DOCA Test for Aldosteronism: Its Usefulness and Implications

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SUMMARY Experience with the DOCA test (measurement of urinary excretion of aldosterone before and after 3 days of administration of 10 mg deoxycorticosterone acetate [DOCA] intramuscularly every 12 hours while on high sodium intake) is presented in 129 hypertensive patients to define its usefulness in discriminating between autonomous and nonautonomous production of aldosterone. All patients who did not have primary aldosteronism had a decrease in urinary excretion of aldosterone to values within the normal range, with a >30% fall from control values. Patients with an aldosterone-producing adenoma had a 5.7% fall and those with idiopathic hyperaldosteronism had a 9.9% fall.

Sodium retention was limited in these patients when compared with that in normal subjects. The least retention occurred in patients with an aldosterone-producing adenoma, whereas patients with low-renin essential hypertension retained more sodium than any other hypertensive group; the latter required greater sodium retention than those with normal-renin essential hypertension to produce a similar decrease in urinary aldosterone. Sodium retention correlated significantly with the percent fall in urinary aldosterone only in the low-renin essential hypertension group. Serum potassium levels fell in all groups. Changes in serum potassium levels and plasma renin concentration did not correlate with changes in urinary aldosterone excretion.

The DOCA test is effective in discriminating between primary aldosteronism and other causes of hypertension. It also demonstrates that in hypertensive patients small changes in sodium retention reduce aldosterone excretion. (Hypertension 3 (suppl II): II-102-II-106, 1981)

KEY WORDS • aldosterone • hypertension • sodium • low-renin essential hypertension • aldosteronism • renin

Patients with hypertension are usually subjected to various tests to determine the cause of the hypertension. A component of several tests is measurement of urinary excretion of aldosterone. Urinary excretion of aldosterone can be extremely high or slightly elevated in patients with primary aldosteronism and normal or elevated in patients with hypertension due to other causes, e.g., low-renin essential hypertension.

In 1967 a test was devised in which deoxycorticosterone acetate (DOCA) was administered for 3 days to hypertensive patients.1 In patients in whom aldosterone production was not autonomous, urinary excretion of aldosterone decreased into the normal range. We report here our experience with this test in 129 hypertensive patients and attempt to define the limits of the test in discriminating between autonomous and nonautonomous production of aldosterone in hypertensive patients.

Subjects and Methods

Subjects

Seven normotensive subjects (NS), ranging from 21 to 52 years of age, who had no evidence of cardiovascular, renal, or endocrine disease served as control subjects. For hypertensive subjects, 129 patients (blood pressure over 140/90 mm Hg) were studied, including 44 with an aldosterone-producing adenoma (APA), which was confirmed by surgery in 40, and 20 with idiopathic hyperaldosteronism (IHA), confirmed by surgery in five (before surgery was contro-
versial for this disorder). Both of these groups with primary aldosteronism had hypertension, hypokalemia, and suppressed plasma renin concentration (PRC). Patients with an APA had a decrease in plasma aldosterone concentration (PAC) in response to upright posture, whereas those with IHA had no change or an increase in PAC. Administration of 181I-19-iodocholesterol or scanning by computerized axial tomography located the tumor or gave evidence of hyperplasia, and scans were negative for a tumor in patients with biochemical evidence of hyperplasia.

Patients with essential hypertension were those who had normal renal function and normal serum electrolyte concentrations in whom no other cause could be found for the high blood pressure. They were divided into two groups: those whose basal PRC was > 1 ng/ml/hr, which increased with upright posture (normal-renin essential hypertension, n = 53), and those whose basal PRC was < 1 ng/ml/hr, which did not respond to the stimulus of upright posture (low-renin essential hypertension, n = 19).

Methods

Subjects were studied in the Clinical Study Center of the San Francisco General Hospital Medical Center. Informed consent was obtained from all subjects as required by the Committee on Human Research of the University of California, San Francisco.

Patients received a weighed diet containing a fixed electrolyte content to which sodium chloride tablets were added to establish a sodium intake of 120 mEq/day. After a period of equilibration, usually 3 to 4 days, a control period of 3 to 4 days was conducted during which sodium and potassium were measured daily in plasma and urine by internal standard flame photometry. Overnight recumbent 0800 hour PRCs and urinary levels of aldosterone were determined by radioimmunoassay at the end of the control period and at the end of the third day of administration of DOCA. When this study was first begun, urinary aldosterone was determined by the double-isotope dilution method, against which the radioimmunoassay was standardized. Deoxycorticosterone acetate, 10 mg, was administered every 12 hours intramuscularly for 3 days, as described previously. Cumulative urinary aldosterone concentration did not change significantly in both subjects. Plasma renin concentration did not change significantly in all groups.

Results

The following results were obtained during the control period and on the third day of DOCA administration, respectively (table 1). Mean blood pressure values (diastolic pressure + 1/3 pulse pressure) were 95 ± 2 SEM and 98 ± 3 mm Hg in normal subjects and 122 ± 2 SEM and 123 ± 3 mm Hg in patients. These changes were not significant. Mean serum potassium concentration fell significantly in all subjects. Plasma renin concentration did not change significantly in all groups.

Cumulative urinary sodium balance was positive in all subjects studied. All patients retained significantly less sodium than normal subjects in 3 days. Sodium retention in patients with an APA was significantly less than in all other groups. However, sodium retention in patients with normal renin essential hypertension did not differ significantly from that in patients with IHA but was significantly less (p < 0.05) than that in patients with low-renin essential hypertension.

Urinary aldosterone levels fell in all cases after administration of DOCA (figs. 1 and 2). The least change occurred in patients with an APA, and the greater fall was in the normal subjects and patients with low-renin essential hypertension. In patients with normal- and low-renin essential hypertension, control

### Table 1. DOCA-Induced Changes in Hypertensive Patients

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Mean blood pressure (mmHg)</th>
<th>Serum potassium (mEq/liter)</th>
<th>Plasma renin concentration (ng/ml/hr)</th>
<th>Cumulative sodium balance (mEq/3 days)</th>
<th>Urinary aldosterone (µg/24 hr)</th>
<th>Fall (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APA (n = 44)</td>
<td>129 ± 2 132 ± 2</td>
<td>3.0 ± 0.7 2.8 ± 0.7*</td>
<td>0.3 ± 0.2 0.3 ± 0.2*</td>
<td>14.0 ± 9.2† 33.6 ± 17.0 31.6 ± 16.5†</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>IHA (n = 20)</td>
<td>123 ± 4 122 ± 3</td>
<td>3.4 ± 0.5 3.1 ± 0.5†</td>
<td>0.3 ± 0.0 0.3 ± 0.0§</td>
<td>73.6 ± 18.0§ 19.2 ± 7.4 17.3 ± 7.6†</td>
<td>9.9</td>
<td></td>
</tr>
<tr>
<td>NREH (n = 53)</td>
<td>121 ± 2 126 ± 2</td>
<td>4.1 ± 0.4 3.6 ± 0.4§</td>
<td>1.1 ± 0.1 0.7 ± 0.1§</td>
<td>74.8 ± 14.1§ 13.4 ± 7.1 7.7 ± 4.1§ 42.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LREH (n = 19)</td>
<td>117 ± 4 123 ± 5</td>
<td>3.6 ± 0.4 3.3 ± 0.6†</td>
<td>0.2 ± 0.1 0.1 ± 0.1§</td>
<td>144.0 ± 23.1† 15.0 ± 1.9 8.1 ± 0.9§ 46.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS (n = 7)</td>
<td>95 ± 2 98 ± 3</td>
<td>4.3 ± 0.4 3.9 ± 0.4†</td>
<td>**         **</td>
<td>203.0 ± 22.0 10.3 ± 5.3 5.1 ± 4.0§ 50.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations. APA = aldosterone-producing adenoma, IHA = idiopathic hyperaldosteronism; NREH = normal-renin essential hypertension, LREH = low-renin essential hypertension; NS = normal subjects.

*p < 0.05; †p < 0.01; §p < 0.001; ¶p < 0.0001; ‡not significant; **the established normal range is 0.7-1.2 ng/ml/hr. All values are mean values ± SEM.

Mean blood pressure is given as diastolic pressure plus one-third pulse pressure.
**FIGURE 1.** Percent fall in mean urinary aldosterone excretion after DOCA in patients with an aldosterone-producing adenoma (APA), idiopathic hyperaldosteronism (IHA), normal-renin essential hypertension (NREH), low-renin essential hypertension (LREH), and normal subjects (NS). The “N” equals the number of patients in each group.

values were frequently above the normal range (4–17 μg/24 hr), but all fell into the normal range in both groups after DOCA. In seven patients with IHA, initial urinary aldosterone values were within the normal range. Only one of the seven patients had a 36% decrease after DOCA; all of the others had either an increase or a maximum decrease of 26%. In six of the patients with an APA, initial control values were within the normal range. One of the six patients had a decrease of only 5.6% after DOCA; the other five either had an increase or urinary aldosterone excretion did not change. Although there was a decrease in mean aldosterone excretion in patients with an APA, the values were in the normal range after DOCA in only three patients.

Decreases in urinary aldosterone excretion did not correlate significantly with changes in serum potassium or PRCs. In the low-renin essential hypertension group, sodium retention and percent fall in urinary aldosterone excretion (fig. 3) correlated significantly (r = 0.51, p < 0.05).

Discussion

In 1967 we described a maneuver to diagnose the presence of an aldosterone-producing adenoma in hypertensive patients.1 It has since been used successfully not only by ourselves in our 129 patients, but also by Streten et al.4 for final confirmation of primary aldosteronism versus other forms of hypertension in 19 of 26 patients.

In our initial report1 we stated that an APA could be detected by the response to the DOCA maneuver. We have now confirmed this observation in a large group of patients with an APA and have extended it to patients with IHA. These two groups fail to have a reduction in urinary aldosterone values into the normal range or to depress normal values by more than 30% after DOCA. The mean fall in urinary aldosterone excretion after DOCA was only 5.7% in patients with an APA and 9.9% in those with IHA, whereas all other groups had mean falls > 40% (fig. 1).

With respect to individual values, six patients with an APA had control urinary aldosterone levels within the normal range and none had a decrease > 5.6% after DOCA. The group with IHA had more control values within the normal range (7 of 20), but all but one had either an increase or a maximal decrease of 26% after DOCA. These are what we consider important facts in establishing the criteria for aldosterone suppression: not only a decrease in urinary aldosterone levels to values within the normal range but also a fall greater than 30% from control values. In all of our patients who did not have primary aldosteronism, as well as in the normal subjects, DOCA suppressed urinary aldosterone excretion according to these guidelines.

The DOCA test produced less sodium retention and rapid renal sodium escape in 3 days in hypertensive patients in contrast to normal subjects (5 to 7 days). Cumulative sodium retention was restricted to a total of approximately 150 mEq in these patients versus 250 to 750 mEq in normal subjects.6, 7 The least sodium retention occurred in the APA group. If sodium retention is equated with increases in extracellular fluid, this group is already fully expanded by the elevated aldosterone production. To a lesser degree this is also true in the IHA group. A notable exception is the group with low-renin essential hypertension: near-maximal sodium retention (for hypertensives) occurred, unlike that in normal subjects who are still retaining salt (have not yet escaped). Although the patients with low-renin essential hypertension retained almost twice the sodium compared with the normal-renin essential hypertension group, both achieved similar suppression of urinary aldosterone excretion. If these groups differ only in renin suppression, the renin-angiotensin system may play a role with respect to the reduced sodium retention in patients with essential hypertension. A limiting factor of sodium retention in the hypertensive patient may well be the documented natriuresis affected by angiotensin II,8 which is diminished in patients with low-renin essential hypertension.

The lack of aldosterone suppression in patients with an APA after DOCA seems to be due to the inability to significantly change serum potassium concentration and PRC and to retain sodium. The decreases in urinary aldosterone levels correlated significantly with the degree of sodium retention in the low-renin essential hypertension group. The aldosterone suppression in the latter group required retention of a greater amount of sodium than in patients with normal-renin essential hypertension but still less than in nonhypertensive subjects. The setting of reduced renin appears to require this degree of sodium retention to suppress
aldosterone production. An additional factor may be the increased sensitivity of aldosterone secretion to changes in the renin system.

Serum potassium concentration decreased in all groups after DOCA, but because individual changes did not correlate with decreases in aldosterone excretion, its role cannot be assessed.

The redefined DOCA test can be used with substantial precision in the diagnosis of primary aldosteronism. In addition, this test demonstrates that even reduced sodium retention in hypertensive patients can suppress aldosterone production.

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