Effects of Hydrochlorothiazide, Amiloride, and Lisinopril on the Metabolic Response to Adrenaline Infusions in Normal Subjects

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Summary. Twelve healthy male volunteers were given adrenaline infusions, 0.05 µg/kg body weight/min over 120 minutes in order to achieve serum adrenaline concentrations comparable with those seen in acute myocardial infarction. The infusions were given on four occasions, at intervals of at least 4 weeks. Before the infusions the subjects were given, in random order, 14 days of pretreatment with placebo, hydrochlorothiazide 50 mg once daily, amiloride 10 mg once daily, or lisinopril 20 mg once daily. The adrenaline infusion induced a drop in serum potassium of the same magnitude in all four groups, with the lowest absolute value after hydrochlorothiazide because of the lowest pre-adrenaline level. The infusion-induced decreases in serum calcium and magnesium were of the same magnitude in all groups, with the absolute calcium being least low in the hydrochlorothiazide group because of the highest preinfusion value. Preinfusion serum urate was highest after hydrochlorothiazide and fell during the adrenaline infusion in all groups, although not significantly. Blood glucose increased during the adrenaline infusion in all groups, but significantly more after hydrochlorothiazide and amiloride than after lisinopril. Heart rate increased during the adrenaline infusion in all groups but least after lisinopril. QTc preinfusion was longer after hydrochlorothiazide than after amiloride and placebo, but the infusion-induced prolongation of QTc was of the same magnitude in all pretreatment groups. Since our results were obtained in short-term experiments in normal subjects, their clinical relevance is questionable, but they support the view that ACE inhibitors may have certain metabolic advantages over diuretics.

Key Words. adrenaline, hypertension, metabolism, amiloride, hydrochlorothiazide, lisinopril, electrocardiogram

Recently there has been much discussion of the long-term effects of the metabolic changes (e.g., raised blood sugar with thiazides) seen with some of the drugs used in the treatment of heart failure and hypertension. In this paper we look at another aspect of the metabolic effects of these drugs, namely, their effects on the metabolic response to adrenaline infusions in normal subjects. Myocardial infarction, a not uncommon event in patients with heart failure and hypertension, is associated with elevated plasma adrenaline levels and with metabolic and ionic changes. These changes may play a role in the malignant arrhythmias sometimes seen with myocardial ischemia and infarction [1,2].

We have previously shown that adrenaline infusions in healthy volunteers [1,3,4] cause metabolic and ionic changes similar to those seen in myocardial infarction, and in the present study we use the same model to investigate whether pretreatment with some of the drugs used in the treatment of heart failure and hypertension has any effect on these changes. We have also measured some of the metabolic and ionic changes induced by these drugs during the 2-week pretreatment period prior to the adrenaline infusion. The drugs we have studied are hydrochlorothiazide (a thiazide, a class of drugs that for years has been first-choice therapy for hypertension and heart failure), lisinopril (an ACE inhibitor, a class of drugs that many think should now be first-choice therapy), and amiloride (a potassium-sparing diuretic). Although amiloride on its own is not a universally accepted therapy, it is used in several centers; also, it is often used in combination with a thiazide, and therefore we decided to study it. In previous studies we have investigated beta blockers and calcium antagonists [1,3].

Patients and Methods

Twelve healthy male volunteers, aged 23–38 (mean 28.8) years, receiving no regular medication, were each given, on four separate occasions, each separated by at least 4 weeks, an adrenaline infusion at a rate of 0.05 µg/min/kg body weight over 120 minutes. The adrenaline infusion was given via a cannulated antecubital vein, with the volunteer at rest in the supine position. A cannula was inserted in the opposite upper limb for blood sampling. Before the adrenaline infusion the volunteers were pretreated for 14 days with placebo, hydrochlorothiazide 50 mg once daily, amiloride 10 mg once daily, or lisinopril 20 mg once daily in a randomized order, with each of the volunteers...
receiving each of the four pretreatments (Latin square design).

On each occasion the adrenaline infusion was started at 1 p.m., and approximately 5 hours before the infusion the volunteer was given a tablet of the current pretreatment. Fifteen minutes before the adrenaline infusion, at the start of the infusion, every 15 minutes during the infusion, and 15 and 30 minutes after the infusion, blood was drawn for analysis of serum potassium, magnesium, calcium, phosphate, urate, albumin, creatinine, and blood glucose using the routine methods of a local laboratory. An electrocardiogram (leads I, II, III, aVR, aVL, and aVF) was recorded continuously from the start of the adrenaline infusion until 30 minutes after the infusion at a speed of 10 mm/sec, which was increased to 50 mm/sec at the times of blood sampling.

The electrocardiogram was analyzed for heart rate, T-wave amplitude, and QRS and QT durations. QT duration was calculated by the use of Bazett’s formula. QT was measured from the beginning of the QRS complex to the end of the T wave, which was defined as the point where the descending limb of the T wave returned to the isoelectric line, defined by the PQ segment. For the calculations, the average of three representative beats in the lead with the longest QT segment during sinus rhythm was used. T-wave amplitude was measured from the isoelectric line to the highest point of the T wave in lead II, in which the duration of the QRS complex was also measured. The average of three representative cardiac cycles during sinus rhythm was used for the calculations. Just after blood sampling, systolic blood pressure and diastolic blood pressure were determined by the cuff method (phase 5 for diastolic blood pressure).

The results are expressed as the mean ± standard deviation. For statistical analysis a multivariate analysis of variance for repeated measures design (MANOVA) was used with time during the adrenaline infusion as the within-subject factors [5]. If the analysis of variance suggested differences in baseline values between the various pretreatments, these differences were evaluated by t tests for paired samples. All statistical tests were two sided. p < 0.05 was considered to be statistically significant.

The protocol was approved by the local ethics committee, and all volunteers gave informed consent before they were included in the study.

**Results**

**Metabolic results**

The effects of an adrenaline infusion on the various metabolic variables measured in the present study are summarized in Table 1. The adrenaline infusion had significant effects on all variables except urate, causing rapid falls in S-potassium and S-phosphate, which were apparent after 15 minutes, whereas the drops in S-calcium and S-magnesium occurred more slowly. A marked increase in the B-glucose was also seen, as well as minor, although still statistically significant, changes in S-albumin and S-creatinine.

**Metabolic effects of the pretreatment before adrenaline infusion**

When the effects of the various pretreatments on the metabolic variables before the start of the adrenaline infusion were compared, hydrochlorothiazide was found to lower S-potassium significantly (p < 0.01) compared with placebo, and to increase significantly S-albumin (p < 0.01) compared with placebo and S-urate (p < 0.001) compared with all the other pretreatments. Pretreatments with amiloride or lisinopril were not associated with any significant effects on the metabolic variables at baseline when compared with placebo.

**Effects of the active pretreatments on the metabolic response to adrenaline infusion**

A significant interaction was found between the effect of the adrenaline infusion and the various pretreatments on B-glucose. Thus, pretreatment with hydrochlorothiazide caused a greater increase in B-glucose during the adrenaline infusion than that seen with placebo (p < 0.044), with a value of 9.44 ± 2.5 mmol/l at time 120 minutes. Also, pretreatment with amiloride was associated with higher B-glucose values during the adrenaline infusion than those seen with placebo, but the overall response was not statistically significant compared with placebo. After pretreatment with lisinopril, B-glucose rose less during the adrenaline infusion (B-glucose = 8.23 ± 1.6 mmol/l at time 120 minutes) than after the other pretreatments, although the difference was not statistically significant when compared with placebo. However, when lisinopril was compared with the diuretics, it was found that both hydrochlorothiazide (p < 0.001) and amiloride (p < 0.01) accentuated the adrenaline-induced increase in B-glucose.

Lisinopril pretreatment also significantly modified the adrenaline-induced changes in S-phosphate (p < 0.001). Thus, after lisinopril the fall in S-phosphate during the adrenaline infusion was smaller than that seen after placebo or hydrochlorothiazide.

The adrenaline-induced falls in S-magnesium and S-potassium were similar after all pretreatments, but due to its potassium-lowering effect before the start of the adrenaline infusion, the lowest S-potassium (2.98 ± 0.37 mmol/l) during the infusion was seen after pretreatment with hydrochlorothiazide.

**Hemodynamic and electrocardiographic results**

These results are summarized in Table 2. Adrenaline caused significant increases in heart rate and systolic blood pressure, and a significant fall in diastolic blood