RENIN AND ALDOSTERONE

Indication

Investigation of patients with hypertension and suspected primary hyperaldosteronism.

Principle

**Aldosterone** is a steroid hormone produced in the glomerulosa cells of the adrenal cortex which promotes exchange of Na\(^+\) and K\(^+\) across cell membranes. An excess of aldosterone leads to sodium retention mediated by the renal tubules, which is accompanied by water retention leading to extracellular fluid volume expansion and hypertension. Furthermore, excretion of K\(^+\) is increased at the distal tubule in exchange for the Na\(^+\) ions producing urine K\(^+\) loss and hypokalaemia. Measurement of aldosterone is necessary in the investigation of patients with hypokalaemia, hypertension and suspected primary hyperaldosteronism (Conn’s syndrome) or secondary hyperaldosteronism (renal artery stenosis, renin secreting tumour). Occasionally it is also required for patients with suspected primary hypoaldosteronism (hyperkalaemia with episodic renal failure).

**Renin** is a proteolytic enzyme which is secreted by the juxta-glomerular apparatus of the kidney and activates the angiotensin system to stimulate aldosterone secretion. Overproduction of renin results in secondary hyperaldosteronism which may potentiate hypertension (by Na\(^+\) retention) and hypokalaemia (by urine K\(^+\) loss) in some subjects. Conversely, patients with primary hyperaldosteronism (Conn’s syndrome) have low plasma renin activity (PRA) and this finding is therefore helpful in differentiating primary and secondary hyperaldosteronism. Measurement of PRA may also be of value in assessing whether intractable hypertension is likely to respond to surgical correction of renal artery stenosis, or total nephrectomy in a patient with chronic renal failure.

Notes

Full investigation of suspected mineralocorticoid hypertension is costly and time consuming. Other causes of hypokalaemia should be excluded, including glucocorticoid excess. A renin/aldosterone ratio is now recommended as an initial screening test using a seated resting morning sample (preferably 9.00 am) taken into an EDTA lavender Vacuette® and transferred to the laboratory within 30 minutes and preferably ideally taken in the outpatient phlebotomy department. Before proceeding to further investigation the patient should satisfy the following criteria (unless primary hypoaldosteronism is suspected):

1. Documented diastolic hypertension without oedema.
2. Normal urine free cortisol output to exclude glucocorticoid excess.
3. Normal 24 h urine protein output and creatinine clearance to elucidate any intrinsic renal disease.
4. Beta blockers and spironolactone/amiloride in particular should be stopped or replaced under clinical supervision for at least 3 weeks.
5. On potassium supplements sufficient to maintain serum K\(^+\) >3.0 mmol/L, if possible, if hypokalaemic.
6. On an unrestricted salt diet (at least 50-100 mmol/day)

In the absence of diuretics, a high serum Na\(^+\) (142-152 mmol/l) and a metabolic alkalosis (elevated bicarbonate) favours primary hyperaldosteronism; a low serum Na\(^+\) (<139 mmol/L) suggest secondary hyperaldosteronism. Biochemical investigation should be completed before proceeding to imaging.

A second screening test is often performed before proceeding to imaging in view of the low diagnostic yield of a single positive result.
Precautions

1. Aldosterone secretion is influenced by many factors including drugs (especially beta blockers), electrolyte intake and posture and misleading results may be obtained if the protocol is not followed strictly.
   The only class of drugs which do not interfere with renin assays appears to be the alpha-receptor blockers (note that accelerated or malignant hypertension is extremely rare in cases of primary hyperaldosteronism). However the effect of drugs other than beta blockers and spironolactone/amiloride are not considered to invalidate the test.

2. Most patients will be potassium depleted. Potassium supplements should be given for sufficient time to bring plasma potassium into the normal range. The supplements should then be discontinued for 24 hours before taking samples. All patients must be receiving a dietary intake of 100-150 mmol/24 h sodium and 50-100 mmol/24 h potassium for at least 3 days before the test, with addition of sodium supplements if necessary (this may be confirmed by 24 h urine sodium output). Inadequate sodium intake may mask hypokalaemia and cause aldosterone levels to rise.

Clinical Procedure

This is now rarely performed. It may occasionally be of use if screening tests are positive and imaging uninformative in the presence of a high index of clinical suspicion.

1. Inform the laboratory when the test is to be performed.

2. The patient is fasted overnight (plain water only allowed) and should not sit up or get up during the 8 h before the sample is taken.

3. Recumbent plasma renin and aldosterone. The patient should remain in hospital, fasted overnight (plain water only allowed) and should not sit up or get up during the 8 h before the sample is taken (lying flat for at least 4 hours before blood collection) in the morning. 10 ml venous blood should be taken in the early morning (08.00-09.00 hours) into an EDTA (lavender) Vacuette® tube (2 tubes), the patient still lying flat in bed. The sample tube should be inversed gently several times and transferred immediately to the laboratory with the request form labelled 'plasma renin and aldosterone - recumbent'. Take sufficient blood into a plain tube (gold Vacuette®) at the same time for a routine electrolyte profile.

4. Ambulatory plasma renin and aldosterone. A second, ambulant sample for renin and aldosterone is taken after the patient has been ambulatory for approximately 4 hours to assess the response of aldosterone to posture. The sample should be collected as before and transferred immediately to the laboratory with the request form labelled 'plasma renin and aldosterone - ambulatory'.

Laboratory Procedure

Separate plasma for renin (within 10 mins of venepuncture at 4°C) and aldosterone. Transfer each plasma into a pair of aliquot tubes, clearly marked with the time of collection and posture of patient, ensuring that there is at least 2 ml in each.

Samples for renin must be stored frozen (preferably at -70°C) and sent frozen by courier to specialised assay centre, samples for aldosterone can be stored at 4°C and sent ambient temperature by first class post if required. Store remaining pair of samples at -70°C until result is returned.
Guide to Interpretation

Reference Ranges

<table>
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<tr>
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<th>After overnight recumbency</th>
<th>After 3-4 hours ambulatory</th>
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</thead>
<tbody>
<tr>
<td>Plasma aldosterone (pmol/l)</td>
<td>100 - 450</td>
<td>100-800, approx. doubles</td>
</tr>
<tr>
<td>Plasma renin activity (pmol/ml/hr)</td>
<td>0.5-2.1</td>
<td>0.8 - 3.5</td>
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The change from resting to ambulatory and the renin/aldosterone ratios are interpreted in conjunction with the referral laboratory.

**NB** Short periods of upright posture or transient stresses will cause increases of plasma aldosterone; this should be taken into account for marginally raised values.

**Primary hyperaldosteronism.** The findings of hypertension, raised plasma aldosterone concentrations and low renin activity often combined with hypokalaemia are strongly suggestive of primary hyperaldosteronism. A fall in aldosterone concentrations upon changing from supine to ambulant posture is strongly suggestive of adrenal adenoma, whereas a rise in aldosterone is often seen in patients with bilateral adrenal hyperplasia.

**Secondary hyperaldosteronism.** The finding of hypokalaemia, hypertension, raised plasma aldosterone concentrations and raised renin activity are characteristic of secondary hyperaldosteronism.

Contact Chemical Pathologist/Consultant Biochemist if further information is required.

References