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EFFECTS OF VARIOUS ADRENAL INHIBITORS IN LOW-RENIN ESSENTIAL HYPERTENSION*

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SUMMARY

The blood pressures of patients with spironolactone-responsive low-renin essential hypertension were favorably affected by double blind treatment with amino-glutethimide (an inhibitor of conversion of cholesterol to all types of hormonal steroids) and by WIN 24,540 (an inhibitor of the conversion of 5-ene to 4-ene steroids) but were not favorably affected by dexamethasone (an inhibitor of ACTH-dependent steroidogenesis) or metyrapone (an inhibitor of 11-hydroxylation). Patients with primary aldosterone responded similarly except that their blood pressures also responded favorably to metyrapone. Patients with essential hypertension and normal plasma renin activity failed to respond to any of these treatments. It is concluded that in patients with low-renin essential hypertension a mineralocorticoid plays a major role in the maintenance of the hypertension. In the majority of patients a non-ACTH dependent 4-ene steroid appears to be involved. Aldosterone does not appear to play a major pathogenetic role in maintaining the hypertension of patients with the syndrome of low-renin essential hypertension.

INTRODUCTION

The discovery that patients with primary aldosteronism [1] have low circulating renin activity, stimulated interest in the determination of plasma renin activity (PRA) in a variety of hypertensive conditions. In the course of these studies it was found that a large subset of patients [2] with essential hypertension had PRA values as low as those of patients with primary aldosteronism. They were believed not to have primary aldosteronism inasmuch as their aldosterone excretion and secretion rates were not elevated. It was postulated that some other adrenal mineralocorticoid(s) might be important in the pathogenesis of hypertension of these patients when it was found that their hypertension responded favorably to spironolactone, [3–5] a mineralocorticoid antagonist, or to adrenalectomy. [4] However, the identities of the mineralocorticoid(s) responsible for low-renin essential hypertension remain unknown. In this paper we shall describe a series of double-blind experiments during which hypertensive patients were treated with various adrenal inhibitors. Knowing the sites of action of these inhibitors and their effects on blood pressure, one might suggest certain characteristics of the steroids which could be responsible for the blood pressure elevation of low-renin essential hypertension.

METHODS

Subjects

Patients participating in this study were selected from the Vanderbilt University Hospital Endocrine Hypertension Clinic and during these studies were followed in the Clinical Research Center Outpatient Facility.

The diagnosis of essential hypertension was made after complete evaluation had excluded the known causes of hypertension. Patients were separated into low- or normal-renin categories by two methods: first, by measurement of peripheral plasma renin activity following stimulation by furosemide-induced diuresis as suggested by Carey *et al.*[3] and by the method of Brunner *et al.*[7] as modified by Hollifield *et al.*[8] All patients selected for study satisfied both sets of criteria for their respective categories. The diagnosis of primary aldosteronism was established by the demonstration of elevated aldosterone in plasma and urine together with suppressed plasma renin activity. All patients with "low-renin essential hypertension" and all patients with "primary aldosteronism" had previously experienced normalization of their blood pressures during spironolactone therapy; in contrast, patients with "normal-renin essential hypertension" had exhibited little or no fall in blood pressure when previously treated with spironolactone.

Study protocols

Double-blind protocols were employed in which the blood pressure-lowering effect of each adrenal inhibitor was compared with that of placebo. Drugs and placeboes were each administered for 6 week treatment periods. All blood pressures were measured by a nurse who was unaware of the medications the patients were receiving. Blood pressures were measured by a mercury manometer on three occasions in the supine position and on three occasions after 10 min in the upright posture. An average of

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the six determinations was expressed as a single value for each week.

The blood pressures obtained during the fifth and sixth week of a treatment period were used for data analysis. To simplify graphic representation of data the physiological mean arterial pressure (1/3 pulse pressure added to the diastolic pressure) is used.

Adrenal inhibitors

Dexamethasone is a synthetic glucocorticoid which is capable of suppressing pituitary ACTH production, hence, the production of ACTH-dependent adrenal steroids. [9] The dose of dexamethasone (0.5 mg twice daily) was chosen empirically based on its ability to reduce excretion of urinary 17,21-dihydroxycorticosteroids to less than 1 mg daily without causing clinical Cushing's syndrome or elevating plasma renin substrate.[10]

Aminoglutethimide (Elipten® Ciba) was administered in doses of 250 mg four times daily. This agent inhibits the conversion of cholesterol to pregnenolone. [11]

WIN 24,540 (Trilostane-Sterling Winthrop) was administered in doses of 30 mg four times daily. This agent inhibits the 3β-OH-steroid-dehydrogenase-5,4-en-isomerase enzyme system which converts 5-ene steroids to 4-ene steroids. [12]

Metyrapone (Metopirone®-Ciba) is an inhibitor of 11β-hydroxylase. [13] It was used in doses of 500 mg 4 times a day. Since metyrapone administration can inhibit cortisol synthesis thus resulting in an increase in ACTH and a consequent increase in the production of desoxycorticosterone which might perpetuate the hypertension in these patients, dexamethasone 0.5 mg twice daily was co-administered with the metyrapone.

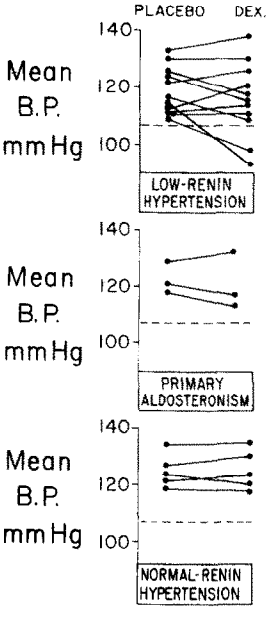

Fig. 1. Effects of dexamethasone on blood pressure in patients with low-renin essential hypertension (upper panel), primary aldosteronism (middle panel) and normal-renin essential hypertension (bottom panel).

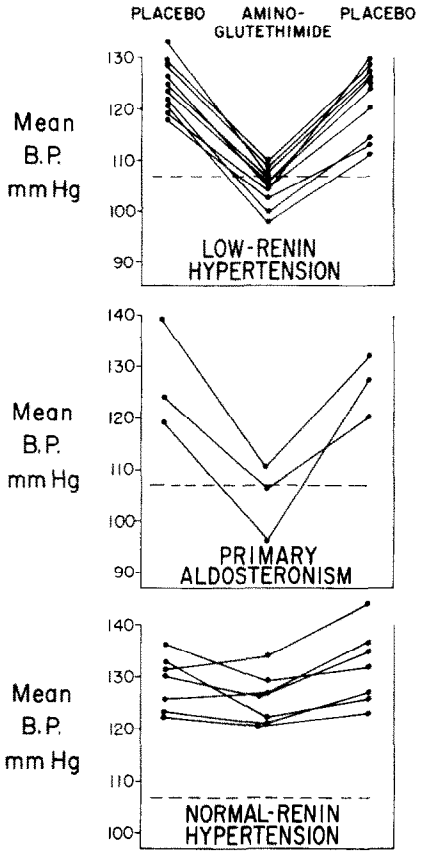

Fig. 2. Effects of aminoglutethimide on blood pressure in patients with low-renin essential hypertension (upper panel), primary aldosteronism (middle panel) and normal-renin essential hypertension (bottom panel).

RESULTS AND COMMENTS

Dexamethasone (Fig. 1)

Treatment with dexamethasone in doses that reduced ACTH-dependent steroids such as cortisol, corticosterone, 17-ketosteroids, and 16β-OH-DHEA to negligible values had little effect on the blood pressures of most patients. However, in 2 of 9 patients with low-renin essential hypertension, the blood pressures fell to normal, suggesting that some ACTH-dependent steroid might have been responsible for the hypertension. Spironolactone, 400 mg daily, was added to the dexamethasone therapy in 5 of the patients with low-renin essential hypertension who had failed to show significant decreases in blood pressure, in response to dexamethasone alone, and each experienced normalization of blood pressure on this regimen. These data suggest that the hypertension of these patients was attributable to some non-ACTH-dependent, spironolactone-blockable mineralocorticoid.

Patients with primary aldosteronism failed to show

significant decreases in blood pressure or in aldosterone excretion during treatment with dexamethasone. These observations support the view that the blood pressure elevation of primary aldosteronism is attributable to aldosterone rather than to some ACTH-dependent steroid.

Patients with essential hypertension and normal plasma renin activity showed no consistent change in blood pressure during treatment with dexamethasone. This indicates that their hypertension is caused by factors other than ACTH-dependent steroids.

Aminoglutethimide (Fig. 2)

All patients with low-renin essential hypertension responded to aminoglutethimide with distinct decreases in blood pressure. This was also true of patients with primary aldosteronism. In contrast, patients with essential hypertension and normal plasma renin activity showed minimal decreases in blood pressure in response to aminoglutethimide. These studies confirm the earlier observations of Woods *et al.*[14]

These observations suggest that aminoglutethimide is not a non-specific antihypertensive agent but that it affects blood pressure only by inhibiting steroid biosynthesis. If this assumption be true, then steroids would appear to play an important role in maintaining the hypertension of patients with primary aldosteronism and of patients with low-renin essential hypertension. On the other hand, steroids would appear to be less important in maintaining the blood pressure elevation of patients with essential hypertension and normal plasma renin activity. This study provides little information as to what kinds of steroids might be responsible for low-renin essential hypertension, inasmuch as aminoglutethimide inhibits the conversion of cholesterol to pregnenolone, the first major step in the biosynthesis of all hormonal steroids.

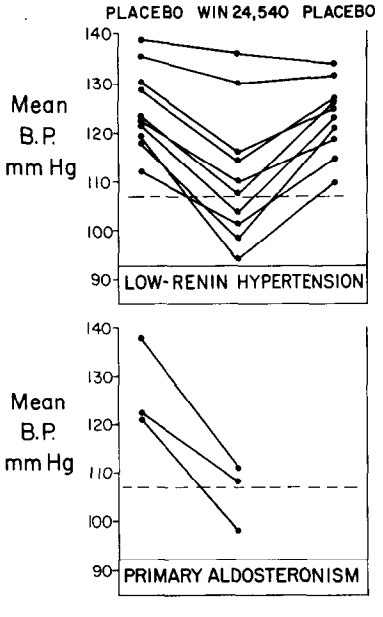

Fig. 3. The effects of WIN 24,540 on blood pressure in patients with low-renin essential hypertension (upper panel) and primary aldosteronism (lower panel).

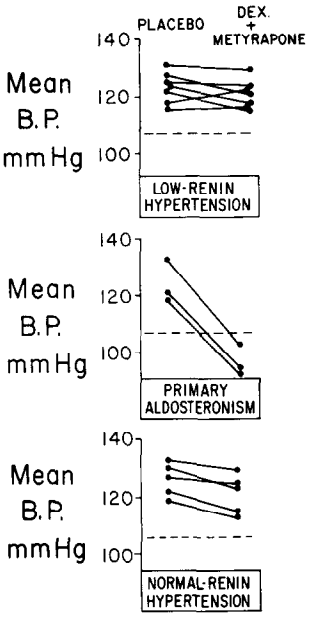

Fig. 4. The effects of dexamethasone-plus-metyrapone on blood pressures of patients with low-renin essential hypertension (upper panel), primary aldosteronism (middle panel), and normal-renin essential hypertension (bottom panel). None of these 7 patients with low-renin essential hypertension responded to dexamethasone alone.

WIN 24,540 (Fig. 3)

Eight of the ten patients with low-renin essential hypertension responded to WIN 24,540 with decreases in blood pressure. Patients with primary aldosteronism showed similar responses.

These observations are consistent with the view that the majority of patients with low-renin essential hypertension produce a 4-ene steroid which plays an important role in maintaining their blood pressure at abnormally high levels. This would also be our interpretation of the responses shown by patients with primary aldosteronism. In the latter circumstance, of course, the 4-ene steroid is aldosterone, but in a low-renin essential hypertension, the 4-ene steroid is of uncertain identity.

Metyrapone (Fig. 4)

Although metyrapone and dexamethasone corrected the hypertension of patients with primary aldosteronism, they had little or no effect on the hypertension of patients with low-renin essential hypertension. As an inhibitor of 11β-hydroxylase, metyrapone has long been known to inhibit the secretion of aldosterone [15], and in both of these groups of patients, urinary aldosterone was demonstrated to fall to negligible values. The fact that inhibition of aldosterone secretion corrected the hypertension of patients with primary aldosteronism supports the view that aldosterone is responsible for the

hypertension in this disorder. The fact that inhibition of aldosterone secretion failed to correct the hypertension of patients with low-renin essential hypertension must be taken as evidence that in these patients the hypertension is attributable to something other than aldosterone, presumably an 11-deoxysteroid. It must be concluded from the evidence at hand that low-renin essential hypertension is not merely mild primary aldosteronism as has sometimes been suggested. [16]

The failure of metyrapone to correct the hypertension of patients with essential hypertension and normal plasma activity is not surprising since there is now little reason to believe that steroids are of great importance in the pathogenesis of hypertension in this group of patients.

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DISCUSSION

Birmingham. I was very interested in your experiments with metyrapone, because years ago we found that if you give metyrapone to rats, what happens is that you get a conversion to the hydroxylated derivative of metyrapone which has a hydroxyl instead of a ketone. Our *in vitro* studies indicated that when you incubate adrenal glands with the hydroxylated compound you get an increased 18 hydroxy DOC production. (*Steroids* **13** (1969) 457). These were *in vitro* studies where we incubated metyrapone with liver but Dr. De Nicola (Buenos Aires) has done injections *in vivo* in rats to show the conversion of metyrapone to metyraprol. Most of it goes immediately to metyrapol. (*Endocrinology* **89** (1971) 1236).

Liddle. I would not like to suggest that in the presence of dexamethasone, metyrapone is capable of inducing or sustaining hypertension. In fact, in primary aldosteronism metyrapone actually corrects hypertension. The fact that it failed to correct the hypertension in low-renin essential hypertension might mean that in this disorder there is some steroid that is not inhibited by metyrapone.

O'Malley. Do you have any idea how much of this material is produced?

Liddle. Of course, what we recover in the urine is only equivalent, biologically to one microgram of aldosterone per day. We really don't have any way of telling what the total body production rate might be. Perhaps what is produced by the patient is equivalent to half a milligram of aldosterone per day since that is about the amount which is responsible for the hypertension of primary aldosteronism.

Grant. We know that the specificity of action of spironolactone is not specific. For example, it causes menstrual disturbances in women and gynaecomastia in men. Thus it has actions which are probably quite unrelated to the antagonization of aldosterone activity. I believe that the manufacturers (G. D. Searle) are hoping to develop a more specific drug.

Liddle. What I believe is that in the absence of mineralocorticoid, spironolactone has not been shown to promote sodium excretion. We have turned this around to argue that when spironolactone does promote sodium excretion and when it does lower the blood pressure then it is probably doing so through antagonizing mineralocorticoid. We have a number of circumstances in which we can show that, in the absence of mineralocorticoid, spironolactone is virtually inactive as far as effects on mineral metabolism or blood pressure are concerned.

James. I was wondering if you had the opportunity to see whether the urinary excretion of your unknown presumed steroid increases in response to administration of ACTH or angiotensin.

Liddle. It's a study that needs to be done but we have not done it. We have a few random observations in which patients with renal vascular hypertension have been included in this sort of study and they have not had elevated amounts of the unknown mineralocorticoid activity.

Stumpf. With respect to the side effect of the pill, did you have an opportunity to test how the sex steroids affect the renal system?

Liddle. If estrogens do anything to blood pressure, they tend to elevate it. Large amounts of androgen would also tend to elevate hypertension. Estrogen might do so through stimulating renal substrate formation. I don't think there has been a demonstration that estrogen or androgens or things which cause gynecomastia or impotency or oligomenorhea, the side effects of spironolactone that you're talking about, I am not aware that all these substances have been shown to lower blood pressure.

Adlercreutz. Have you ever studied hypokalemic patients without hypertension and with normal aldosterone for mineralocorticoid activity in urine?

Liddle. We have not.

Ulick. Is there any measurable adrenocortical secretion on the regimen of dexamethasone plus metyrapone when you observed no effect on blood pressure? Have you ever examined what steroids, if any, were produced under that regimen?

Liddle. I think the steroids we're capable of measuring all tend to fall under these circumstances. Now of course most of them have already fallen just through administration of dexamethasone and then aldosterone which has persisted will fall further when one adds metyrapone. We have not done other studies except for the bioassays which does not identify steroids of course. We have not measured some of the things that you're capable of measuring, such, as 18 hydroxy B and so forth.