ALDOSTERONE/RENIN STUDIES: SCREENING PROTOCOL

INTRODUCTION

Aldosterone and renin levels are useful in investigation of suspected disorders of aldosterone production such as:

- primary hyperaldosteronism
- secondary aldosteroneism due to Bartter's syndrome
- Hypoaldosteronism (primary or hyporeninaemic)
- Pseudohypoaldosteronism (resistance to aldosterone).

WHO SHOULD BE SCREENED FOR PRIMARY HYPERALDOSTERONISM?

1. Patients with sustained severe hypertension (>150/100 mm Hg) on 3 measurements obtained on different days
2. Patients with hypertension (>140/90 mm Hg) who do not respond to three or more conventional antihypertensives, or controlled blood pressure <140/90 mm Hg on four or more antihypertensives.
3. Hypertensives with spontaneous or diuretic induced hypokalaemia
4. Hypertensive and adrenal incidentaloma
5. Hypertensive and sleep apnoea
6. Hypertensive and family history of early onset hypertension or cerebrovascular incident <40 years
7. All hypertensive first degree relatives of patients with primary hyperaldosteronism

OTHER INDICATIONS:

1. Diagnosis / differentiation between, primary and secondary causes of hyper- or hypoaldosteronsim
2. Management of renal artery stenosis (renin)
3. Diagnosis and location of renin secreting tumours (renin)

PATIENT PREPARATION

The renin-aldosterone axis is primarily regulated by renal blood flow. Patients under investigation should therefore be normally hydrated, have an adequate sodium intake and be normokalaemic or maximum potassium level obtainable (gross potassium depletion inhibits aldosterone production and may give artefactually low results). Correction of potassium should be with potassium supplements ***not*** potassium sparing diuretics. Any potassium replacement should be stopped for 24 hours before the test.

Stop beta blockers for 2 weeks prior to testing and stop mineralocorticoid receptor antagonists 6 weeks before sampling.

Ideally patients should not be taking any drugs that interfere with fluid balance or potassium (see appendix). Doxazosin, prazosin and slow release verapamil do not interfere and patients requiring hypotensive agents can receive these. When used as a screening investigation it is often impractical to stop all interfering drugs and results may be interpreted with knowledge of current medications.

Please ensure that all relevant clinical details (e.g. blood pressure) and current medication (including oral contraceptives/HRT) are noted on the request form.

Failure to give adequate clinical information will delay sample analysis. It is imperative that Biochemistry are informed beforehand so that arrangements can be made for specimen handling.

PROTOCOL

This test should not be performed on inpatients unless agreed with Consultant Biochemist.

1. **Patient should delay morning medication until after samples have been taken.**
2. **Samples to be collected early morning (8.00 to 10.00 am).**
3. **Allow the patient to rest quietly for at least 10 minutes before taking blood.**
4. **Take blood samples for:** **Aldosterone & Renin** **7ml EDTA tube**

   For children less than 6 years of age a minimum of one full paediatric EDTA (red top) tube

   U&E's **7ml SST tube**
5. **Take samples to Biochemistry laboratory immediately (within 30 minutes of sampling).**

INTERPRETATION

If the ratio of aldosterone (pmol/L) to renin (pmol/ml/h) is greater than 1,700, plasma renin ≤0.3 pmol/ml/hr and plasma aldosterone above 275 pmol/L, the patient almost certainly has primary hyperaldosteronism (Conn's).

If the ratio is between 850 and 1,700 and patient was on anti-hypertensives affecting the aldosterone-renin system then change to an alpha-blocker and repeat the test after at least 2 weeks (6 weeks if spironolactone is to be discontinued) – see appendix note 2. If the ratio is less than 680 the primary hyperaldosteronism is unlikely.

Note that a very low renin activity may skew the aldosterone:renin ratio where aldosterone is low or not elevated. This is not consistent with primary hyperaldosteronism.

CONFIRMATORY TESTING

Endocrine Society guidelines recommend that patients with a positive aldosterone:renin ratio should undergo one or more confirmatory test, such as the saline infusion test, to either exclude or confirm the diagnosis. Exception is in the setting of spontaneous hypokalaemia with plasma renin <0.3 pmol/ml/hr and aldosterone >550pmol/L – where confirmatory testing may not be required.

APPENDIX 1: Notes about Aldosterone / Renin Studies.

Effect of drugs

Drug group	Examples	Effect on renin	Effect on aldosterone	Comments
Non-steroidal anti-inflammatory drugs (NSAIDs)	Aspirin, ibuprofen, indomethacin	↓	↓	Generally consistent effect, probably mediated via renal prostaglandins
β-Blockers	Atenolol, carvedilol, metoprolol, propranolol	↓	↓	Generally consistent effect
Potassium-sparing diuretics	Amiloride, spironolactone, trimterene	↑	↑	Very large increases in renin observed.
ACE inhibitors	Captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, ramipril	↑	↓	Consistent and large increases in renin nearly always seen; effects on aldosterone inconsistent.
Angiotensin Receptor blockers (ARBs)	Losartan, candesartan	↑	↓	
Thiazide diuretics	Chlorthalidone, hydro-chlorothiazide, metolazone, xipamide	↑	↑	Generally consistent effect with renin; more variable with aldosterone
Loop diuretics	Frusemide	↑	↓	Only small changes seen; effect on aldosterone variable
Dihydropyridine Calcium channel antagonists	Amlodipine, Felodipine, licidipine, nicardipine, nifedipine	↑↓ **None**	↑↓ **None**	Very variable effects; significant increases and decreases have been reported, as well as no significant differences
Laxatives	Most types when used in excess	↑	↑	Probably linked to dehydration with abuse
Oestrogen Preparations and pregnancy		↑	↑	

Notes

1. Renin is lowered by increased BP, erect to supine, salt loading, β-blockers, PG synthetase inhibitors and hypokalaemia.
2. Ideally discontinue medication interfering with the aldosterone-renin system for at least 2 weeks before the test (or 6 weeks if spironolactone or oestrogens to be discontinued), but an alpha-blocker such as doxazosin is allowed. If unable to stop for 2 weeks then stop for 1-2 days (except spironolactone which must be stopped for 6 weeks) and then collect screening test samples.
3. If the patient's hypertension is such that all drug therapy cannot be withdrawn a best pragmatic approach is to stop ACE inhibitors, beta-blockers for 2 weeks and to avoid Ca-channel blockers on the day of the test.
4. Oestrogens increase renin activity but lower renin concentration. Discontinue for 6 weeks before sampling if possible.

CONTACTS

Basildon Hospital Biochemists: ext. 3029 / 3539 / 3095 / 3025

Southend Hospital Biochemist: ext. 8795

REFERENCES

1. Supra-regional assay service – aldosterone test information http://www.sas-centre.org/assays/hormones/aldosterone.html (accessed 18/5/2020)
2. Cartledge S, Lawson N. Aldosterone and renin measurements. *Ann Clin Biochem* 2000; **37**: 262-278
3. Imperial endocrinology handbook. http://imperialendo.co.uk/Bible2018.pdf. (accessed 18/5/2020)
4. The management of primary aldosteronism: Case detection, diagnosis, and treatment: An Endocrine Society Clinical Practice Guideline. *J. Clin Endocrinol Metab.* May 2016, 101(5):1889-1916