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 HCO_3, 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 HCO_3, 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**

Plasma Renin Activity	*Aldosterone*	*Description*	*Differential Diagnosis*
⇑	⇑	Secondary hyperaldosteronism	Dehydration; Diuretics; Laxatives; Vomiting; Cardiac Failure; Liver disease; Nephrotic syndrome; Salt-losing nephropathy; Bartter's syndrome Renovascular Disease
⇓	⇒		Low-renin essential hypertension Hypokalaemia masking aldosterone excess
⇓	⇑	Low-renin hyperaldosteronism	see Table 2
⇓	⇓		see Table 3

Table 2 Differential diagnosis of low-renin hyperaldosteronism

Response to angiotensin II†	*Response to ACTH*§	*Lateralisation of abnormal adrenal gland*¥	*Urine 18-hydroxy cortisol (nmol/day)*	*Diagnosis*	*Prevalence approx %*
+	-	normal	< 1000	Normal	
++	-	bilateral	< 1000	Idiopathic adrenal hyperplasia	60
++	-	unilateral		Aldosterone producing AII-responsive adenoma	< 1
-	+	unilateral	1000 - 3000	Conn's adenoma	40
-	+	unilateral		Primary adrenal hyperplasia	< 1
-	+	bilateral	> 3000	Glucocorticoid suppressible hyperaldosteronism	1
-	-	unilateral (tumour > 3 cm diameter)		Adrenal carcinoma producing aldosterone	<1

† 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

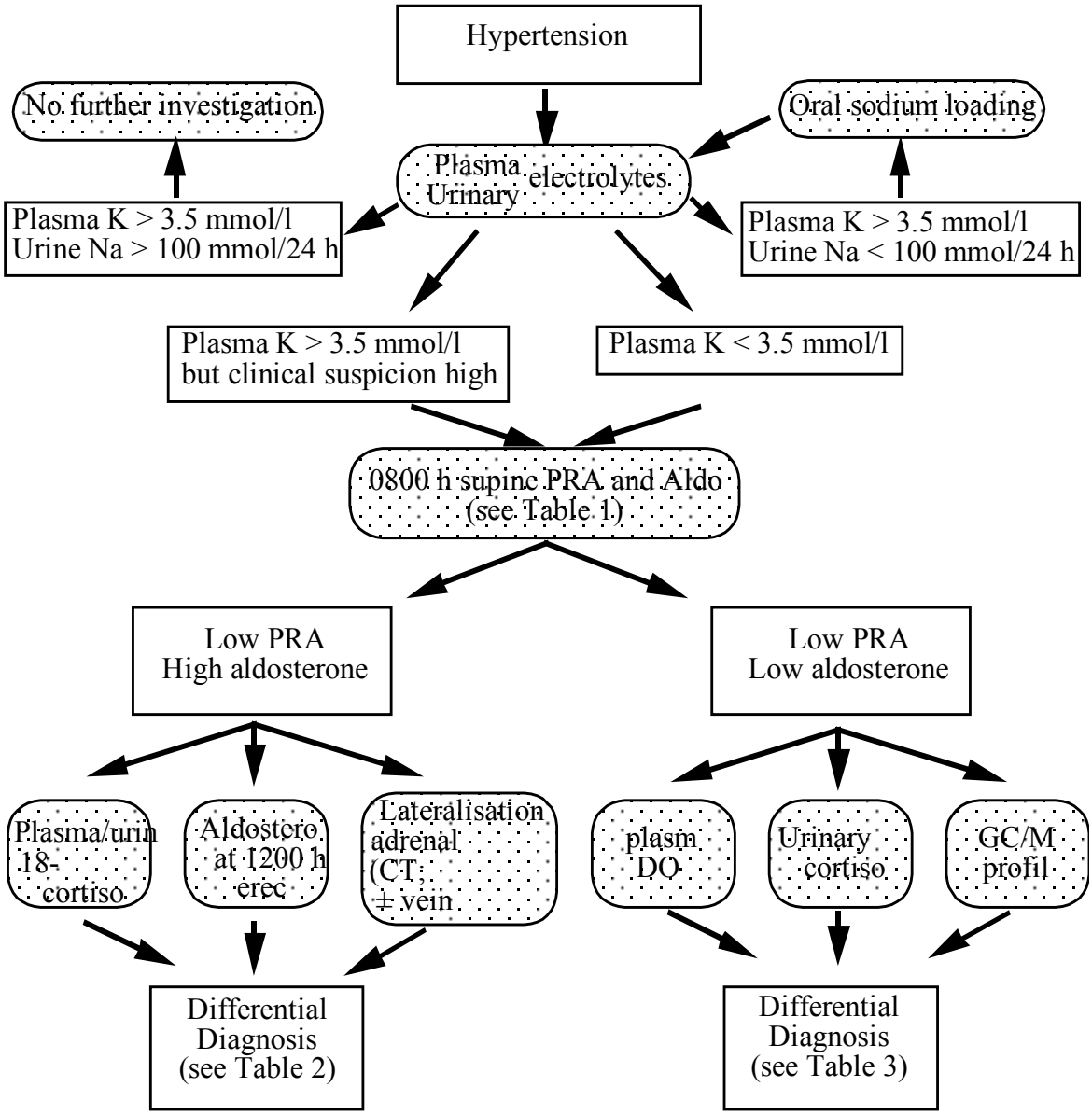
Table 3 Differential diagnosis of low-renin low-aldosterone hypertension

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

† 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



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