

Effect of Aminoglutethimide on Blood Pressure and Steroid Secretion in Patients with Low Renin Essential Hypertension

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J Clin Invest. 1978;62(1):162-168. <https://doi.org/10.1172/JCI109101>.

Research Article

An inhibitor of adrenal steroid biosynthesis, aminoglutethimide, was administered to seven patients with low renin essential hypertension, and the antihypertensive action of the drug was compared with its effects on adrenal steroid production. In all patients aldosterone concentrations in plasma and urine were within normal limits before the study. Mean arterial pressure was reduced from a pretreatment value of 117 ± 2 (mean \pm SE) mm Hg to 108 ± 3 mm Hg after 4 days of aminoglutethimide therapy and further to 99 ± 3 mm Hg when drug administration was stopped (usually 21 days). Body weight was also reduced from 81.6 ± 7.2 kg in the control period to 80.6 ± 7.0 kg after 4 days of drug treatment and to 80.1 ± 6.7 kg at the termination of therapy. Plasma renin activity was not significantly increased after 4 days of treatment but had risen to the normal range by the termination of aminoglutethimide therapy. Mean plasma concentrations of deoxycorticosterone and cortisol were unchanged during aminoglutethimide treatment whereas those of 18-hydroxydeoxycorticosterone, progesterone, 17α -hydroxyprogesterone, and 11-deoxycortisol were increased as compared to pretreatment values. In contrast, aminoglutethimide treatment reduced mean plasma aldosterone concentrations to about 30% of control values. Excretion rates of 16β -hydroxydehydroepiandrosterone, 16-oxo-androstenediol, 17-hydroxycorticosteroids and 17-ketosteroids, and the secretion rate of 16β -hydroxydehydroepiandrosterone were not significantly altered by aminoglutethimide treatment whereas the excretion rate of aldosterone was reduced from 3.62 ± 0.5 (mean \pm SE) in the control period [...]

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Effect of Aminoglutethimide on Blood Pressure and Steroid Secretion in Patients with Low Renin Essential Hypertension

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ABSTRACT An inhibitor of adrenal steroid biosynthesis, aminoglutethimide, was administered to seven patients with low renin essential hypertension, and the antihypertensive action of the drug was compared with its effects on adrenal steroid production. In all patients aldosterone concentrations in plasma and urine were within normal limits before the study. Mean arterial pressure was reduced from a pretreatment value of 117 ± 2 (mean \pm SE) mm Hg to 108 ± 3 mm Hg after 4 days of aminoglutethimide therapy and further to 99 ± 3 mm Hg when drug administration was stopped (usually 21 days). Body weight was also reduced from 81.6 ± 7.2 kg in the control period to 80.6 ± 7.0 kg after 4 days of drug treatment and to 80.1 ± 6.7 kg at the termination of therapy. Plasma renin activity was not significantly increased after 4 days of treatment but had risen to the normal range by the termination of aminoglutethimide therapy. Mean plasma concentrations of deoxycorticosterone and cortisol were unchanged during aminoglutethimide treatment whereas those of 18-hydroxydeoxycorticosterone, progesterone, 17α -hydroxyprogesterone, and 11-deoxycortisol were increased as compared to pretreatment values. In contrast, aminoglutethimide treatment reduced mean plasma aldosterone concentrations to about 30% of control values. Excretion rates of 16β -hydroxydehydroepiandrosterone, 16-oxo-androstenediol, 17-hydroxycorticosteroids and 17-ketosteroids, and the secretion

rate of 16β -hydroxydehydroepiandrosterone were not significantly altered by aminoglutethimide treatment whereas the excretion rate of aldosterone was reduced from 3.62 ± 0.5 (mean \pm SE) in the control period to 0.9 ± 0.2 $\mu\text{g}/24$ h after 4 days and to 1.1 ± 0.3 $\mu\text{g}/24$ h at the termination of aminoglutethimide treatment.

The gradual lowering of blood pressure and body weight during aminoglutethimide therapy is consistent with the view that the antihypertensive effect of the drug is mediated through a reduction in the patients' extracellular fluid volume, probably secondary to the persistent decrease in aldosterone production. The observation that chronic administration of aminoglutethimide lowered blood pressure in these patients and elevated their plasma renin activity to the normal range without decreasing production of the adrenal steroids, deoxycorticosterone, 18-hydroxydeoxycorticosterone, and 16β -hydroxydehydroepiandrosterone, makes it unlikely that these steroids are responsible either for the decreased renin or the elevated blood pressure in patients with low renin essential hypertension.

INTRODUCTION

Patients with hypertension and low plasma renin activity (PRA)¹ can be subdivided further into those with an elevated, normal, or reduced aldosterone excretion rate. Patients in the first category have primary aldosteronism (1) whereas those in the last two categories mainly have low renin essential hyper-

Part of this work has been published in abstract form. 1976. *Clin. Res.* 24: 424A. (Abstr.)

Dr. Wayne Snodgrass was supported by a staff fellowship, Pharmacology Research Associate Training Program, National Institute of General Medical Sciences.

Received for publication 31 May 1977 and in revised form 9 March 1978.

¹Abbreviations used in this paper: DOC, deoxycorticosterone 17KS, 17-ketosteroids; 17OHCS, 17-hydroxycorticosteroids; 16β -OH DHEA, 16β -hydroxydehydroepiandrosterone; 18-OH DOC, 18-hydroxydeoxycorticosterone; PRA, plasma renin activity.

tension (2-5). The finding that low renin hypertension was present in 9-50% of hypertensive patients, depending upon the age of the population studied (6, 7), generated considerable interest in the pathophysiological mechanisms which might contribute to a low plasma renin. The report by Woods et al. (8) that aminoglutethimide, an inhibitor of adrenal steroid biosynthesis, normalized blood pressure in hypertensive patients with low PRA raised the possibility that these patients could be treated specifically. This possibility was supported by the finding that spironolactone, an antagonist of the renal action of aldosterone and other mineralocorticoid hormones, more effectively lowered blood pressure in patients with low vs. normal renin essential hypertension (9). Because aldosterone production is not elevated in patients with low renin essential hypertension, an intensive search for a new sodium retaining steroid other than aldosterone was instituted. Subsequently, increased secretion or excretion of deoxycorticosterone (DOC) (10), 18-hydroxydeoxycorticosterone (18-OH DOC) (11, 12), and 16 β -hydroxydehydroepiandrosterone (16 β -OH DHEA) (13) has been reported in groups of patients with low renin hypertension as compared to groups of patients with normal renin hypertension or normotensive subjects. However, no cause-and-effect studies have been carried out to compare blood pressure changes and steroid secretion in the same patients. In the present study, therefore, the effect of aminoglutethimide on the production of selected adrenal steroids is compared directly with its anti-hypertensive effect in seven patients with low renin essential hypertension.

METHODS

Patient selection. Seven patients (one black female, one black male, three white females, two white males) were selected from the National Institutes of Health Hypertension Clinic who fulfilled the following criteria. Blood pressure, with the patient sitting, was greater than 95 mm Hg diastolic on readings taken at home by the patient and by one of us in the clinic. PRA, while the patient was taking an ad libitum sodium intake, was below the range of normal values established for 89 age-matched, normotensive control subjects as evaluated by the renin-sodium index (5). In addition, PRA response to 2 h of upright posture was subnormal as compared to values from age-matched, normotensive subjects after sodium balance had been achieved on a 10-meq/day sodium diet or after furosemide administration (14-16). Furosemide, 40 mg, was given orally at 8 a.m., 12 noon, and 6 p.m. on the day before the test and the sodium intake was restricted to 10 meq/day. Blood for PRA was obtained the following morning at 8 a.m. after 2 h of upright posture. These patients had normal aldosterone excretion rates and plasma aldosterone concentrations, were normokalemic, and had normal intravenous pyelograms. Patients had either never been treated for hypertension (three) or their medications had been discontinued for at least 6 wk before the study (four).

Protocol for aminoglutethimide administration. The study

was approved by the clinical research review committee of the National Heart, Lung, and Blood Institute, and all patients gave written informed consent before participating in the study. The patients were hospitalized and given a daily diet containing 209 meq sodium to avoid stimulation of PRA. Urine was collected continuously in 24-h aliquots for determinations of creatinine, sodium, potassium, 17-hydroxycorticosteroids (17OHCs), 17-ketosteroids (17KS) and aldosterone excretion rates. After overnight recumbency, blood was collected at 8 a.m. on the 3rd hospital day for PRA and for plasma steroids including aldosterone, progesterone, 17 α -hydroxyprogesterone, DOC, 18-OH DOC, 11-deoxycortisol, and cortisol. Patients then stood until 12 noon at which time blood was obtained for PRA and plasma steroids. Blood for measurement of plasma steroids was obtained at 6 p.m. while posture was not controlled and again at 12 midnight and 6 a.m. after the patients had retired to bed at 10 p.m. Blood was collected in tubes containing disodium EDTA for PRA determinations and in tubes containing heparin sodium for measurements of plasma steroids. On the morning of the 4th hospital day, each patient was then given an intravenous injection of [3 H]16 β -OH DHEA and urine was collected for the subsequent 3 days for determination of secretory and excretory rates. Patients were then given aminoglutethimide, 250 mg, by mouth every 6 h, and on the 4th day of aminoglutethimide treatment, blood was again collected at the times and in the postures indicated above for measurement of PRA and plasma steroids, and the injection of [3 H]16 β -OH DHEA intravenously for determination of secretory and excretory rates was repeated. Patients were then discharged and followed in the outpatient clinic at weekly intervals for 3 wk. Patients recorded their blood pressures at home 2-4 times per day throughout the outpatient phase of the study. Patients continued to ingest a high sodium diet at home. Two of the seven patients were readmitted to the hospital after 3 wk of aminoglutethimide treatment for repeat determinations of PRA and plasma and urinary steroids according to the protocol outlined above.

Methods. Urinary creatinine was measured by standard automated methods, urinary sodium and potassium by flame photometry with lithium as internal standard, and urinary 17OHCs and 17KS (17) by previously published methods. PRA was measured at Hazleton Laboratories, Vienna, Va., under contract no. 272-76-C-0641CC with the National Heart, Lung, and Blood Institute. The amount of angiotensin I generated during a 3-h incubation at pH 6.4 was determined by radioimmunoassay (18).

Steroid measurements. Excretion of aldosterone-18-glucuronide was determined by radioimmunoassay, without prior chromatography, after 24-h hydrolysis at pH 1 (19).

Plasma concentrations of aldosterone (20), progesterone (21), 17 α -hydroxyprogesterone (22), cortisol,² and 11-deoxycortisol² were determined by radioimmunoassay at Hazleton Laboratories. Plasma deoxycorticosterone (19) was measured by radioimmunoassay after its separation from other steroids on a Kontes 250 \times 9-mm column (Kontes Glass Co., Vineland, N. J.) containing 9 g of Sephadex LH-20 (Pharmacia Fine Chemicals, Piscataway, N. J.) with a chloroform:hexane:water (50:50:0.25) solvent system.

16 β -OH DHEA excretion and secretion rates. Tritiated 16 β -OH DHEA was prepared by a stereospecific radiochemical synthesis.³ Excretion rates of 16 β -OH DHEA and 16-oxo-

² Unpublished observations.

³ R. B. Franklin, J. R. Mitchell, A. A. Taylor, and S. D. Nelson. An isotope dilution method for the measurement of the excretion and secretion rates of 16 β -hydroxydehydroepiandrosterone in human urine. Manuscript submitted for publication.

androstenediol and secretion rates of 16 β -OH DHEA were then determined by gas chromatographic and mass spectrometric techniques to be published elsewhere.³

Plasma 18-OH DOC. All solvents were spectrophotometric grade and used without further purification. Plasma (2 ml) was extracted with dichloromethane (15 vol) and subjected to overnight periodic acid oxidation (23) to form the gamma-lactone of 18-OH DOC. The lactone was separated from other steroids on a Kontes 250 \times 9-mm column containing 9 g of Sephadex LH-20 (chloroform:hexane:water, 50:50:0.25, solvent system) by collection of the 5–11-ml eluate fraction. The gamma-lactone of 18-OH DOC was measured by radioimmunoassay.

Antibody against 18-OH DOC gamma-lactone. The gamma-lactone of standard 18-OH DOC (Steraloids, Inc., Wilton, N. H.) was formed by periodic acid oxidation (23), converted to the O-methylxime with carboxymethylxime, and coupled to bovine serum albumin with carbodimide as described by Erlanger et al. (24). The conjugate was emulsified in complete Freund's adjuvant, killed tubercle bacilli and pertussis vaccine, and injected intradermally into rabbits every 4–6 wk. Blood was obtained monthly for characterization of the antiserum. The antibody, which was used in the assay at a final dilution of 1:8,000, cross-reacted 60% with 18-hydroxycorticosterone-gamma-lactone, 3% with aldosterone etiolactone, and less than 0.1% with DOC etioacid, 18-OH DOC, 18-hydroxycorticosterone, deoxycorticosterone, corticosterone, aldosterone, progesterone, testosterone, 17 α -hydroxyprogesterone, and dehydroepiandrosterone.

Statistics. Data were analyzed statistically by Student's two-tailed *t* test.

RESULTS

Table I compares mean arterial pressure, upright PRA, aldosterone excretion rate and body weight in 7 patients with low renin essential hypertension taking a high sodium diet before, after 4 days of therapy, and again

TABLE I
Effects of Aminoglutethimide in Low Renin Hypertension

	Aminoglutethimide*		
	Control (mean \pm SEM)	4 Days (mean \pm SEM)	Termination (mean \pm SEM)
Mean arterial pressure, mm Hg	117 \pm 2	108 \pm 3 \ddagger	99 \pm 3 \ddagger
Upright PRA, ng/ml/h	1.3 \pm 0.4	1.7 \pm 0.5	3.9 \pm 1.3 \ddagger
Aldosterone excretion rate, μ g/24 h	3.6 \pm 0.5	0.9 \pm 0.2 \ddagger	1.1 \pm 0.3 \ddagger
Body weight, kg	81.6 \pm 7.2	80.6 \pm 7.0	80.1 \pm 6.7 \ddagger

* Aminoglutethimide, 1 g/day, was administered to four patients for 21 days and was discontinued after 10–14 days in three others. All patients were hospitalized during the control period and during the first 4 days of aminoglutethimide administration. Studies at the termination of aminoglutethimide treatment were carried out in the outpatient clinic in five patients and in the hospital in two patients.

\ddagger Values significantly different from control values by paired Student's *t* test with *P* < 0.05.

at the termination of aminoglutethimide (1 g/day) treatment. Four of the seven patients took aminoglutethimide for 21 days; the drug was discontinued in three other patients after 10–14 days because of the development of skin rash or fever. Blood pressure and aldosterone excretion rate were significantly decreased after 4 days of aminoglutethimide treatment but the slight decrease in body weight and increase in upright PRA were not statistically significant. At the termination of aminoglutethimide therapy, aldosterone excretion rate remained low with values similar to those observed after 4 days of treatment. Blood pressure and body weight were further decreased and PRA had increased significantly. Urinary sodium excretion after 4 days of aminoglutethimide and at the termination of treatment was not different from values during the control period. Metabolic balance studies were not performed to measure cumulative sodium loss, but the fall in body weight during treatment probably reflects a net loss of sodium and water.

Plasma concentrations of aldosterone, cortisol, DOC, 18-OH DOC, progesterone, 17 α -hydroxyprogesterone, and 11-deoxycortisol were determined at 8 a.m., noon, 6 p.m., midnight, and 6 a.m. during a control day and again at the same times 4 days after initiation of aminoglutethimide treatment (Fig. 1). The steroid values shown at each of the indicated times are mean (\pm SEM) values for the seven patients. During the control period, the circadian patterns for plasma cortisol, DOC, 17 α -hydroxyprogesterone, and 11-deoxycortisol were typical of these steroids whose secretion is primarily regulated by ACTH. Plasma progesterone concentrations did not vary significantly throughout the day primarily because of the inclusion of high progesterone values from two of the women who were in the luteal phase of their menstrual cycles. In contrast to previous reports of a fall in plasma concentrations of 18-OH DOC throughout the morning (25) no detectable decrease in plasma 18-OH DOC values were noted until 6 p.m. in this study. The plasma concentration of aldosterone was increased by standing between 8 a.m. and 12 noon. After 4 days of aminoglutethimide therapy, values for plasma aldosterone were markedly reduced and the typical aldosterone response to standing was no longer observed. Although the circadian patterns for cortisol and DOC were unchanged, the plasma concentrations for their steroid biosynthetic precursors, progesterone, 17 α -hydroxyprogesterone, and 11-deoxycortisol were increased and the circadian patterns of these steroids were exaggerated, as compared to control values, probably due to increased pituitary release of ACTH. Plasma concentrations of 18-OH DOC were also increased and a definite rise with standing was observed after aminoglutethimide therapy. When control values were compared with those during aminoglutethimide treatment, the mean values

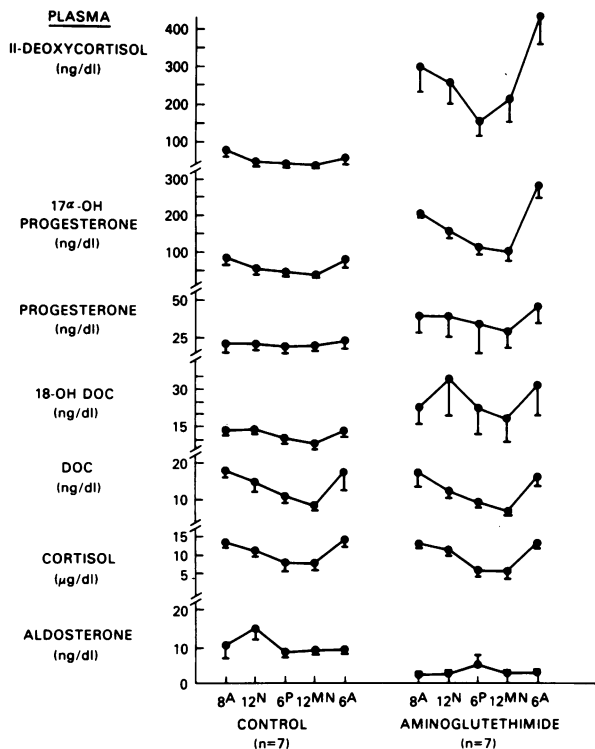


FIGURE 1 Plasma concentrations of selected steroids in seven patients with low renin essential hypertension before (control) and 4 days after initiation of aminoglutethimide therapy. Mean (\pm SEM) values for the seven patients are plotted at each of the times indicated at the bottom of the figure.

for the 35 samples (five determinations in each of the seven patients) for plasma cortisol (11.0 ± 0.8 vs. 10.7 ± 0.7 μ g/dl, mean \pm SE) or plasma DOC (14.0 ± 1.3 vs. 12.6 ± 1.0 ng/dl) concentrations were not significantly different. Mean values during control vs. treatment intervals for the 35 plasma determinations of 18-OH DOC (12.2 ± 0.7 vs. 26.5 ± 4.7 ng/dl), 11-deoxycortisol (61.4 ± 7.8 vs. 275 ± 31.0 ng/dl) progesterone (21.0 ± 2.0 vs. 39.0 ± 7.0 ng/dl), and 17 α -hydroxyprogesterone (65.9 ± 7.9 vs. 170.3 ± 13.7 ng/dl) were increased with aminoglutethimide treatment (Fig. 1). In contrast, mean values for the 35 plasma aldosterone determinations during treatment with aminoglutethimide were 30% of control values (3.4 ± 0.6 vs. 10.5 ± 1.0 ng/dl), and plasma aldosterone was often undetectable by the radioimmunoassay, the sensitivity of which was 2.5 ng/dl. Thus, only plasma aldosterone was decreased, whereas other plasma steroid concentrations remained unchanged or were increased during treatment with aminoglutethimide (Fig. 1).

These effects persisted throughout 21 days of aminoglutethimide therapy in the two patients who were restudied (Fig. 2). Mean values for the 10 plasma cortisol samples (5 determinations each in the 2 patients) during the control period were not significantly dif-

ferent from the values after either 4 or 21 days of aminoglutethimide treatment (14.2 ± 1.6 vs. 12.8 ± 1.4 vs. 13.8 ± 1.4 μ g/dl, mean \pm SE). Similarly, mean values for the 10 control plasma DOC samples (10.5 ± 1.5 vs. 10.6 ± 1.4 vs. 11.7 ± 1.2 ng/dl) and the 10 control 18-OH DOC samples (9.1 ± 1.1 vs. 10.4 ± 1.9 vs. 9.9 ± 1.3 ng/dl) were not significantly different from those measured after either 4 or 21 days of aminoglutethimide therapy. Plasma concentrations of progesterone (16.0 ± 1.5 , 27.2 ± 1.9 , and 23.9 ± 1.9 ng/dl at control, day 4, and day 21 of aminoglutethimide, respectively), 17 α -hydroxyprogesterone (68 ± 19 , 159 ± 21 , and 208 ± 18 ng/dl) and 11-deoxycortisol (102 ± 18 , 317 ± 55 , and 331 ± 42 ng/dl) were significantly increased above control values at both 4 and 21 days of treatment. In contrast, plasma concentrations of aldosterone remained markedly decreased throughout aminoglutethimide therapy (6.2 ± 1.2 vs. 3.3 ± 0.4 vs. 3.1 ± 0.3 ng/dl). Treatment with aminoglutethimide also markedly decreased the aldosterone excretion rate in all patients (Fig. 3), and the low values persisted until therapy was stopped (Table I). Aminoglutethimide treatment, however, had no significant effect on the excretion rates of 16 β -OH DHEA, 16-oxo-androstenediol, 17OHCS, or 17KS, nor on the secretory rate of 16 β -OH DHEA in the 7 patients (Fig. 3).

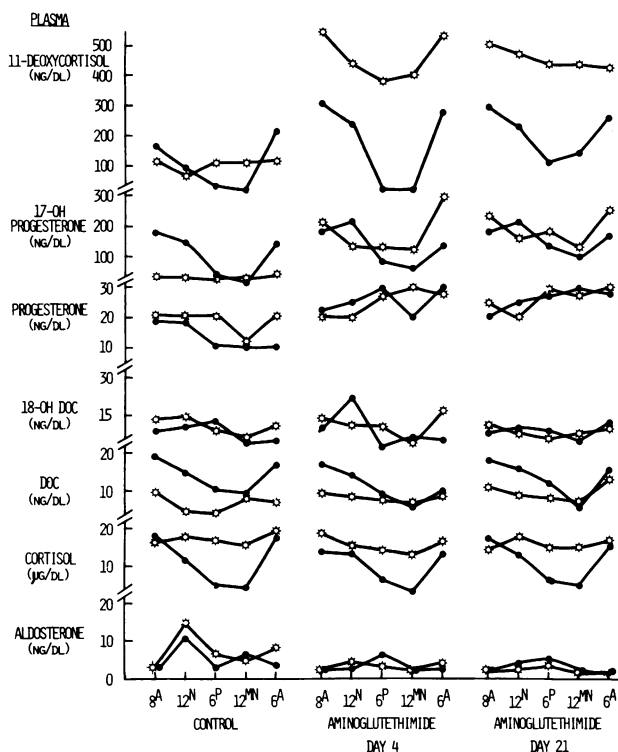


FIGURE 2 Plasma concentrations of selected steroids in two patients with low renin essential hypertension before (control) and again 4 and 21 days after initiation of aminoglutethimide therapy. Individual values for each of two patients are plotted at the bottom of the figure.

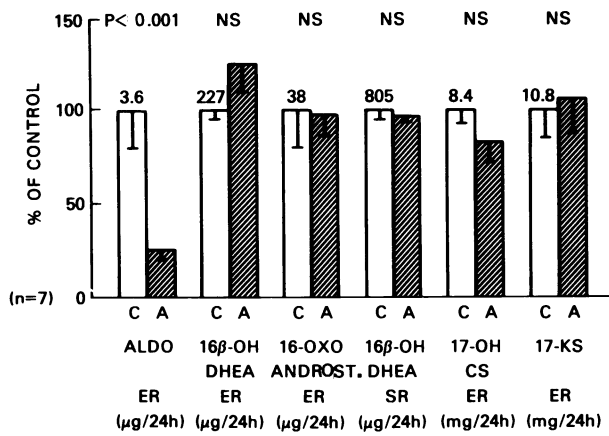


FIGURE 3 Excretion rates of aldosterone (ALDO ER), 16 β -hydroxydehydroepiandrosterone (16 β -OH DHEA ER), 16-oxo-androstenediol (16-oxo-ANDROST. ER), 17-hydroxy corticosteroids (17OHCS ER), and 17-ketosteroids (17-KS ER) and secretion rate of 16 β -hydroxydehydroepiandrosterone (16 β -OH DHEA SR) before (C) and after (A) 4 days of aminoglutethimide treatment in seven patients with low renin essential hypertension. Values are plotted as a percentage of the mean value (indicated by the number above the bar) during the control period. *P* values for statistical comparisons of C vs. A for each are shown at the top of the figure.

DISCUSSION

This study confirms a previous report (8) that aminoglutethimide effectively lowers blood pressure in patients with low renin essential hypertension. Aminoglutethimide apparently exerts its antihypertensive effect by inhibiting adrenal steroid biosynthesis because the drug lowers blood pressure in patients with Cushing's syndrome only when it effectively reduces secretion of adrenal steroids (26). The drug also fails to lower the blood pressure of normotensive volunteers or of patients with Addison's disease (26, 27). The gradual lowering of blood pressure and body weight during aminoglutethimide therapy in our low renin patients is also consistent with the view that the antihypertensive effect of the drug is mediated through a reduction in extracellular fluid volume, probably secondary to the sustained suppression of aldosterone production (Table I). Although aldosterone secretion rates were not measured in these patients, the finding that aminoglutethimide reduced both plasma aldosterone concentration and the urinary excretion of the 18-glucuronide metabolite of aldosterone strongly supports a decrease in adrenal aldosterone production induced by the drug rather than an alteration in the extraadrenal metabolism of aldosterone by aminoglutethimide.

The secretion of aldosterone by the adrenal zona glomerulosa remains inhibited by aminoglutethimide even after months of continuous therapy, and compensatory increases in plasma renin do not overcome the inhibition (26). In contrast, whereas secretion of cor-

tisol and related steroids by the adrenal zona fasciculata is decreased by aminoglutethimide, the effect is not sustained because the initial fall in plasma cortisol concentration leads to a compensatory increase in ACTH release (26–28). ACTH, in turn, stimulates the adrenal formation of Δ^5 -pregnenolone from cholesterol, the major step in steroid biosynthesis that is inhibited by aminoglutethimide (27). The increases in plasma concentrations of progesterone, 17 α -hydroxyprogesterone, 11-deoxycortisol, and 18-OH DOC observed in our 7 patients after 4 days of aminoglutethimide treatment and in 2 of these patients after 21 days of therapy probably reflects such a compensatory increase in ACTH because concentrations of plasma cortisol were maintained in spite of chronic administration of aminoglutethimide.

The observation that aminoglutethimide lowered blood pressure in our patients without decreasing the production of the adrenal steroids, DOC, 18-OH DOC, and 16 β -OH DHEA, makes it unlikely that these steroids are involved in the pathogenesis of low renin essential hypertension. Similarly, these steroids are apparently not responsible for the low plasma renin activity in these patients because their production is not decreased when PRA rises to the normal range during long-term treatment with aminoglutethimide (Fig. 2). However, it remains to be determined if an heretofore unidentified adrenal steroid(s), or a steroid such as 16 α , 18-dihydroxydeoxycorticosterone whose secretion rate was not measured in this study, might play an etiologic role in the pathogenesis of low renin hypertension. It is more likely that one of the steroids measured in this study or an unidentified adrenocortical hormone is of pathogenetic importance in the small number of low renin patients who demonstrate subnormal aldosterone production; such patients were not evaluated in the present study.

Additional evidence against the hypothesis that the secretion of an unidentified sodium retaining steroid is responsible for the low PRA and elevated blood pressure in patients with low renin essential hypertension is the normal aldosterone excretion rate present in almost all patients with low renin essential hypertension (5, 6, 29). The normal excretion rate contrasts markedly to the decreased aldosterone excretion seen with states of known mineralocorticoid excess, such as congenital adrenal hyperplasia with 11 β -hydroxylase deficiency (30), or exogenous deoxycorticosterone administration (31). The normal aldosterone excretion rate in patients with low renin essential hypertension results from an increased aldosterone response per unit of renin (16, 29). These patients also show an exaggerated aldosterone response per unit of infused angiotensin II, which suggests that the molecular abnormality is probably a supersensitivity to angiotensin II at the adrenal receptor for aldosterone synthesis (16, 29). It is not

clear at present whether the supersensitivity to angiotensin II is a primary adrenal defect or whether it occurs in response to an abnormally low production of renin by the kidney with a secondary increase in adrenal receptor sensitivity similar to that seen in smooth muscle during denervation supersensitivity (32).

It is also not clear why therapy with aminoglutethimide lowers blood pressure less in normal renin patients than in patients with low renin hypertension (8). Maintenance of blood pressure, however, depends not only upon aldosterone-regulated changes in blood volume but also upon the direct vasoconstriction produced by angiotensin II (33). Thus, administration of aminoglutethimide to patients with normal renin essential hypertension decreases their aldosterone production, and presumably their blood volume (8, 27), but the rapid rise in renin and angiotensin II concentrations would be expected to lead to vasoconstriction, thereby compensating in part for the tendency towards reduced blood pressure secondary to the decrease in blood volume. In contrast, patients with low renin essential hypertension have low plasma concentrations of angiotensin II (34, 35), and may be more dependent upon blood volume for maintenance of blood pressure. Thus, their hypertension might be expected to respond more readily to the antialdosterone actions of aminoglutethimide. A greater dependency of their blood pressure on volume rather than on vasoconstrictor factors might also explain the greater antihypertensive response to diuretic therapy of patients with low vs. normal renin essential hypertension (9).

ACKNOWLEDGMENTS

The authors thank Ciba-Geigy Corp., Pharmaceuticals Div., Summit, N. J., for providing the aminoglutethimide (Elipten) used in this study. Robert Levine, George Corcoran, and Christopher Conner provided expert technical assistance.

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