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Effect of Norethisterone-Acetate on Salt Excretion and on the Renin-Aldosterone System in Man*

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Der Einfluß von Norethisteron-Acetat auf Natriumausscheidung und Renin-Aldosteron-System beim Menschen

Zusammenfassung. Der Mechanismus, über den Norethisteron-Acetat die früher von uns beschriebene Mehrausscheidung von Aldosteron-18-glucuronid bewirkt, wurde weiter untersucht (an 10 männlichen Versuchspersonen). Die orale Einnahme einer Tagesdosis von 30 mg des Gestagens für 1 Woche führte zu einer signifikanten Steigerung der Ausscheidung von Natrium und von Aldosterone-18-glucuronid. Die Aldosteron-Sekretionsrate nahm zu, der Anstieg war aber nicht signifikant. Plasma-Aldosteron, Plasma-Angiotensin II und Plasma-Renin-Aktivität änderten sich nicht. Plasma-Renin-Substrat stieg signifikant an. Norethisteron-Acetat oder ein Metabolit stimuliert möglicherweise sowohl die Aldosteron-Sekretion wie den -Metabolismus. Der Anstieg von Renin-Substrat ist wahrscheinlich durch östrogene Eigenschaften der Substanz bedingt. Der Mechanismus der Natriurese bleibt ungeklärt.

Schlüsselwörter: Gestagene – Natriurese – Angiotensin – Aldosteron.

Summary. The mechanism of a previously described rise in the excretion rate of aldosterone-18-glucuronide under the influence of norethisterone-acetate was further investigated in 10 male volunteers. Oral administration of 30 mg norethisterone-acetate daily for 1 week caused a significant natriuresis and a rise in the excretion rate of aldosterone-18-glucuronide. Aldosterone secretion rate rose slightly but insignificantly. Plasma aldosterone, renin activity, and angiotensin II remained unaltered while plasma renin substrate increased markedly. Norethisterone-acetate, or one of its metabolites, may directly stimulate aldosterone secretion and metabolism rendering plasma aldosterone levels unaltered. The rise in renin substrate is obviously due to estrogenic properties of the compound studied. The mechanism of natriuresis remains unexplained.

Key words: Progestagenic Compounds – Natriuresis – Angiotensin – Aldosterone.

In a previous communication [1] on the effect of 5 different progestagenic compounds on sodium balance and the renin-aldosterone system, we described a marked increase in the excretion rate of aldosterone-18-glucuronide after oral administration of norethisterone-acetate in 4 men, which did not seem to be secondary to an activation of the renin-angiotensin system. The present paper describes results of a more detailed study on this important progestagenic compound with respect to aldosterone secretion.

Methods

The experimental setup was similar to that in the previous report [1]. The same diet containing 83 meq of sodium and approximately 75 meq of potassium per day was given to 10 healthy male volunteers (20–27 years of age; 62–81 kg of weight) for 14 days, while they followed their normal activities as medical students. From day 5 to 11, they took 10 mg norethisterone-acetate 3 times daily (Primolut®-Nor, Schering) in tablet form. The total daily dosage was 30 mg. They collected their urine every day for the measurement of sodium, potassium and aldosterone-18-glucuronide. Excretion rates on days 3 and 4 served as controls. Blood for the determination of plasma sodium, potassium, renin activity, renin substrate, angiotensin II and aldosterone was collected on days 4, 8 and 11 at 10 a.m. after the experimental subjects had been up and about for at least 2 h. After drawing the blood, 10 μCi of ^{3}H-aldosterone were injected intravenously and the secretion rate of aldosterone was calculated according to Lommer et al. [2]. The specific activity of urinary aldosterone-18-glucuronide of the 24-h period following tracer injection was used as a measure of tracer dilution by endogenous aldosterone secretion. During this collection period, 74–88% of the ^{3}H injected had been excreted into the urine.

Most analytical methods were described in the previous report [1]. Plasma aldosterone was measured by a radioimmunoassay according to Schöneshöfer et al. [3] after purification by paper chromatography. The aldosterone antibody was a gift of the National Institute of Health, Bethesda, Maryland, USA. Statistical evaluation of the data was done according to Sachs [4]. For the method of calculating per cent changes during treatment, we refer to our previous paper [1].

Results

Most results are summarized in Figure 1. On the 2 control days, mean sodium excretion was slightly lower than sodium input (72 versus 83 meq/24 h). Mean potassium excretion during the control period was also 72 meq/24 h. Between the 3rd and the 6th day of treatment sodium excretion was slightly, but significantly higher than in the control period. During the whole treatment period, cumulative urinary sodium excretion was by 85 meq greater than the intake. After cessation of treatment, an almost even sodium balance was observed. On two days during treatment, potassium excretion was significantly higher than in the control period. Since the exact potassium intake is unknown, changes in balance during treatment cannot be calculated. Mean plasma sodium concentration (140.3 meq/l with an SEM of ± 0.86 meq/l in the control period) did not change significantly. Mean plasma potassium was 4.25 ± 0.14 meq/l in the control period. After 4 and 7 days of treatment it fell to 3.98 ± 0.10 meq/l ($p > 0.05$) and 3.91 ± 0.12 meq/l ($p < 0.05$), respectively.

Neither plasma renin activity nor plasma angiotensin II concentrations changed significantly. As in our previous study, a significant increase in renin substrate concentration was observed as early as on the 4th day of treatment. Aldosterone secretion rates rose slightly during treatment, but the change was not significant. The excretion rate of aldosterone-18-glucuronide, however, rose with borderline significance when per cent changes were statistically evaluated. Plasma aldosterone, on the other hand, fell slightly although not significantly, during the administration of norethisterone-acetate.

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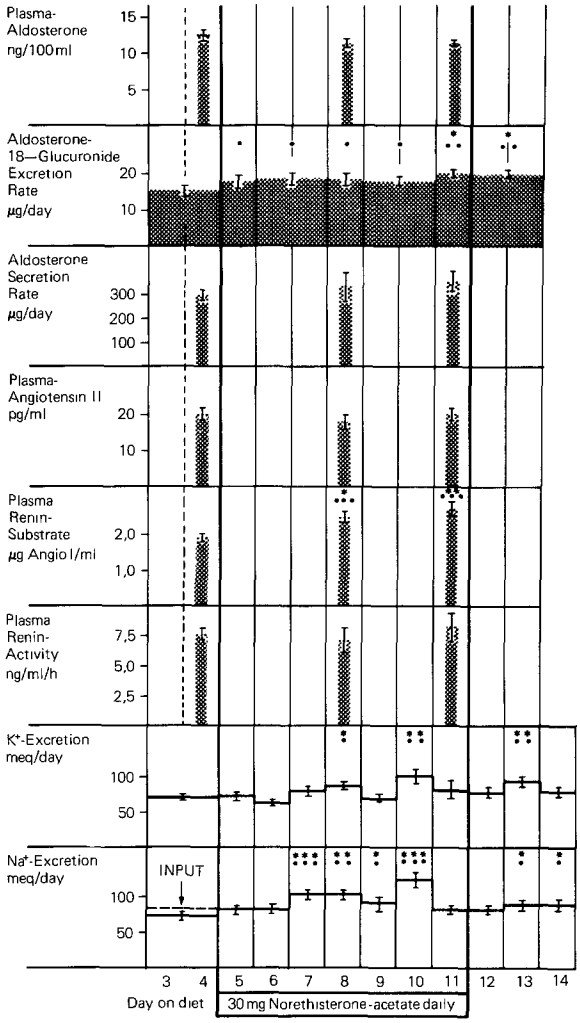

Fig. 1. Sodium and potassium excretion and various parameters of the renin-aldosterone system before, during and after the oral administration of norethisterone-acetate to 10 healthy young male volunteers on slight sodium restriction. Means ± standard errors of the means are given. Mean excretion rates in the control period were calculated from 20 separate measurements of days 3 and 4 on the diet. Asterisks indicate the significance of absolute changes, closed dots that of per cent changes. * or · = $p < 0.05$; ** or ·· = $p < 0.01$; *** or ··· = $p < 0.001$

Discussion

The results of the study presented confirm those of our previous, less extensive experiment on the effect of norethisterone acetate in 4 male subjects. During treatment, a significant natriuresis was observed which was accompanied by an increase in the excretion rate of aldosterone-18-glucuronide. The latter change, however, was more marked in the previous than in the present study. In contrast to the effect of progesterone, that of norethisterone-acetate could not be simply explained by an activation of the renin-angiotensin system as a consequence of renal sodium loss. This discrepancy prompted the present study. In accord with our own observations [1] and those of Crane and Harris [5], the significant rise in plasma renin substrate can be attributed to estrogenic properties of the derivative of 19-nor-testosterone investigated. Plasma renin activity and angiotensin II levels however did not change. Although the slight rise in aldosterone secretion was not significant, one could argue that aldosterone secretion and the formation of aldosterone-18-glucuronide in the kidney and/or liver [6] are both directly stimulated by norethisterone-acetate or one of its metabolites. Simultaneous stimulation of aldosterone secretion and metabolism renders plasma aldosterone unaltered. The effect on the major metabolic pathway to tetrahydro-aldosterone-glucuronide, however, is unknown. All changes observed, except those on renin substrate, are too small to warrant a safe interpretation. The cause of natriuresis and of the slight fall in plasma potassium remains unexplained by the interpretation given. Our results of a short-time experiment with a rather large daily dose of norethisterone-acetate do not support the suspicion [7] that the compound would lead to major disturbances in the electrolyte metabolism and in the homeostasis of the renin-angiotensin system. They give no explanation for the finding by Crane and Harris [7] that exchangeable sodium increases during prolonged treatment with this steroid, thus adding potentially harmful metabolic effects to those of estrogens as constituents of oral contraceptive drugs. It cannot be excluded, however, that metabolic effects of greater magnitude occur in the female sex, since sex differences in the effect of a synthetic estrogen on the renin-aldosterone system have been found [8].

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