-agonist. These patients are usually also taking steroids (inhaled or oral) or oral theophylline, both of which can predispose or aggravate hypokalemia following \( \beta_2 \)-agonist.\(^{37,38}\) There are also patients with airways disease who have not used \( \beta_2 \)-agonist recently and therefore may not have experienced down regulation of their \( \beta_2 \)-receptors. These patients may experience a substantial hypokalemic response with inhaled \( \beta_2 \)-agonist.

In conclusion, we have shown that enalapril and spironolactone protect against hypokalemia after inhalation of terbutaline over 4 h in normal volunteers. This protective effect was afforded by virtue of both drugs elevating baseline potassium levels. Although the magnitude of fall in potassium was unaltered, the overall effect on mean potassium was significantly attenuated. However, we would not advocate the routine use of potassium-sparing drugs in patients receiving inhaled \( \beta_2 \)-agonists. Patient studies are now indicated to investigate further the clinical relevance of hypokalemia and ECG sequelae of inhaled \( \beta_2 \)-agonists in the setting of both acute and stable airflow obstruction.

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