Outpatient screening procedures for primary aldosteronism

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Summary

1. The sensitivity and specificity of several individual and combined measurements for the diagnosis of primary aldosteronism have been calculated in 22 patients with established primary aldosteronism and 140 essential hypertensive controls.

2. Excellent sensitivity and specificity (93–100%) in the diagnosis of primary aldosteronism cannot be accomplished with any single test but can be achieved with combinations of (a) a low 'stimulated' plasma renin activity (PRA) (after frusemide and orthostasis) together with either hypokalaemia or a high 'stimulated' plasma aldosterone concentration (above 944 pmol/l), or (b) a low 'stimulated' PRA, together with either hypokalaemia or a high saline-suppressed plasma aldosterone concentration (above 236 pmol/l), or (c) a pressor response to saralasin together with elevated values of NaCl-suppressed or frusemide-stimulated plasma aldosterone concentration. Procedures (a) or (c) can be completed in 3–4 h; (b) requires 8 h.

Key words: aldosterone, primary aldosteronism, screening procedures.

Introduction

The description of normokalaemic primary aldosteronism [1] and subsequent evidence that it is not uncommon [2, 3] indicated that measurement of the serum potassium concentration was not a reliable method of excluding primary aldosteronism in patients with hypertension. Stimulated plasma renin activity (PRA) is usually low in primary aldosteronism but its specificity as a diagnostic test is unacceptably low [3, 4]. Abnormal resistance of the plasma aldosterone concentration to suppression by an infusion (2 litres) of 0-9% NaCl solution [5] appeared to be a promising test, but this, too, has a sensitivity of only 77% [3]. For these reasons, the combination of relative unsuppressibility of plasma aldosterone concentration after infusion of NaCl solution with a low serum potassium and the absence of an hypotensive response to saralasin has been proposed as an effective screening procedure [3]. In this paper we compare the sensitivity (i.e. percentage of patients in whom the tests correctly diagnosed primary aldosteronism) and specificity (i.e. percentage of patients in whom the tests correctly excluded the diagnosis of primary aldosteronism) of these combinations with those of combinations which included the measurement of plasma aldosterone after stimulation by intravenous frusemide and orthostasis.

Methods

Patient selection

Patients were referred by physicians and clinics in the Upstate New York area for an 8 h hypertension evaluation, which included measurements of (a) serum K on admission (08.00 hours), (b) PRA and (c) plasma aldosterone at 11.00 hours after intravenous frusemide (40 mg) given at 08.00 hours, recumbency from 08.00 to 09.00 hours and leisurely ambulation from 09.00 to 11.00 hours, (d) blood pressure response to infusion of saralasin at increasing rates [6] and of plasma aldosterone [7] after the intravenous infusion of 0-9% NaCl solution (2 litres) from 12.30 to 16.00 hours in recumbency. The patients reported here had been off all antihypertensive therapy at least 3 days (usually 3 weeks) before the studies.
Primary aldosteronism was diagnosed when suspicious findings on these tests [serum K < 3·5 mmol/l, together with PRA < 1·7 ng h⁻¹ ml⁻¹ or PAC > 236 pmol/l (8·5 ng/dl) after the NaCl infusion] were followed either by the finding that PAC was not suppressed below 236 pmol/l on the morning after intramuscular administration of deoxycorticosterone acetate (DOCA), 10 mg every 12 h for 3 days [8], or by evidence of an adrenal tumour on computed tomography, confirmed in nine of the 22 patients by surgical excision of an adenomatous gland, followed by a fall in blood pressure. The 22 patients with primary aldosteronism included 11 whose data were reported, in part, previously [3] and 11 new patients in all of whom measurements of plasma aldosterone after frusemide and orthostasis had been made. The 140 essential hypertensive controls were patients studied concurrently, in whom all of the same laboratory tests had been performed. These patients were thought not to have primary aldosteronism because (a) PAC fell below 236 pmol/l after the NaCl infusion, and (b) the combination of hypokalaemia (K < 3·5 mmol/l) and a low stimulated PRA (<1·7 ng h⁻¹ ml⁻¹) was absent, or if (a) or (b) was positive, (c) plasma aldosterone fell below 236 pmol/l after DOCA (10 mg intramuscularly every 12 h for 3 days).

**Laboratory methods**

Serum K concentration was measured on an Autoanalyzer flame photometer. PRA was measured by radioimmunoassay of generated angiotensin I [7]. Plasma aldosterone was measured by radioimmunoassay, by using the NIH sheep antibody [9].

**Results**

**Serum potassium concentration and PRA**

In seven of the 22 (32%) patients with primary aldosteronism serum K was normal (>3·5 mmol/l). PRA was below normal (1·7 ng h⁻¹ ml⁻¹) in 20 of the 22 (91%) patients with primary aldosteronism but was also subnormal in 57 of the 140 (41%) patients with essential hypertension.

Blood pressure rose in response to saralasin (by >4 mmHg) in 14 of the 15 patients with primary aldosteronism but also in 36% of the hypertensive controls.

**Plasma aldosterone concentrations**

After the infusion of 2 litres of 0·9% NaCl solution, plasma aldosterone was suppressed below 236 pmol/l in all except 10 of the hypertensive controls. Four of these 10 hypertensive controls showed hypotensive responses to saralasin and high stimulated PRA values, indicating that resistance to suppression of their plasma aldosterone by NaCl resulted from the excessive stimulatory effect on aldosterone production of their presumably high plasma angiotensin II levels. Plasma aldosterone fell below 236 pmol/l in 14-3% of the patients with primary aldosteronism.

After 'stimulation' by frusemide and orthostasis for 2 h, plasma aldosterone was higher in the 22 patients with primary aldosteronism (mean 2072 ± SEM 319 pmol/l, and always above 700 pmol/l) than in the hypertensive controls (755 ± 46 pmol/l, P < 0·001), in 39% of whom the concentration exceeded 700 pmol/l.

**Relationship between 'stimulated' levels of PRA and plasma aldosterone**

These variables were positively correlated (r = +0·40, P < 0·001) in the essential hypertensive controls. In the patients with primary aldo-

**Table 1. Reliability of single and multiple diagnostic screening procedures for primary aldosteronism**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Serum K &lt;3·5 mmol/l</td>
<td>66·7</td>
<td>93·3</td>
</tr>
<tr>
<td>(2) PRA (stimulated) &lt;1·7 ng h⁻¹ ml⁻¹</td>
<td>90·9</td>
<td>62·1</td>
</tr>
<tr>
<td>(3) PAC (stimulated) &gt;944 pmol/l</td>
<td>81·8</td>
<td>75·7</td>
</tr>
<tr>
<td>(4) PAC (supp.) &gt;236 pmol/l</td>
<td>85·7</td>
<td>92·9</td>
</tr>
<tr>
<td>(5) Saralasin increased diastolic BP &gt;4 mmHg</td>
<td>93·3</td>
<td>64·3</td>
</tr>
<tr>
<td>(6) K &lt;3·5 mmol/l and PRA &lt;1·7 ng h⁻¹ ml⁻¹</td>
<td>63·6</td>
<td>96·7</td>
</tr>
<tr>
<td>(7) K &lt;3·5 mmol/l and stim. PAC &gt;944 pmol/l</td>
<td>50·0</td>
<td>100·0</td>
</tr>
<tr>
<td>(8) K &lt;3·5 mmol/l and supp. PAC &gt;236 pmol/l</td>
<td>50·0</td>
<td>99·2</td>
</tr>
<tr>
<td>(9) PRA &lt;1·7 ng h⁻¹ ml⁻¹ and supp. PAC &gt;236 pmol/l</td>
<td>85·7</td>
<td>98·6</td>
</tr>
<tr>
<td>(10) PRA &lt;1·7 ng h⁻¹ ml⁻¹ and stim. PAC &gt;944 pmol/l</td>
<td>72·7</td>
<td>96·4</td>
</tr>
<tr>
<td>(11) PRA &lt;2·0 ng h⁻¹ ml⁻¹ and stim. PAC &gt;944 pmol/l</td>
<td>81·8</td>
<td>96·4</td>
</tr>
<tr>
<td>(12) PRA &lt;2·0 ng h⁻¹ ml⁻¹ and supp. PAC &gt;236 pmol/l</td>
<td>86·1</td>
<td>96·4</td>
</tr>
<tr>
<td>(13) PRA &lt;2·0 ng h⁻¹ ml⁻¹ either stim. PAC &gt;944 pmol/l or K &lt;3·5 mmol/l</td>
<td>100</td>
<td>96·4</td>
</tr>
<tr>
<td>(14) PRA &lt;2·0 ng h⁻¹ ml⁻¹ supp. PAC &gt;236 pmol/l or stim. PAC &gt;944 pmol/l</td>
<td>100</td>
<td>96·4</td>
</tr>
<tr>
<td>(15) Saralasin-raised BP + stim. PAC &gt;944 pmol/l</td>
<td>93·3</td>
<td>97·1</td>
</tr>
<tr>
<td>(16) Saralasin-raised BP + supp. PAC &gt;236 pmol/l</td>
<td>93·3</td>
<td>99·3</td>
</tr>
</tbody>
</table>
steronism ‘stimulated’ plasma aldosterone was usually high in spite of lower PRA (0.73 ± 0.11 ng h⁻¹ ml⁻¹) than in the control subjects (2.84 ± 0.41 ng h⁻¹ ml⁻¹, P < 0.001).

Sensitivity and specificity of the individual procedures for the detection of primary aldosteronism were inadequate to allow their satisfactory use as exclusive screening tests for primary aldosteronism (Table 1).

When the results of these determinations were considered in groups, the sensitivity and specificity of various combinations of the tests for the diagnosis of primary aldosteronism increased (Table 1). The two best combinations of measurements, providing a sensitivity of 100% and a specificity of 96-4% in the groups of patients studied, were (1) stimulated PRA below 2.0 ng h⁻¹ ml⁻¹ associated with either a serum K concentration below 3.5 mmol/l or a ‘stimulated’ plasma aldosterone above 944 pmol/l, and (2) stimulated PRA below 2.0 ng h⁻¹ ml⁻¹ associated with either a serum K concentration below 3.5 mmol/l or a ‘suppressed’ plasma aldosterone above 236 pmol/l. The combination of a pressor response to saralasin together with an elevated ‘stimulated’ or ‘suppressed’ plasma aldosterone also yielded satisfactory sensitivity (93-3%) and specificities (97.1 and 99.3% respectively) for the diagnosis of primary aldosteronism.

Discussion
To determine the presence of primary aldosteronism among patients with hypertension, reliable and inexpensive screening procedures are needed. The present results support earlier observations indicating that the requisite sensitivity and specificity cannot be accomplished with the use of any single screening test, but can be achieved with combinations of two or three procedures [3]. These procedures include generally available, simple measurements: serum K concentration, blood pressure response to saralasin, and determinations of PRA and plasma aldosterone concentration after an intravenous injection of frusemide and 2 h in the upright position. Although it is unlikely that the sensitivity of these procedures for the diagnosis of primary aldosteronism would continue to be 100% in a larger series of patients, the proposed combination of measurements is certainly worthy of further study. We recognize that the determinations of specificity are dependent upon our assumption that no patients with primary aldosteronism would fail to have either a combination of hypokalaemia and low PRA or an abnormal ‘stimulated’ or ‘suppressed’ plasma aldosterone. This assumption seems fairly reasonable but it has to be admitted that there are no completely dependable ways of excluding primary aldosteronism.

Primary aldosteronism is only one of several types of ‘secondary’ hypertension. It would be advantageous to be able to utilize the same screening procedures for all secondary forms of hypertension. The present results indicate that a series of measurements which can be performed under outpatient conditions in a 3–4 h period can be used to screen for primary aldosteronism, as well as for renovascular and other ‘angiotensinogenic’ forms of hypertension [10], low renin hypertension (the authors’ unpublished observations) and renoprival hypertension.

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References