Interaction between Corticosteroid and β-Agonist Drugs*

Biochemical and Cardiovascular Effects in Normal Subjects

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The aim of this study was to investigate whether the administration of prednisone potentiates any of the acute biochemical and cardiovascular effects of high-dose inhaled β-agonist drugs. These agents are known to cause dose-related changes in plasma potassium and glucose, as well as ECG changes in heart rate, corrected QT interval (QTc), T wave, and U wave. On theoretical grounds, the concomitant use of systemic corticosteroids might enhance these actions. Twenty-four healthy subjects were randomized to receive one of three treatments: salbutamol 5 mg or fenoterol 5 mg or normal saline solution. Each drug was administered twice, 30 min apart by nebulizer, and the procedure was repeated after each subject had received prednisone 30 mg daily for one week. Plasma potassium and glucose levels were measured, and ECGs were obtained after each treatment, together with 12-h Holter monitoring for arrhythmias. Changes in plasma potassium and glucose following nebulized β-agonist were significantly greater after treatment with prednisone. Baseline potassium level fell from 3.75 mmol/L (95 percent CI 3.61, 3.89) to 3.50 mmol/L (95 percent CI 3.36, 3.64), and thereafter all values were significantly lower at each time point (p = 0.003). The lowest mean plasma potassium was obtained 90 min after fenoterol administration with prednisone pretreatment: 2.78 mmol/L (95 percent CI 2.44, 3.13). Increases in heart rate and QT, interval following both β-agonist drugs were significant, but T-wave amplitude reductions did not reach significance. Prednisone treatment did not significantly alter the cardiovascular responses. Supraventricular and ventricular ectopic activity was related to β-agonist use, but no potentiating effect was noted following steroid treatment. We conclude that the acute biochemical effects of β-agonist administration are augmented by prior treatment with prednisone, but this is not the case for ECG effects. However, the degree of hypokalemia noted as a result of this drug interaction may be of clinical significance in the hypoxic conditions of acute airways obstruction.

(Chest 1992; 102:519-24)

CI = confidence interval; QTc = corrected QT interval

Following the sharp rise in asthma mortality that occurred in New Zealand during the early 1980s, strenuous efforts have been made to identify factors that may have contributed. From the outset, there has been speculation that drug-related toxicity may be important, especially in circumstances where the unsupervised use of high doses of bronchodilators is a common event. The interaction between β-agonists and theophylline has been considered, but conclusive evidence as to their importance has been lacking. More recently, case-control epidemiologic studies have implicated the prescription of fenoterol as a risk factor for asthma mortality. This β-agonist has been widely used in New Zealand, and unit doses by conventional metered dose inhaler are higher than for salbutamol (albuterol) or terbutaline. Furthermore, in one of these studies, it appeared that asthmatics dependent on oral corticosteroids were at even greater risk than others.

Corticosteroid treatment is recommended to all asthmatics experiencing rapid deterioration in their symptoms, and has been shown to reduce the severity of exacerbations as well as subsequent hospital admission rates. Self-management plans involving the use of short courses of prednisone at times of acute deterioration are currently being promoted. However, the simultaneous use of higher than normal doses of β-agonists in such circumstances raises the possibility of an important drug interaction. In particular, both drugs are known to give rise to hypokalemia, and it is theoretically possible that in the course of an acute attack, the additive effects of hypoxemia, excessive dosing, and biochemical disturbances might result in adverse cardiovascular events.

The aim of this study was to test the hypothesis that the combined use of inhaled β-sympathomimetic agonists and oral prednisone results in significantly greater biochemical and cardiovascular disturbance than would occur when using sympathomimetic agents alone, and that the magnitude of the effect may be of clinical importance in acute severe asthma.

Methods

Subjects

Twenty-four healthy male volunteers (age range, 18 to 33 years)
were studied. Each underwent a full physical examination and ECG assessment prior to participation. Any volunteer with a history of cardiovascular disease, hyperthyroidism, or previous β-agonist use was excluded. Written informed consent was obtained from each subject, and the study protocol was approved by the ethical committee of the Otago Area Health Board.

**Study Design**

Subjects were randomly assigned to receive one of three drug treatments on each of two separate occasions: (a) salbutamol nebulizer solution 5 mg; (b) fenoterol nebulizer solution 5 mg; (c) nebulized normal saline solution (0.9 percent) as placebo. Treatments were administered in a single-blind manner. Each of the active agents was made up in volume to 4 ml using normal saline solution and nebulized via a nebulizer (Hudson Nebumist), driven by oxygen at a flow rate of 6 L/min until dry. A second equal dose was administered exactly 30 min following the first.

Subjects attended at 8 am following a light breakfast, and a Holter monitor for continuous ECG recording during the 12-h interval immediately following nebulized β-agonist administration was put in place. After emptying the bladder, each subject remained supine for the first 5 h of each study day. An intravenous cannula was inserted into an antecubital vein, and kept patent using heparinized saline solution. Five milliliter blood samples were obtained immediately before, and 15, 30, 45, 60, 90, 120, and 240 min following administration of the first dose of nebulized bronchodilator. Samples were immediately centrifuged, and plasma potassium and glucose concentrations were measured in the hospital laboratory within 1 h. A standard 12-lead ECG was obtained at baseline, and again at 35, 65, 125, and 245 min. All urine output for the 24-h period from time zero was collected for subsequent measurement of potassium concentrations. Subjects were asked to exercise only lightly for 24 h after leaving the laboratory, and they were asked to refrain from alcohol consumption.

Each of the above procedures was repeated in full exactly one week later. During the intervening period, each subject received oral prednisone 30 mg daily, commencing 24 h after the first study day, the last dose being administered on the morning of the second study day.

From each ECG, the following data were obtained from lead 2: heart rate (beats per minute); R-R interval; QT (QT) interval corrected using Bazett's formula, and T-wave amplitude. The presence/absence of U wave of greater than 1 mm in amplitude was recorded from lead V1. From the Holter monitor recording, the following data were obtained for the 12-h interval from time zero: frequency of supraventricular ectopic beats; frequency of ventricular ectopic beats; and presence of malignant arrhythmias.

**Statistical Analysis**

The results are presented as means and 95 percent confidence intervals (95 percent CI). The data were analyzed using the SPSSX MANOVA procedure for repeated measures analysis of variance, where the bronchodilator treatment was used as a between-subject variable, and both steroid treatment and time were used as within-subject variables. Polynomial contrasts were used to evaluate the changes occurring over time. For the analysis of heart rate, a baseline value was used as a covariate. χ² testing and Spearman correlation coefficients were used for comparisons of nonparametric data.

**RESULTS**

**Biochemical Data**

The administration of salbutamol and fenoterol resulted in immediate significant falls in the plasma potassium concentration compared with placebo (p<0.001; Fig 1a). Mean values for the maximum fall in plasma potassium were 0.51 mmol/L (95 percent CI 0.35, 0.67) for salbutamol and 1.13 mmol/L (95 percent CI 0.82, 1.43) for fenoterol (p<0.0005). Even after 4 h, the fenoterol-treated subjects had not recovered their baseline potassium levels. The lowest individual value for plasma potassium was 2.6 mmol/L, recorded in a subject who received fenoterol, and whose baseline plasma potassium level was 4.1 mmol/L. The 24-h plasma potassium excretion did not differ between bronchodilator treatments (Table 1).

Following treatment with prednisone, the mean baseline plasma potassium concentration fell from 3.75 mmol/L (95 percent CI 3.61, 3.89) to 3.50 mmol/L (95 percent CI 3.36, 3.64). Values following prednisone treatment were significantly lower at each time
The following changes were significant (p = 0.008) and this effect was significantly augmented by steroid treatment (p = 0.004). In addition, the duration of B-agonist-induced hyperglycemia was more prolonged following prednisone (p = 0.002) (Fig 1b).

Cardiovascular Data

Both salbutamol and fenoterol treatments resulted in significant increases in heart rate and QT interval, maximal at 45 and 60 min, respectively (p < 0.001; Fig 2a and 2b). Changes in the T-wave amplitude failed to reach statistical significance (p = 0.18), but were observed in the majority of cases (Fig 2c). In each instance, the effect of fenoterol was more marked than for salbutamol. Transient T-wave inversion was noted following fenoterol administration in two subjects, and following salbutamol administration in two subjects. The changes in plasma potassium levels for these four subjects did not differ significantly from those occurring in other subjects who received active treatment. The development of U waves occurred following salbutamol and fenoterol with similar frequency (Table 1 — Additional Biochemical and ECG Data Obtained before and after Prednisone 30 mg Daily for Seven Days*).

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<th>Salbutamol</th>
<th>Fenoterol</th>
<th>Placebo</th>
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<tr>
<td></td>
<td>Before</td>
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<tr>
<td>K+ excretion, mmol/L</td>
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<td>Significant U wave, &gt;1 mm</td>
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<td>4</td>
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<td>T-wave inversion, No. of subjects</td>
<td>10.4 ± 4.7</td>
<td>11.8 ± 2.9</td>
<td>2.3 ± 1.1</td>
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<td>Supraventricular ectopic beats per 12 h, mean No. per subject</td>
<td>17.4 ± 16.4</td>
<td>23.9 ± 22.7</td>
<td>55.3 ± 53.4</td>
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*Eight subjects were allocated to each of the three treatment groups.
Holter monitoring revealed that both supraventricular and ventricular ectopic activity was significantly greater following active treatments compared with placebo, but that individual results significantly affected the mean data. There was no correlation between changes in plasma potassium level and QT, interval or the frequency of supraventricular/ventricular ectopic activity except following fenoterol with prednisone pretreatment when a highly significant correlation was found between plasma potassium levels and the frequency of ventricular ectopic beats. In only one instance was an abnormal rhythm noted (ventricular bigeminy) following salbutamol, and this occurred in a subject whose ECG was also characterized by transient T-wave inversion.

None of the cardiovascular measurements was significantly different on the second study day following prednisone treatment.

DISCUSSION

The results of the present study confirm previously identified biochemical and cardiovascular changes that follow the short-term administration of inhaled β-agonist drugs. Hypokalemia, hyperglycemia, increases in heart rate and QT, interval, reductions in the magnitude of the T-wave, and increased frequency of supraventricular premature beats were all observed. In most instances, these effects were greater following fenoterol administration than following salbutamol, except for supraventricular ectopic activity, which was more marked with salbutamol.

The effect of pretreatment using prednisone resulted in a number of significant changes. Firstly, the hyperglycemic effect of β-agonist treatment was increased in both magnitude and duration, even though no significant changes occurred in the prebronchodilator baseline values. Usually β-agonist-induced glycogenolysis is controlled by simultaneous insulin release, but presumably the anti-insulin effect of prednisone resulted in relative loss of glycemic control in our subjects. More importantly, mean baseline plasma potassium levels fell by 0.25 mmol/L to 3.50 mmol/L following steroid therapy, and thereafter a parallel shift downwards for the hypokalemic response to β-agonist was observed. The magnitude of these changes was similar to those observed following adrena-line administration to subjects pretreated with thia-zide-induced hypokalemia. However, this augmentation of hypokalemia was not accompanied by any similar effect on heart rate, QT, interval, T-wave amplitude, U-wave development, or frequency of ectopic beats, suggesting that the magnitude of the ECG changes following β-agonists does not necessarily correlate with plasma potassium levels.

It may be that in circumstances where higher doses of prednisone are used, then the extent of this drug interaction may be more marked. The dose of prednisone used in this study was similar to that which is advised for asthmatic subjects experiencing exacerbations of their asthma, and ethical considerations precluded the use of higher doses in our normal subjects. In the study of Lipworth et al., where mean baseline potassium concentrations fell from 3.78 to 3.07 mmol/L following thiazide diuretic treatment, a similar parallel downward shift in the hypokalemic response to salbutamol was noted. But just as in the present study, no interactive effects were noted on T-wave amplitude, QT, interval, or ST-segment depression. Thus, if hypokalemia is a suitable marker of the overall magnitude of this drug interaction, it seems unlikely that using higher doses of prednisone would have achieved a different outcome with respect to ECG changes.

A number of theoretical considerations encouraged us to consider a potential interaction between corticosteroid and β-agonist treatment, particularly with regard to hypokalemia. Firstly, in the clinical context in which these agents are likely to be simultaneously administered, hypokalemia secondary to respiratory alkalosis may be present. Secondly, almost all systematically administered glucocorticoid drugs also possess mineralocorticoid action resulting in hypokalemia. Thirdly, physiologic changes in plasma potassium are subject to catecholamine control, mediated by adenylate-cyclase Na-K pump activity. Thus, in acute severe asthma, when high doses of exogenous β-sympathomimetic are routinely administered, hypokalemia is often encountered. Together with other investigators, we have confirmed this observation. Fourthly, one of the effects of steroid administration in acute severe asthma—which is considered beneficial—is to enhance cyclic-AMP mediated responses to β-adrenergic stimulation. Steroid therapy increases both β-adrenergic receptor numbers, as well as their coupling to adenylate cyclase. In turn, this might predispose to more profound catecholamine-induced effects when sympathomimetic agents and corticosteroids are simultaneously used.

Our results suggest an additive rather than a synergistic interaction between prednisone and the two β-agonists used. It would appear that baseline plasma potassium levels are the most important factor determining the subsequent magnitude of hypokalemia following β-agonist use. However, since our results were obtained in normal subjects, the potential effects of prior down-regulation of β-receptor function might exaggerate the changes observed in this investigation in asthmatic patients. By contrast, it has been suggested that the effect of previous β-agonist therapy may be to attenuate such changes.

Continuous ECG monitoring confirmed that β-agonist therapy significantly increased the frequency
of both supraventricular and ventricular ectopic beats, and transient T-wave inversion as well as the advent of ventricular bigeminy was noted. In contrast to a previous report,24 such observations were not associated solely with fenoterol, but they also occurred with salbutamol. The frequency distribution for these events was uneven, and individual susceptibility to ectopic activity could not be predicted on the basis of plasma potassium changes. Although prednisone had no consistent effect on the frequency of ectopic activity, we consider these observations to have been important.

It remains controversial as to whether the above drug-related biochemical and ECG changes predispose to an increased risk of sudden death from acute severe asthma when they occur in association with hypoxemia and increased endogenous catecholamine production. Indeed, the exact relationship between drug treatment and morbidity and mortality from asthma continues to create debate. For the most part, attention has focused on the potential for acute toxicity during severe attacks and/or when excessive doses of bronchodilators are being administered.2,3 Evidence is largely circumstantial. Epidemiologic data point to a rise in asthma deaths following the introduction of isoproterenol (isoprenaline)25 and fenoterol.6 Following myocardial infarction, hypokalemia is a risk factor for life-threatening arrhythmia.20-27 and in the experimental setting, the combination of hypoxia and isoprenaline results in cardiac asystole.28 By contrast, in a recent investigation of near-fatal asthma attacks, respiratory rather than cardiovascular complications appear to have been the predominant feature.29 Anecdotally, the adverse consequences of hypokalemia are not a major clinical consideration when dealing with severe asthma in hospital,30 and malignant dysrhythmias do not require to be treated frequently. The question thus remains as to whether acute drug-related effects have, per se, been responsible for asthma deaths.

In conclusion, our study has demonstrated that the coadministration of oral corticosteroids potentiates the biochemical effects of high-dose inhaled β-agonist treatment, notably hypokalemia. No significant interaction was noted for ECG disturbances. Nevertheless, given the frequency with which this combination of drugs is used in patients who are acutely hypoxic, who may have coexisting ischemic heart disease, or who are receiving other medication likely to cause hypokalemia, the arrhythmogenic potential of the interaction requires consideration. Careful attention to treating hypokalemia in such circumstances is strongly advised.

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