

# Long-term treatment of mineralocorticoid excess syndromes

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*Recognition of the pathogenesis of secondary forms of hypertension is often considered the key to appropriate choice of treatment. We here present the results of a prolonged clinical follow-up (from 1 to 20 years) of a large number of patients with mineralocorticoid excess syndromes (MES), including over 100 patients with primary aldosteronism (PA), 3 cases with dexamethasone-suppressible aldosteronism (DSA), 3 cases of apparent mineralocorticoid excess (AME) Type II, and 4 patients with 17-hydroxylase deficiency (17OHDS). The patients with PA have been divided in two subgroups, one of 69 cases followed between 1973 and 1982, and the second of 37 patients studied between 1983 and 1992; 33 further cases were not evaluated due to poor compliance. In group I, 26 patients underwent surgery (23 unilateral adenoma, 1 primary hyperplasia, 2 bilateral nodular hyperplasia); at 5 years 50% had normal blood pressure, 25% had mild hypertension and 25% had moderate to severe hypertension. Forty-three patients with either adenoma (APA) or idiopathic aldosteronism (IHA) received long-term spironolactone treatment. Among them, 13 required the addition of thiazide and/or  $\beta$ -blockers, while 13 were switched to an amiloride/thiazide combination ( $\pm$  beta blockers) due to side-effects to spironolactone (gynecomastia 6/20 males, menstrual upset or breast pain in 7/23 females). In group II, 12 patients underwent surgery (11 adenoma, 1 primary hyperplasia) with a similar outcome at 3 years as in group I; 25 patients were put on either K canrenoate (11) or  $\text{Ca}^{++}$  channel blockers (14) with or without KCl supplementation; in 8 cases these two drugs were combined according to blood pressure levels achieved during the follow-up. ACE inhibitors, thiazide, ketanserine, and ketoconazole were given in selected cases. Gynecomastia occurred only in 2 out of 16 males while on K canrenoate and no side effects were reported in females on the same regimen. The other patients with ACTH-dependent MES were all treated initially with dexamethasone (DEX) at low doses (0.25–1 mg q.d). In all cases potassium remained within the normal limits; blood pressure was not adequately controlled in all 3 cases of DSH and in the oldest patient with 17OHDS and AME Type II, respectively, in spite of the normalization of the hormonal patterns.  $\text{Ca}^{++}$  antagonists have been added in these cases, and K canrenoate substituted for DEX in the AME Type II patient. In conclusion, surgical removal or long term treatment of ME with specific antagonists or inhibitors may be inadequate to normalize high blood pressure in almost a half of the patients with MES. This could be due, inter alia, to the persistence of vascular abnormalities, to the coexistence of essential hypertension, or to our only partial understanding of the pathophysiology of some of these syndromes (e.g., IHA and AME). (Steroids 60:81–86, 1995)*

**Keywords:** primary aldosteronism; mineralocorticoid excess syndromes; spironolactone; K canrenoate; Ca antagonists

## Introduction

The principal steroids with mineralocorticoid (MC) activity secreted by the adrenal cortex are aldosterone, from the zona glomerulosa, and deoxycorticosterone (DOC) and cortisol, which are zona fasciculata hormones. Aldosterone is the most potent MC, followed by DOC, while cortisol has

only 1/400 the MC activity of aldosterone. These steroids produce hypertension by several mechanisms; in longstanding MC hypertension peripheral vascular resistance is increased, but the initiating effects are most likely early plasma volume and extracellular fluid expansion<sup>1</sup>; a direct action of MC on central nervous system and an increased sensitivity to catecholamines may also play a role in the pathogenesis of MC hypertension.<sup>2</sup> The mechanisms by which cortisol induces hypertension are probably more related to its glucocorticoid activity,<sup>3</sup> with the exception of the syndrome of apparent MC excess.<sup>4</sup>

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Insight into early mechanisms of MC hypertension has come from studies following discontinuation of the aldosterone-receptor antagonist spironolactone (Sp) in patients with an aldosterone-producing tumor. An increase of sodium retention with a weight gain of approximately 1–2 kg is followed by sodium escape, renal potassium wasting, and increase of blood pressure.<sup>5</sup> Spironolactone is in fact the most specific treatment of MC excess syndrome, and particularly of primary aldosteronism.<sup>6–8</sup> However, it is a common observation that the pharmacological management of these secondary forms of hypertension is not as simple and predictable as one would expect from the above considerations.<sup>9–11</sup>

In this paper we wish to review the results of a prolonged clinical follow up (from 1 to 20 years) of a large group of patients with mineralocorticoid-excess syndrome (MES), including over 100 patients with primary aldosteronism, 3 patients with dexamethasone-suppressible hyperaldosteronism, 4 patients with 17-hydroxylase deficiency, and 3 patients with the syndrome of apparent mineralocorticoid excess Type II.

## Experimental

One hundred six patients with primary aldosteronism were included in this study, with the diagnosis based on the usual criteria (hypertension with hypokalemia in most cases, suppressed plasma renin activity (PRA), high urinary aldosterone).<sup>12</sup> The differential diagnosis between aldosterone-producing adenoma (APA) and idiopathic aldosteronism (IHA) was made on the basis of the results of plasma aldosterone response to upright posture and angiotensin II infusion, and on adrenal computerized tomography and scintiscan; in several cases adrenal vein catheterization was also performed for aldosterone measurement in the effluent. All patients were studied in the Institute of Semeiotica Medica of the University of Padua Medical School, while on a diet containing 120–150 mEq of Na<sup>+</sup> and 60–80 mEq of K<sup>+</sup>. The patients with APA underwent surgery in the Department of Surgery, University of Padua Medical School; both groups of patients (APA post-surgery and IHA) were then followed as outpatients in the Clinic of the Institute of Semeiotica Medica for a period ranging from a minimum of 1 year to a maximum of 20 years, by the same group of investigators.

The patients were further divided in two subgroups, one of 69 cases followed between 1973 and 1982, and the second one including 37 patients studied between 1983 and 1992. Thirty-three additional cases were not further evaluated due to poor compliance.

In the first subgroup (n = 69), 26 patients underwent surgery. In 23 a unilateral adenoma was found; 1 had unilateral hyperplasia, and 2 had a bilateral adrenalectomy for nodular hyperplasia. Forty-three patients with adenoma or idiopathic aldosteronism received long-term medical treatment (spironolactone alone or associated with thiazide and/or  $\beta$ -blockers, or substituted by an amiloride/thiazide combination due to side-effects). The duration of follow-up of these patients ranged from 1 to 20 years.

Among the second subgroup (n = 37), 12 patients underwent unilateral adrenalectomy (11 cases of adenoma and 1 of primary hyperplasia); 25 patients were classified as idiopathic aldosteronism and treated with the aldosterone antagonist K<sup>+</sup> canrenoate and/or Ca<sup>++</sup>-channel blockers plus potassium supplements. ACE-inhibitors, ketanserin and ketoconazole, were given in selected cases. The duration of follow-up in these patients ranged from 1 to 10 years.

## Glucocorticoid-remediable hyperaldosteronism (n = 3)

Three patients (brothers aged 35, 23, and 19) with glucocorticoid-remediable hyperaldosteronism were included in this study. The diagnosis was made on the basis of clinical criteria: hypertension, mild hypokalemia, suppressed PRA, and slightly elevated plasma and urinary aldosterone levels, exacerbation by ACTH stimulation and prompt and persistent suppression by dexamethasone administration. The patients were treated initially with dexamethasone alone and subsequently with a combination of different antihypertensive drugs.<sup>13</sup>

## 17 $\alpha$ -hydroxylase deficiency (n = 4)

Four patients with 17 $\alpha$ -hydroxylase deficiency were studied. Two were genetically female, and two were male pseudohermaphrodites. The diagnosis was made on the basis of the primary amenorrhea, lack of secondary female traits, hypertension, hypokalemia, high DOC and corticosterone (B) levels, low F, and suppressed PRA and aldosterone levels. The patients were all treated with dexamethasone, with other antihypertensive drugs subsequently added in one patient.<sup>14</sup>

## Apparent mineralocorticoid excess syndrome (n = 3)

Three patients with the syndrome of apparent mineralocorticoid excess (AME) Type II were studied for more than 10 years. Two patients were brother and sister; the third had no other relatives affected. Diagnosis was made on the basis of the presence of hypertension, hypokalemia, suppressed PRA and aldosterone, normal MCH, low excretion of alloTHF, THF, and THE, with a normal THF + alloTHF/THE ratio, but decreased cortisol turnover quotient. All 3 patients were initially treated with dexamethasone, but subsequently one of them was switched to other antihypertensive drugs.<sup>15</sup>

## Results

### Primary aldosteronism: subgroup 1 (n = 69)

**Surgical treatment.** Among the 26 patients who underwent surgery, a unilateral adrenal adenoma was found in 23. In these patients, after a mean period of follow-up of 5.5 years the mean blood pressure decreased from 198  $\pm$  16/123  $\pm$  9 mm Hg to 142  $\pm$  15/96  $\pm$  9 mm Hg.

Normalization of both systolic and diastolic blood pressure was reached in 13 patients; in 6 only a partial decrease of blood pressure was obtained, and in 4 patients the hypertension remained unchanged. In all patients normal serum potassium levels were found during follow-up. In one patient unilateral hyperplasia was found; serum K<sup>+</sup> and blood pressure were normal up to 7 years after operation. In 2 patients with IHA who underwent bilateral adrenalectomy moderate hypertension persisted, and antihypertensive treatment had to be added to the conventional replacement therapy.

**Medical treatment.** Spironolactone: Forty-three patients with primary aldosteronism (most of them with IHA, and 2 with APA who refused operation) were treated initially with spironolactone, in general at a starting dose of 300 mg/day (mean dose 313  $\pm$  85 mg), which was progressively decreased after the first month to a maintenance dose of 100

mg/day (mean  $90 \pm 23$ ). Mean baseline levels of systolic and diastolic blood pressure were  $193 \pm 26/119 \pm 11$  mm Hg. After 1 month, the mean blood pressure was  $147 \pm 17/97 \pm 12$  mm Hg. Diastolic blood pressure was normal in 58% of the patients. After 5 years only 14 of 29 remained on spironolactone alone. Mean blood pressure was  $142 \pm 10/94 \pm 9$  mm Hg, and diastolic blood pressure was normal in 46% of the cases.

**Spironolactone and Thiazide (Chlorthalidone):** In 7 patients who were partially resistant to spironolactone a combination of spironolactone (100 mg/day) and chlorthalidone (50–100 mg/day) was given. Blood pressure decreased from  $157 \pm 17/107 \pm 13$  to  $134 \pm 17/93 \pm 8$  mm Hg within the first month and remained at similar levels on the following 2 years. Serum  $K^+$  was lower than that reached with Sp alone, but still within the normal range.

**Spironolactone and  $\beta$ -blockers:** In 6 patients, propranolol (120 mg/day) was added to spironolactone after 3 months of therapy; mean blood pressure decreased from  $162 \pm 12/98 \pm 7$  to  $150 \pm 10/93 \pm 6$  mm Hg and remained at the same levels for the following 12 months.

**Amiloride and hydrochlorothiazide (+timolol or atenolol):** In 13 patients (6 males and 7 females) Sp had to be withdrawn due to the appearance of side effects (gynecomastia and menstrual disorders). Since amiloride is available in Italy only as a fixed combination (5 mg + 50 mg of hydrochlorothiazide),  $\beta$ -blockers (atenolol 100 mg or timolol 10 mg/day) were routinely added. After 3 months of therapy, mean blood pressure was  $133 \pm 12/88 \pm 6$  mm Hg, and serum  $K^+$  was normal.

*Primary aldosteronism: subgroup 2 (n = 37)*

**Surgical treatment (Table 1).** Unilateral adrenalectomy was performed in 12 patients. In 11, a unilateral adenoma was found, while in 1 patient a diagnosis of unilateral adrenal hyperplasia was made. The short and long term results of blood pressure control and serum  $K^+$  as well as hormone data are presented in Table 1. Mean blood pressure decreased significantly over the first 3 months from  $180 \pm 5/112 \pm 4$  to  $138 \pm 3/88 \pm 2$  mm Hg. Potassium increased from  $2.9 \pm 0.1$  to  $4.5 \pm 0.1$  mEq/L. PRA increased to normal levels, while aldosterone decreased to low-normal levels. After a mean follow up of 2 years, mean blood pressure was  $132 \pm 5/91 \pm 2$  and potassium was 4.6 mEq/L. At an individual level, 8 patients with APA and 1 with PAH had normal BP, while in 3 patients mild to moderate hypertension persisted.

**Table 1** Primary aldosteronism: subgroup II—37 patients; Type of treatment: surgery (n = 12)

	Baseline	Short term	Long term
Systolic (mm Hg)	$180 \pm 5$	$138 \pm 3^a$	$132 \pm 5^a$
Diastolic (mm Hg)	$112 \pm 4$	$88 \pm 2^a$	$91 \pm 2.6^a$
Ks (mEq/L)	$2.9 \pm 0.1$	$4.5 \pm 0.1^a$	$4.6 \pm 0.1^a$
PRA (mg/mL/3 h)	$0.3 \pm 0.1$	$4.6 \pm 2.7$	—
P Aldosterone (mg/dL)	$52.3 \pm 5.5$	$7.8 \pm 1.7^a$	—
U Aldosterone ( $\mu$ g/d)	$40.9 \pm 7.2$	$8.5 \pm 4.2^a$	—

<sup>a</sup>P < 0.05.

**Medical treatment (Table 2).** Twenty-five patients who had been classified as having idiopathic hyperaldosteronism were put on either the aldosterone antagonist  $K^+$  canrenoate (n = 11) or on  $Ca^{++}$ -channel blockers (in most cases nifedipine; occasionally lacedipine, nitrendipine, or amlodipine) (n = 14) and potassium supplementation when baseline serum  $K^+$  was frankly subnormal (Table 2). At a starting dose of 200 mg, which was then decreased to 100 mg/after 1–3 months,  $K^+$  canrenoate induced a fall in BP from  $178 \pm 6/110 \pm 4$  to  $159 \pm 4/102 \pm 3$  mm Hg in 3 months and to  $156 \pm 8/97 \pm 3$  mm Hg after 1 or more years (n = 5). In 4 patients nifedipine was added to  $K^+$  canrenoate to achieve better control of blood pressure, while in 2 cases  $K^+$  canrenoate was discontinued due to the appearance of gynecomastia. In the 14 patients on  $Ca^{++}$  antagonists (nifedipine 40 mg/day, or comparable doses of other compounds of the same family), the levels of baseline blood pressure and the changes obtained after short- and long-term treatment were superimposable on those obtained with  $K^+$  canrenoate (Table 2). Potassium was normalized in these patients when  $K^+$  supplements were added, and in 2 patients while only on  $Ca^{++}$ -antagonist, and remained normal in those patients in whom it was already so from the beginning.

As expected, PRA was increased by  $K^+$  canrenoate and not by  $Ca^{++}$  antagonists. Plasma and urinary aldosterone remained unchanged during aldosterone-antagonist administration and were significantly decreased in those patients on chronic  $Ca^{++}$  channel blockers.

*Glucocorticoid-suppressible hyperaldosteronism*

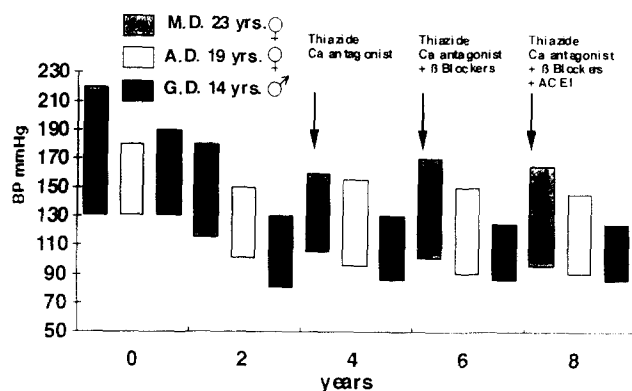
The 3 patients with DEX suppressible hyperaldosteronism were initially treated for a month with DEX. In two blood pressure was reduced to normal by this treatment, while in the third no major effect on blood pressure was obtained. He was then treated with  $K^+$  canrenoate and methyl-dopa with satisfactory results. The other two patients remained on DEX at 0.5 mg/day which maintained  $K^+$  levels within the normal limits, but their blood pressure rose progressively while on treatment. They were finally switched to a combination of  $Ca^{++}$ -channel blockers and  $K^+$  canrenoate; their blood pressure was stable around 140/90 mm Hg for years. The third patient, in spite of an apparent good control of blood pressure, died suddenly of a stroke at the age of 26 y.

*17 $\alpha$ -hydroxylase deficiency (Figure 1)*

We were able to follow 4 patients with this disease for several years. In the short term, DEX (1 mg/day) reduced blood pressure to normal values in 3 of the patients, and partially in one, who was the oldest at the time of the diagnosis (26 y). The same was true during long-term follow up (over 10 y); daily doses of DEX between 0.25 and 0.5 mg were able to suppress DOC plasma values, although incompletely, and normalize serum  $K^+$ . PRA and aldosterone were maintained within the normal levels, after an initial period of several months of persisting suppressed values, especially for aldosterone. In the fourth case, thiazide,  $\beta$ -blockers,  $Ca^{++}$ -channel blockers and ACE inhib-

**Table 2** Primary aldosteronism: subgroup 2—37 patients. Type of treatment: medical (n = 25)

	Baseline		Short-term		Long-term	
	K <sup>+</sup> canren n = 11	Ca <sup>++</sup> antag n = 14	K <sup>+</sup> canren n = 11	Ca <sup>++</sup> antag n = 14	K <sup>+</sup> canren n = 5	Ca <sup>++</sup> antag n = 6
Systolic (mm Hg)	178 ± 6	169 ± 4	159 ± 4 <sup>a</sup>	161 ± 5 <sup>a</sup>	156 ± 8	157 ± 2
Diastolic (mm Hg)	110 ± 1	108 ± 2	102 ± 3 <sup>a</sup>	103 ± 4 <sup>a</sup>	97 ± 3 <sup>a</sup>	96 ± 3
Ks (mEq/L)	3.3 ± 0.2	3.4 ± 0.1	3.9 ± 0.2 <sup>a</sup>	4.0 ± 0.1 <sup>a</sup>	4.0 ± 0.2 <sup>a</sup>	4.3 ± 0.1
PRA (mg/mL/3 h)	0.31 ± 1.6	0.58 ± 0.2	1.06 ± 0.56	0.86 ± 0.24	—	—
P Aldosterone (mg/dL)	34 ± 7.1	45 ± 5.2	37 ± 5.9	33 ± 5.6	—	—
U Aldosterone (μg/d)	25 ± 3.3	37 ± 4.8	23 ± 3.9	26 ± 5.8	—	—

<sup>a</sup>P < 0.05.**Figure 1** Long-term follow-up of 3 siblings with 17 $\alpha$ -hydroxylase deficiency.

itors had to be added at different times to control the severe hypertension. Left ventricular hypertrophy and II degree retinopathy were present from the beginning in this patient.

#### Apparent mineralocorticoid excess-Type II (Figure 2)

The 3 patients with AME type II were all treated with DEX at a starting dose of 2 mg/day for a month, and subsequently with 0.5 or 0.25 mg/day. The 2 male patients from Sardinia were adequately controlled for several years in terms of blood pressure and K<sup>+</sup>; at the same time their growth rate increased markedly and pubertal maturation occurred. The third patient was not controlled by 0.5 mg of DEX, and mild Cushingoid features appeared. She was switched to a combination of K<sup>+</sup> canrenoate with atenolol or nifedipine, and subsequently lisinopril was also employed, with good results. No signs of target organ impairment were detected in these patients during the follow-up (Figure 2).

#### Discussion

The possibility of correcting high blood pressure levels by specific pharmacological or surgical intervention is one of the most obvious reasons for attempting to recognize the secondary forms of hypertension. This is especially true for the endocrine causes of hypertension, since surgical removal of hormone producing tumors appears a curative maneuver, for example in primary aldosteronism due to uni-

lateral adenoma. Although the mechanism by which aldosterone induces hypertension is still incompletely known, removal of the adenoma is usually followed by a rapid amelioration of the hypertension. However, both in the literature and in our own experience, long-term cure rates are far from satisfactory.<sup>1,9,11,16-19</sup> In fact, in the patients presented in this paper, only little over half of the cases who underwent unilateral adrenalectomy for the presence of an adenoma had a complete cure of hypertension, although hypokalemia resolved in all, as well as the abnormalities of the renin-angiotensin-aldosterone system. A quarter of the patients had a partial remission, with reduction of their blood pressure levels to mild elevation, while in the rest hypertension remained unchanged. We have not yet performed a careful analysis of the possible correlations between cure or persistence of hypertension and parameters such as family history, age, degree of pre-operative hypertension, levels of aldosterone, size of the tumor, or presence of signs of target organ impairment.

More expected were the clinical data obtained after long-term medical treatment in a large group of patients with idiopathic aldosteronism. As clearly appears from the analysis of blood pressure response to spironolactone in the first subgroup, at least 30% of the patients were not controlled by this drug alone, and additional antihypertensives (thiazide and/or  $\beta$ -blockers) had to be given for adequate reduction of blood pressure. Furthermore, another 30% of patients were changed to a different potassium-sparing drug, amiloride, due to the occurrence of side effects of spironolactone.

In the last decade (second subgroup of patients) the availability of a slightly different aldosterone antagonist (K<sup>+</sup> canrenoate)<sup>20</sup> and the increasing evidence of the therapeutic properties of Ca<sup>++</sup>-channel blockers in primary aldosteronism<sup>21-23</sup> have changed attitudes toward the treatment of primary aldosteronism. Potassium canrenoate is a water soluble derivative of spironolactone, sharing the same active metabolite canrenone, but has probably a different pattern of metabolism which avoids the formation of intermediate products with anti-androgenic effects.<sup>24</sup> A result is the decreased incidence of side effects as shown by several trials in essential hypertensive<sup>25,26</sup> and cirrhotic patients. Only two of the 16 male patients on long term K<sup>+</sup> canrenoate either alone or in combination reported gynecomastia, and no menstrual disturbances occurred in women.

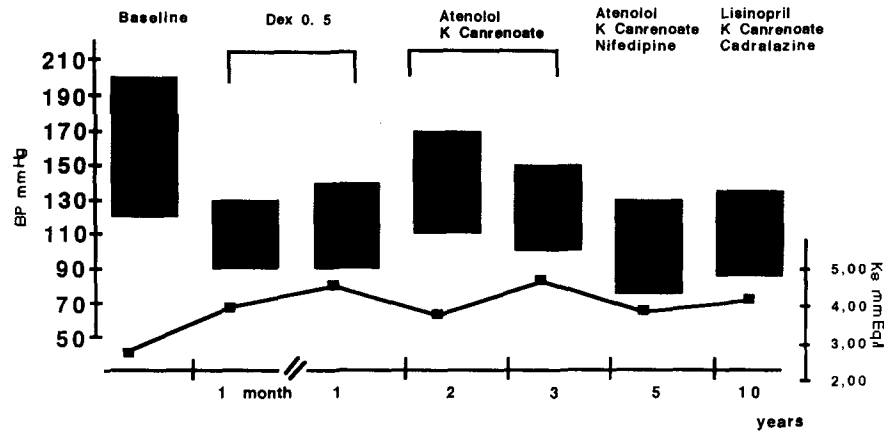


Figure 2 Long-term follow-up patient with AME Type 2.

In terms of blood pressure, the results obtained both in short-term and in long-term treatment with  $K^+$  canrenoate were not significantly different from those obtained in the previous group with spironolactone at corresponding doses. A  $Ca^{++}$ -antagonist had to be added in one third of the patients in order to improve the blood pressure control. In the same group, more than half were treated from the beginning with  $Ca^{++}$ -antagonists only. This approach was stimulated by the reports of Nadler et al.<sup>21</sup> and by our own preliminary experiences in an acute study<sup>27</sup> and a short-term trial<sup>28</sup> in two groups of patients with either APA or IHA, which demonstrated good antihypertensive effects of nifedipine in both conditions, and even a decrease of aldosterone levels in patients with IHA. The results obtained by more prolonged treatment in this study confirmed that nifedipine and antialdosterone compounds have a similar effect on the control of hypertension in IHA.

In most patients normal or slightly subnormal  $K^+$  levels were maintained or even normalized by  $Ca^{++}$ -channel blockers. Potassium supplements were used from the beginning only in few patients with more severe degrees of hypokalemia. Patients on these drugs have less side effects than those on aldosterone antagonists, even if the latter can be used in selected cases at quite low doses which are unlikely to exert antiandrogenic effects.

The antihypertensive efficacy of  $Ca^{++}$ -channel blockers may also rely on increased  $Ca^{++}$  entry into VSMC as a consequence of activation of the  $Na^+-Ca^{++}$  pump; this is ascribed to an increase of  $Na^+$  influx as a consequence of  $Na^+-K^+$  pump inhibition by the ouabain-like factor which is reported to be elevated in primary aldosteronism. On the other hand, spironolactone and canrenone have been recently shown to interfere with the slow  $Ca^{++}$ -channel activity.<sup>29,30</sup>

In a limited number of cases,  $\beta$ -blockers and ACE inhibitors<sup>31</sup> have been combined with potassium-sparing agents or even to thiazides to better control high blood pressure. Their effectiveness is not surprising in patients with IHA, since their characteristics are not much different from those of low renin essential hypertension. Furthermore, the simultaneous use of diuretics, by inducing a certain degree of sodium depletion, results in an increased

sensitivity to the antihypertensive agents. Furthermore, we have previously demonstrated in a short-term study that ACE inhibitors themselves have a discrete hypotensive effect in patients with IHA, together with a variable reduction of aldosterone levels. This may be due to interference with the enhanced sensitivity of adrenal cortex to angiotensin II in these patients, and even on a direct effect on adrenal renin, with circulating angiotensin II almost undetectable.

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