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Effects of Combined Therapy with Amiloride and Hydrochlorothiazide on Plasma and Total Body Potassium, Blood Pressure, and the Renin-Angiotensin-Aldosterone System in Hypertensive Patients

U. G. Svendsen[1, 3], H. Ibsen[1, 4], S. Rasmussen[2], A. Leth[1], M. D. Nielsen[2], H. Dige-Petersen[2], and J. Giese[2]

[1] Medical Department C., [2] Department of Clinical Physiology, Glostrup Hospital, University of Copenhagen,
[3] Medical Department TA, and [4] Medical Department B, State University Hospital, Rigshospitalet, Copenhagen, Denmark

Summary. After a run-in period of 8 weeks on a regimen of hydrochlorothiazide (HCT, median dosage 75 mg/day), patients with essential hypertension were randomly allocated to continued hydrochlorothiazide therapy (Group I) or additional treatment with amiloride (Group II, median dosage 15 mg/day, or 5 mg per 25 mg hydrochlorothiazide) for the following 12 weeks. Thereafter all the patients were changed to treatment with a fixed combination tablet containing 5 mg amiloride and 50 mg hydrochlorothiazide (Moduretic), keeping the thiazide dosage unchanged for an additional 12 weeks. In Group I patients there was no change in plasma potassium, total body potassium content or the renin-angiotensin-aldosterone system during the 12 weeks on HCT. When the treatment was changed to Moduretic, significant increases were found of 10% in plasma potassium and 3% in total body potassium content. No important stimulation of the renin-angiotensin-aldosterone system was found. In Group II patients addition of an average of 15 mg amiloride to the hydrochlorothiazide treatment led to significant increases in plasma potassium and total body potassium content of approximately 15% and 4%, respectively. There was also a significant increase in the plasma concentrations of renin, angiotensin II and aldosterone. Reducing the average dose of amiloride to 7.5 mg/day by use of Moduretic did not lead to decrease in plasma potassium or total body potassium content. Plasma concentrations of renin, angiotensin II, and aldosterone were decreased, but the individual changes varied markedly and no significant overall change was found.

Key words: amiloride, hydrochlorothiazide; hypertension, total body potassium, plasma potassium, renin-angiotensin-aldosterone system

Potassium retaining diuretics are useful for correction of thiazide-induced hypokalaemia and depletion of total body potassium. Amiloride has produced increases in total body potassium content (TK) and plasma potassium (PK) when added to thiazides in the treatment of hypertension [9, 10, 11, 12] and those in heart failure [1]. It was recently reported that amiloride (median dosage 15 mg/day) added to hydrochlorothiazide (HCT; median dosage 75 mg/d) led to a sustained increases in PK and TK of approximately 15% and 4%, respectively, throughout a 12 week study period [12].

Amiloride is usually administered as a combination tablet (Moduretic), containing 5 mg amiloride and 50 mg HCT. It is important to examine the potassium retaining efficacy of this fixed combination of a thiazide and a potassium sparing diuretic. The aim of the present study was to study the effect of treatment with Moduretic on PK, TK and the plasma concentrations of renin (PRC), angiotensin II (Ang II) and aldosterone (PAC) in hypertensive patients.

Patients and Methods

Twenty-eight patients were investigated (12 men and 16 women; median age 48.5 years, range 26-71 years; median height 167 cm, range 151-183 cm; and median weight 72,5 kg, range 48.5-109 kg). All patients had mild essential hypertension and were being treated with thiazide medication alone. None had evidence of cardiac failure, and all had normal kidney function, assessed as the plasma creatinine concentration.

No dietary restriction was employed, and patients were instructed not to change their usual diet throughout the period of the investigation.

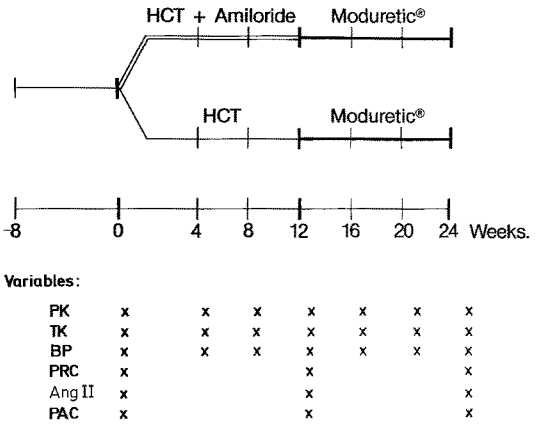

Fig. 1. Design of the study (see text)

The following treatment protocol was employed (Fig. 1). Regardless of previous treatment, the patients were observed for 8 weeks while on hydrochlorothiazide 50–100 mg/day (approximately 1 mg/kg body weight, median dosage 75 mg/day) with no additional potassium chloride or potassium-sparing diuretics.

At the end of the 8 week prestudy period on HCT alone (Week 0), patients were randomly assigned to one of two groups: HCT monotherapy (Group I, 13 patients) or HCT with amiloride (Group II, 15 patients). One patient was immediately transferred from Group I to Group II because the plasma potassium concentration was 2.2 mmol/l, and 2.5 mmol/l was defined as the upper limit of a supposed danger zone (agreed prior to randomization). The final allocation was 12 patients in Group I and 16 patients in Group II. The dose of HCT was the same in both groups. Amiloride was added in the dose of 5 mg/25 mg HCT, the median dosage being amiloride 15 mg/d.

After the initial 12 week study period the treatment of all patients was changed to amiloride/HCT by administration of a combination tablet containing 50 mg HCT and 5 mg amiloride (Moduretic), thus keeping constant the original dose of HCT.

In both groups measurements were made in Weeks 0, 4, 8, 12, 16, 20 and 24 of PK, TK and blood pressure (BP). PRC, Ang II, and PAC were measured in Weeks 0, 12 and 24. PK was measured by flame photometry. PRC, Ang II and PAC were measured as previously described [4, 7, 8]. TK was determined with a low background, high-sensitivity whole-body counter for measurement of ^{40}K [12]. TK has been expressed as mmol K/m^2 body surface area. Individual calibration factors in each patient were estimated once in the study period using ^{42}K with a 24-h equilibration period once during the study period. The coefficient of variation of the whole-body counting procedure was 3.2%, as calculated from 104 ^{40}K-studies in 10 normal subjects during the study period; their TK varied from 1300 to 2700 mmol/m^2 body surface area.

Blood pressure (BP) was measured in the Outpatient Clinic with an arm cuff and a standard mercury manometer, after a 10 min rest in the supine position, and after 1 min in the upright position. Diastolic BP was taken as the disappearance of the Korotkoff sounds (Phase V). At each visit the mean of three readings was calculated.

Results are given in the text as median values and the range in parenthesis. The Wilcoxon rank-sum test for paired observations was used for assessment

Table 1. Total body potassium content (TK), plasma potassium concentration (PK), plasma concentrations of renin (PRC), angiotensin II (Ang II) and aldosterone (PAC) during hydrochlorothiazide-monotherapy (Week 0). (Median values with range in parentheses). There were no significant differences in the variables between Groups I and II

	Group I	Group II
TK (mmol/m^2 BSA)	1662 (1400–2118)	1536 (1117–2034)
PK (mmol/l)	3.5 (2.9–4.1)	3.3 (2.2–3.8)
PRC (mIU/l)	45 (11–299)	81 (15–212)
Ang II (pmol/l)	14 (4–61)	22 (6–148)
PAC (pmol/l)	236 (55–443)	208 (106–471)

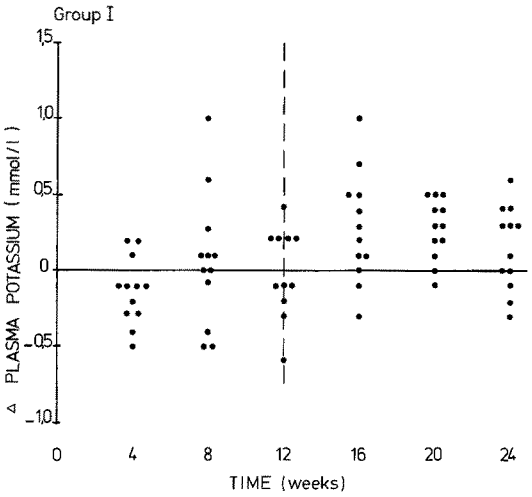

Fig. 2. Changes in plasma potassium concentration (PK) during continued hydrochlorothiazide therapy (Weeks 0–12) and Moduretic treatment (Weeks 12–24)

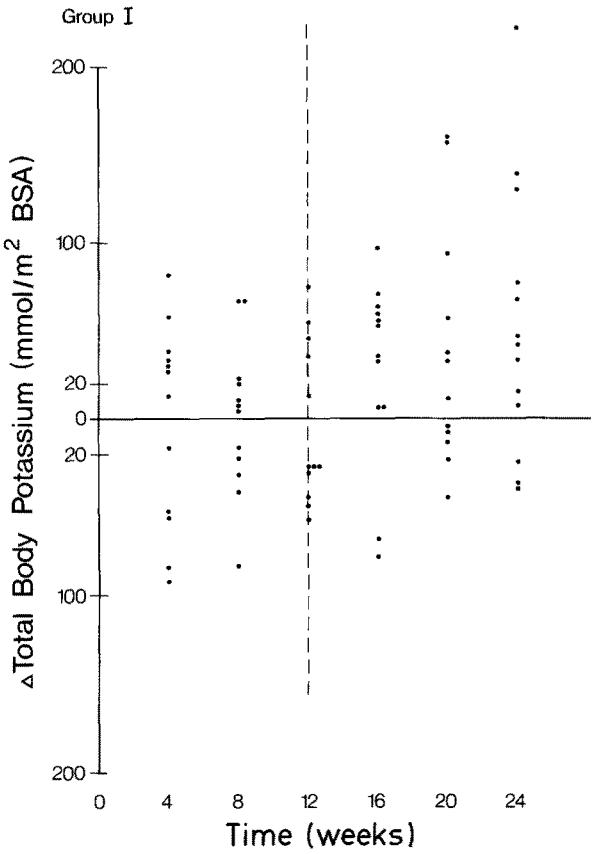

Fig. 3. Changes in total body potassium content (TK) during continued hydrochlorothiazide therapy (Weeks 0–12) and Moduretic treatment (Weeks 12–24)

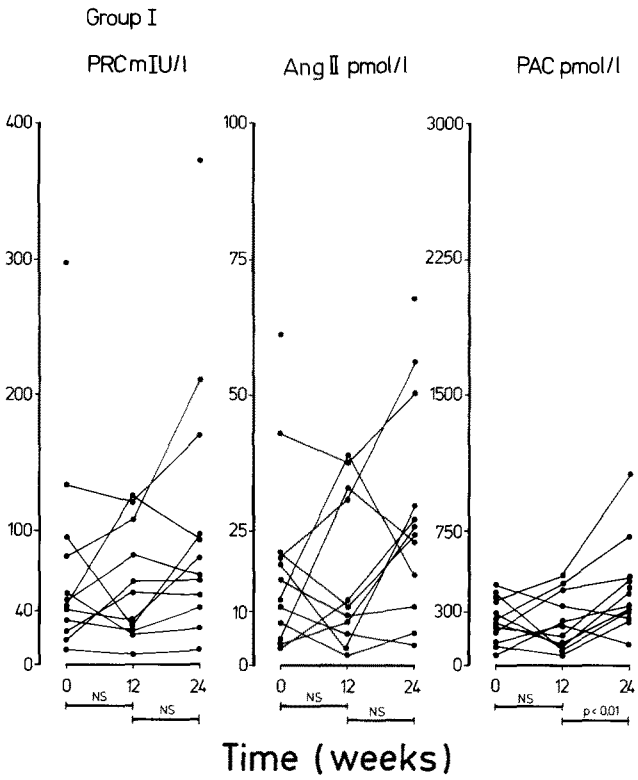

Fig. 4. Plasma concentrations of renin (PRC) angiotensin II (Ang II) and aldosterone (PAC) during continued hydrochlorothiazide therapy (Weeks 0–12) and Moduretic treatment (Weeks 12–24)

of changes in BP and in the renin-angiotensin-aldosterone system. For analysis of changes in PK and TK, a two sided analysis of variance with curvilinear regression was employed [5]. Orthogonal polynomials were used for curve fitting in order to optimal use of the equispaced investigational design. With this technique it was important that measurements were available for each of the seven predefined time points (0, 4, 8, 12, 16, 20, 24 weeks). For assessment of the course of PK with time 11 complete sets of patient data were available for Group I and II, and for TK there were 12 sets of patient data for both groups.

Results

The control values for TK, PK, PRC, Ang II, and PAC in Week 0 before additional amiloride treatment (Group II) or continued HCT treatment (Group I) are shown in Table 1.

In Group I patients there was no change in PK or TK during the subsequent 12 weeks of continued HCT therapy (Figs. 2, 3). When the treatment was changed to Moduretic, keeping the initial dose of HCT unchanged, a significant ($p < 0.05$) increase in PK of approximately 10% was found (Fig. 2). The maximal changes were observed in Weeks 16 and 20, with a subsequent minor decrease in Week 24. At

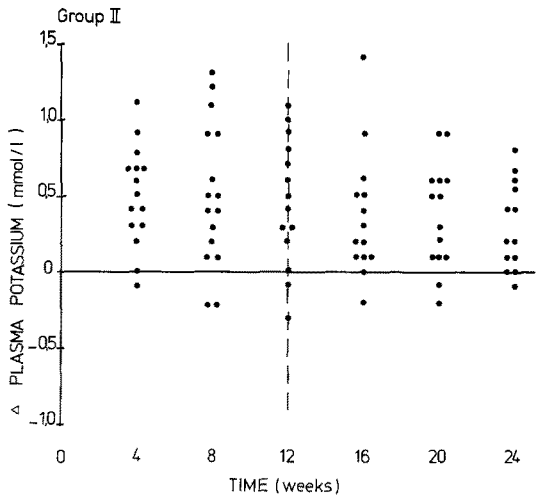

Fig. 5. Changes in plasma potassium concentration (PK) during treatment with hydrochlorothiazide plus amiloride (Weeks 0–12) and Moduretic treatment (Weeks 12–24)

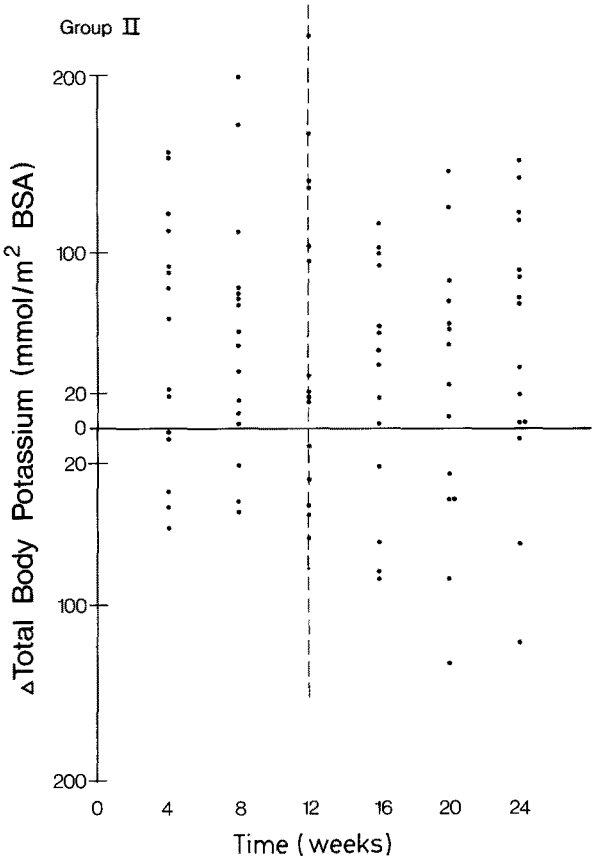

Fig. 6. Changes in total body potassium content (TK) during treatment with hydrochlorothiazide plus amiloride (Weeks 0–12) and Moduretic treatment (Weeks 12–24)

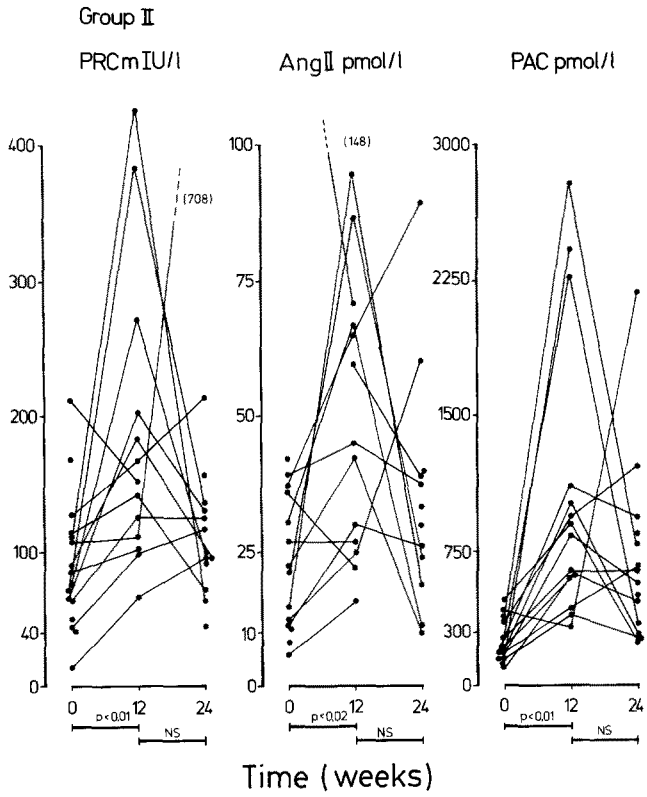

Fig. 7. Plasma concentrations of renin (PRC) angiotensin II (Ang II) and aldosterone (PAC) during treatment with hydrochlorothiazide plus amiloride (Weeks 0–12) and Moduretic treatment (Weeks 12–24)

that time the level did not differ significantly from at in Week 12. The increase in TK (Fig. 3), approximately 3% on Moduretic, was significant ($p < 0.025$) throughout the investigational period, the levels in Week 24 being significantly higher than in Week 12. PRC, Ang II and PAC (Fig. 4) did not change between Weeks 0 and 12 during continued HCT treatment in the initial part of the study. Institution of Moduretic treatment (Weeks 12–24) led to an increase ($p < 0.001$) in PAC of about 65% between Weeks 12 and 24, but not to a significant change in PRC or Ang II (Fig. 4). In Week 12 on HCT treatment, systolic and diastolic BP in the supine position were 143 mmHg (range: 132 to 163) and 96 mmHg (85 to 105), respectively. No change was observed either in diastolic or systolic BP when the treatment was changed to Moduretic.

In Group II patients the combined treatment with a mean 15 mg/d amiloride (Weeks 0 to 12) led to increases in PK and TK, of about 15% and 4%, respectively (Figs. 5, 6), with peak values in Week 8 and subsequent minor decreases, although both PK and TK were higher in Week 12 than Week 0. Reducing the dose of amiloride to half whilst keeping HCT dose constant by changing the treatment to Moduretic did not lead to decrease in TK or PK.

Throughout Weeks 12 to 24, TK and PK remained unchanged as compared to the levels in Week 12, and at all times in that period they higher than in Week 0. The additional administration of amiloride 15 mg/day to Group II in the initial part of the study induced significant increases in all of the variables of the renin-angiotensin-aldosterone system (Fig. 7).

During treatment with the reduced dose of amiloride, by administration of Moduretic, there was a tendency to a decrease in PRC, Ang II and PAC. However, although the individual changes varied markedly the median values were not significantly lower in Week 24 than in Week 12. Systolic and diastolic BP in Week 12 on amiloride/HCT treatment in Group II patients were 147 mmHg (range 125 to 182 mmHg) and 98 mmHg (range 86 to 107), respectively, in the supine position. Reducing the dose of

amiloride to half by changing the treatment to Moduretic did not affect the blood pressure.

From a clinical point of view the number of patients with hypokalaemia in spite of Moduretic treatment is of interest: in Week 24 7 out of 25 patients on Moduretic showed PK values between 3.1-3.4 mmol/l.

Discussion

The present study has shown that, when adding amiloride 7.5 mg/day to HCT 75 mg/d treatment by changing treatment to Moduretic, significant increases in PK and TK of about 10% and 3%, respectively, were found. Some investigators have claimed loss of the potassium-retaining effect of amiloride with time [3].

In Group I patients the increase in TK induced by a low dose of amiloride was found to be maintained throughout the 12 week study period. However, the influence on PK seemed to decrease with time, and after 12 weeks on Moduretic, in Week 24, the increase in PK was no longer significant. We have no ready explanation for the discrepancy between the changes in TK and PK.

In the initial 12 week study period, amiloride 15 mg/day added to HCT 75 mg/day in Group II patients induced a significant and sustained increase in PK and TK, of approximately 15% and 4%, respectively. Although these results have been discussed in detail in a recent publication [12], they are presented here for the purpose of clarity.

A reduction in the dose of amiloride to a mean 7.5 mg/d by changing the treatment to Moduretic did not influence the level of PK and TK. The increase in PK and TK induced by the high dose of amiloride was maintained unchanged throughout the following 12 weeks of treatment with the low dose, and the levels of PK and TK in Week 24 were still significantly higher than in Week 0.

Thus, within the duration of the present study no important difference was found between the potassium-retaining capacity of the high and low doses of amiloride.

The results suggest that the combination tablet Moduretic is useful in limiting potassium loss during thiazide treatment, but it must be realized that great individual variation exists in the degree of change in potassium homeostasis during treatment with thiazides and amiloride [2, 6, 11]. As demonstrated here, the combination tablet may not be sufficient in all cases, since 7 out of 25 patients on Moduretic showed PK values below 3.5 mmol/l (range 3.1 to 3.4).

The addition of amiloride, by changing HCT treatment to Moduretic in Group I patients, led to a tendency to increase PRC and Ang II between Weeks 12 and 24, but the changes showed great individual variation and were not statistically significant. PAC showed a modest increase of approximately 65%.

The reduction in the dose of amiloride in Group II patients resulted in a fall in PRC, Ang II, and PAC as compared to the levels whilst on the higher dose. Again, the values showed great individual variation, and the decrease between Weeks 12 and 24 was not statistically significant. Nevertheless, the results in Groups I and II taken together imply dose-related stimulation of the renin-angiotensin-aldosterone system by amiloride.

Blood pressure was not affected by changing the treatment regimen by adding low dose amiloride to the HCT treatment. In a previous publication [12] the high dose of amiloride was reported to cause a minor reduction in systolic BP in the upright position and no change in supine blood pressure.

Overall, the dose of amiloride in the combination tablet Moduretic (5 mg amiloride/50 mg HCT) led to significant increases in plasma potassium and in total body potassium. No important difference was detected between the potassium retaining capacity of the low and high doses of amiloride. The influence of amiloride on the renin-angiotensin-aldosterone system was related to dose. No important change was observed in blood pressure between the high and low amiloride dose treatments.

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Ulrik Gerner Svendsen, D.M.SC.
Medical Department TA 7551
State University Hospital
Rigshospitalet
Tagensvej 20
DK-2200 Copenhagen N
Denmark