GUIDELINES FOR THE INVESTIGATION OF
MINERALOCORTICOID EXCESS

When to Investigate

*Unprovoked hypokalaemic alkalosis*
usually supported by high-normal plasma [Na]

N.B. 30 % of low-renin hyperaldosteronism are normokalaemic
> 50 % of glucocorticoid-suppressible hyperaldosteronism are normokalaemic

Hypokalaemia may not be apparent when Na intake is < 100 mmol/day

*High clinical suspicion*
e.g. strong family history early hypertension and stroke
documented adrenal tumour

*Patients with poorly controlled hypertension (> 160/100 mmHg) on at least three*
*anti-hypertensive agents*

Before investigating these patients consider:
- Non compliance (non-concordance)
- Excessive sodium intake (check urinary Na and act accordingly)
- ‘White Coat’ hypertension – detected with ABPM

How to Investigate

*Patient preparation*

These tests are best performed without therapy:
- Prior to drug withdrawal, measure seated (after 30 minutes sitting) aldosterone:PRA ratio and obtain a 24 hour urine collection for Na, K and 18-hydroxycortisol.
- Where possible omit all drugs for 6 weeks (incl Aspirin).
- If BP needs to be controlled (e.g. previous CVA) then give debrisoquine 10mg bd, increasing as required by 10mg every 3 days. Nifedipine and verapamil are more readily available alternatives.
Day 1

- Begin 24 h urine collection in plain container
- Plasma supine
  
  N.B. patient must be supine for at least 30 mins; sample taken between 8.00-8.30; correct time to be documented
  
  U/E incl HCO₃, Renin, Aldosterone, Cortisol
  
  If therapy is imminent and the tests are unlikely to be easily repeated
  store plasma for 11-deoxycorticosterone to be measured later, if required

- Plasma erect (1130-1200)
  
  N.B. patient must be standing erect for at least 30 mins; sample taken between 12.00-12.30; correct time to be documented
  
  Renin, Aldosterone, Cortisol

Day 2

- Return 24 h urine in plain container, send for
  
  Na, K and 18-hydroxycortisol
  
  If therapy is imminent and the tests are unlikely to be easily repeated
  store a 50 ml aliquot at -20°C for cortisol and GCMS of corticosteroid precursors and metabolites to be performed later, if required

- Plasma supine
  
  N.B. patient must be supine for at least 30 mins; sample taken between 8.00-8.30; correct time to be documented
  
  U/E incl HCO₃, Renin, Aldosterone, Cortisol
  
  If therapy is imminent and the tests are unlikely to be easily repeated
  store plasma for 11-deoxycorticosterone to be performed later, if required

- Plasma erect
  
  N.B. patient must be standing erect for at least 30 mins; sample taken between 12.00-12.30; correct time to be documented
  
  Renin, Aldosterone, Cortisol
Further Investigations

These depend on the results from days 1 and 2 and, with the exception of adrenal vein sampling, can usually be performed at a later date while the patient is taking therapy, or can be performed on stored samples from days 1 and 2 as above.

When there is uncertainty about the diagnosis of mineralocorticoid excess, discuss with consultant. Although rarely necessary, renin stimulation tests (such as frusemide challenge) or aldosterone suppression tests (such as Captopril tests or following fludrocortisone and salt loading) can be performed. Corroborative evidence of significant mineralocorticoid excess comes from a therapeutic response to spironolactone over several weeks, where other agents were ineffective, although this is not a sensitive or specific test. Adequate doses of spironolactone (up to 400 mg/d) should be employed.

When glucocorticoid-suppressible hyperaldosteronism is suspected, it is traditional to give dexamethasone 0.5 mg qds for 3 weeks and observe whether biochemistry and blood pressure improve. Chimaeric 11ß-hydroxylase/aldosterone synthase genes are universal in this condition and the diagnosis may be confirmed by genetic testing in Prof John Connell’s laboratory in Glasgow.

Interpretation of Results

Criteria for satisfactory tests

- Urine Na should exceed 100 mmol/d; if tests are inconclusive supplement with 1 g tds for 4 days and repeat
- Profound hypokalaemia may suppress aldosterone production; if renin is suppressed but aldosterone is normal, consider repeating tests after potassium supplementation till plasma [K] > 3.0 mmol/l
- To assess ACTH responsiveness, ACTH must fall between 0900 and 1200; if cortisol is not lower at 1200 than at 0900 then the tests must be repeated

For differential diagnosis see flow diagram and tables:
Table 1  
Analysis of supine plasma renin activity and aldosterone in the differential diagnosis of hypokalaemic alkalosis

<table>
<thead>
<tr>
<th>Plasma Renin Activity</th>
<th>Aldosterone</th>
<th>Description</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>↑</td>
<td>Secondary hyperaldosteronism</td>
<td>Dehydration; Diuretics; Laxatives; Vomiting; Cardiac Failure; Liver disease; Nephrotic syndrome; Salt-losing nephropathy; Bartter's syndrome Renovascular Disease</td>
</tr>
<tr>
<td>↓</td>
<td>⇒</td>
<td>Low-renin essential hypertension</td>
<td>Hypokalaemia masking aldosterone excess see Table 2</td>
</tr>
<tr>
<td>↓</td>
<td>↑</td>
<td>Low-renin hyperaldosteronism</td>
<td>see Table 2</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
<td></td>
<td>see Table 3</td>
</tr>
<tr>
<td>Response to angiotensin II†</td>
<td>Response to ACTH§</td>
<td>Lateralisation of abnormal adrenal gland¥</td>
<td>Urine 18-hydroxy cortisol (nmol/day)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------</td>
<td>-----------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>normal</td>
<td>&lt; 1000</td>
</tr>
<tr>
<td>++</td>
<td>-</td>
<td>bilateral</td>
<td>&lt; 1000</td>
</tr>
<tr>
<td>++</td>
<td>-</td>
<td>unilateral</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>unilateral</td>
<td>1000 - 3000</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>unilateral</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>bilateral</td>
<td>&gt; 3000</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>unilateral (tumour &gt; 3 cm diameter)</td>
<td></td>
</tr>
</tbody>
</table>

† ie aldosterone erect ≥ 133 % supine  
§ ie aldosterone, in erect posture, at 1200 h < at 0800 h, when cortisol at 1200 h < at 0800 h  
¥ by CT, scintigraphy, or adrenal vein sampling
Table 3  Differential diagnosis of low-renin low-aldosterone hypertension

<table>
<thead>
<tr>
<th>Plasma 11-deoxy corticosterone (DOC)</th>
<th>Urinary free cortisol</th>
<th>GC/MS profile</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼ or ▼</td>
<td></td>
<td></td>
<td>Exogenous mineralocorticoid administration</td>
</tr>
<tr>
<td>▼ ⇒</td>
<td></td>
<td>(THF+alloTHF):THE ratio:</td>
<td>Liddle's syndrome†</td>
</tr>
<tr>
<td>▼ ⇒ mildly ↑ or ⇒</td>
<td></td>
<td>• &gt; 7.0:1</td>
<td>Type 1 congenital 11ß-hydroxysteroid dehydrogenase deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• marginally ↑</td>
<td>Liquorice administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &lt; 1.5:1 (normal)</td>
<td>Type 2 congenital 11ß-hydroxysteroid dehydrogenase deficiency</td>
</tr>
<tr>
<td>↑ ⇒ or ↑</td>
<td></td>
<td>indicates site of block</td>
<td>Carbenoxolone administration</td>
</tr>
<tr>
<td>usually ↑</td>
<td>↑↑</td>
<td></td>
<td>Congenital adrenal hyperplasia 11ß-hydroxylase deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17α-hydroxylase deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ectopic ACTH syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Primary cortisol resistance</td>
</tr>
</tbody>
</table>

† No improvement in mineralocorticoid excess with spironolactone but responds to inhibitors of renal tubular ionic transport

GC/MS = Gas chromatography and mass spectrometry
THF = 5ß-tetrahydrocortisol
alloTHF = 5α-tetrahydrocortisol
THE = tetrahydrocortisone
Interpretation of Investigations of Mineralocorticoid Excess

Hypertension

- No further investigation
- Oral sodium loading
  - Plasma K > 3.5 mmol/l
  - Urine Na > 100 mmol/24 h
  - Plasma K > 3.5 mmol/l
  - Urine Na < 100 mmol/24 h

Plasma K > 3.5 mmol/l but clinical suspicion high

0800 h supine PRA and Aldo (see Table 1)

Low PRA
- High aldosterone
- Low aldosterone

Plasma/urinary 18-cortiso
Aldosterone at 1200 h erc
Laterisation adrenal (CT, + vein)

Differential Diagnosis (see Table 2)

Plasma DO
Urinary cortisol
GC/M profile

Differential Diagnosis (see Table 3)

Original protocol prepared by Brian Walker, 6/93
Revised October, 2002