Idiopathic primary hyperaldosteronism: Normalization of plasma aldosterone after one month withdrawal of long-term therapy with aldosterone-receptor antagonist potassium canrenoate

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ABSTRACT. We have re-evaluated 15 patients with idiopathic primary aldosteronism one month after withdrawal of therapy with aldosterone-receptor antagonist potassium canrenoate. Therapy had lasted for 3 to 24 yr. Median blood pressure (BP) in the sitting position at the time of diagnosis was 160/100 (ranges 150-200/95-110 mmHg); while 1 month after withdrawal of therapy median BP was 145/90 (ranges 125-160/80-100 mmHg). One month after withdrawal, the ratio aldosterone (ng/dl)/plasma renin activity (ng/ml/h) in the upright position was increased only in 3 cases (median 18, range 6.1-125). We found a significant inverse correlation between the upright aldosterone/plasma renin activity (aldo/PRA) ratio, 1 month after withdrawal, and the number of years of therapy with potassium canrenoate. We conclude that long-term therapy with the aldosterone-receptor blocker, potassium canrenoate, can normalize the aldo/PRA ratio in many cases of idiopathic primary hyperaldosteronism after one-month withdrawal of the drug. These data are consistent with possible regression of idiopathic primary hyperaldosteronism after long-term therapy with potassium canrenoate, or in alternative to a persistent effect of potassium canrenoate, on aldosterone synthesis.

INTRODUCTION

Primary aldosteronism (PA) is characterized by an increase in the aldosterone/plasma renin activity (aldo/PRA) ratio in the upright position, and lack of adequate suppression of plasma aldosterone with saline infusion or with fludrocortisone. Different types of PA have been described. Its most common forms are unilateral adenoma and idiopathic PA (IPA), while less frequent forms are: glucocorticoid suppressible PA, adrenal or ectopic carcinoma, unilateral adenoma responsive to angiotensin II and familial PA Type II (1-4). IPA is diagnosed by an aldosterone response to upright position in the absence of morphological data of unilateral adenoma [magnetic resonance imaging (MRI), computerized tomography (CT) scan and adrenal scintigraphy], aldosterone and cortisol measurements in adrenal veins that are not consistent with unilateral secretion (1-3). The pathogenesis of this form of PA has been related to hypersensitivity, to angiotensin II, or to the presence of a paracrine secretion of angiotensin II or of other growth factors at the adrenal level (1-3, 5). The prevalence of PA has increased since the demonstration of frequent normokalemia in these patients and the utilization of the aldo/PRA ratio for diagnosis (1-3, 5). In the 1980s, Biglieri et al. (6) proposed an evolutionary hypothesis of PA. The authors suggested that the process could start with low-renin essential hypertension and progress to bilateral hyperplasia of the zona glomerulosa, unilateral hyperplasia and finally unilateral adenoma. This hypothesis was consistent with the description of unilateral adenomas in the follow-up of patients with IPA. The same authors later admitted that there is no proof of this theory. Patients with unilateral adenoma, in fact, are usually younger than those with IPA (7), and cases of unilateral adenoma in newborns have been described (8).

IPA does not require surgery and the choice of treatment is mineralocorticoid-receptor antagonists, like spironolactone, potassium canrenoate or canrenone...
(1, 9-12). Therapy with amiloride can be used when spironolactone or its derivatives are not tolerated. Potassium canrenoate has the same aldosterone antagonist properties as spironolactone and lower anti-androgen activity (13). A more specific mineralocorticoid receptor-blocker, eplerenone, has also recently been introduced for treatment of hyperaldosteronism, having considerably lower anti-androgenic activity (9, 14, 15). The dose of mineralocorticoid-receptor antagonist can be progressively reduced to the lowest amount necessary to control blood pressure (BP) and serum potassium, thus avoiding side effects, usually 25-50 mg a day. In some cases, mineralocorticoid-receptor antagonists are administered with added conventional hypotensive therapy, to improve BP control and to reduce the dosage of the drug in the presence of side effects like gynecomastia or hyperkalemia (1, 10). Therapy usually leads to blockade of mineralocorticoid receptors, with volume depletion due to aldosterone antagonism and activation of the renin-aldosterone system. The therapy in addition can prevent the progression of aldosterone-related deleterious effects at the level of heart and vessels (14). The aim of the study was to evaluate BP, the renin-angiotensin-aldosterone system, the aldo/PRA ratio in upright position as well as serum electrolytes in 15 cases of primary aldosteronism, after withdrawal of therapy with mineralocorticoid receptor antagonists.

MATERIALS AND METHODS

Patients
We recruited 15 consecutive patients (9 males and 6 females) affected by IPA treated with potassium canrenoate for a considerable length of time (2.5-25 yr). The subjects were followed-up periodically as outpatients with control of BP and renal function every 6 months, and with a CT scan every 2 yr. The diagnosis of PA was made by plasma aldosterone values at/or beyond the upper level of the normal range, an ald (ng/dl)/PRA (ng/ml/h) ratio in the upright position >40 and lack of suppression of plasma aldosterone to <10 ng/dl after volume expansion (2 l of saline in 4 h or 3 days of fludrocortisone, 0.4 mg/day). Morphological imaging techniques (CT scan, MRI and, when necessary, adrenal scintigraphy) were also performed. Adrenal vein sampling and dexamethasone treatment were performed in selected cases. IPA was diagnosed among patients with PA by the response of PRA and plasma aldosterone to one h in the upright position and lack of unilateral morphological abnormalities on the imaging techniques, with the exception of one case with associated incidentoma, who had evidence of unilateral adenoma at the CT scan, associated with bilateral hyperplasia, as demonstrated by adrenal scintigraphy and measurement of aldosterone and cortisol in adrenal veins. The patients gave informed consent to withdraw from therapy for one month and to be re-evaluated. Median age at the time of diagnosis was 44.5 yr (range 21-60) and 60 yr (range 27-73) at re-evaluation. All subjects had a free diet without sodium restriction. BP and serum potassium values were in the normal range at the last examination during treatment (Table 2). Cardiac and renal function and CT scan did not show any change over the course of treatment. The median period from start of treatment to withdrawal was 10 yr (range 2.5-25). All subjects were treated with potassium canrenoate at the time of withdrawal (from 25 to 100 mg a day). Some patients were also taking hypotensive drugs (Table 2). Potassium canrenoate was withdrawn one month and the other hypotensive drugs 10 days prior to the re-evaluation.

The data obtained at the time of diagnosis were taken from patient records. BP (mean of 3 determinations) was taken after 10 min in the sitting position with a Riva-Rocci sphygmomanometer. Serum sodium and potassium, PRA and plasma aldosterone in the lying and upright positions and the aldo/PRA ratio (in upright position only) were determined one month after withdrawal of potassium canrenoate.

Methods
PRA and plasma aldosterone were measured by commercial kits (Medical System, Italy, normal range for PRA was: 0.2-3.3 ng/ml/h reclining and 1.3-5.2 ng/ml/h upright; for plasma aldo was: 1.5-14 redining, 4-30 ng/dl upright).

Statistical analysis
Single values, median and range were calculated for each parameter. Linear regression analysis was used to evaluate the correlation between time of therapy and upright aldosterone/PRA.

RESULTS

Data at the time of diagnosis (Table 1)
All patients had hypertension (median systolic 160, range 150-200, and median diastolic 100, range 90-110 mmHg). Median serum sodium was in the normal range, while potassium was low in 9 cases (median 3.4, range 2.3-4.4 mEq/l). Median PRA reclining was 0.2 (range 0.02-1.00) and 0.5 ng/ml/h (range 0.1-1.2) in the upright position. Median plasma aldosterone reclining was 25 ng/dl (range 12-78 ng/dl), and 49 ng/dl (range 31-105 ng/dl) in the upright position. Al-do (ng/dl)/PRA (ng/ml/h) ratio in the upright position was 120 (range 50-245), and the median aldosterone level after volume expansion test was 29 ng/dl (range 12-50 ng/dl). Plasma cortisol was in the normal range and not modified by one h in the upright position.

Data at the time of withdrawal (Table 2)
All the patients had good control of BP and serum potassium. Median BP was 130/85 mmHg (range 120-140/80-90) and median serum K+ was 4.0 mEq/l (range 3.9-4.5).

Data at the time of re-evaluation (Table 2)
Nine of the patients had increased systolic and 7 had increased diastolic BP. Four patients were normotensive, and 6 had both increased systolic and diastolic BP. Median systolic BP was 145 mmHg (range 125-160) and diastolic 90 mmHg (range 80-100). Only 3 subjects had