Outpatient Fludrocortisone Suppression Test: A Safe and Effective Alternative to Inpatient Testing/ Original Article

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Key words

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Abstract

The Fludocortisone Suppression Test is regarded by many investigators as the most reliable confirmatory test for primary aldosteronism. It is generally conducted as an inpatient, reportedly for accuracy as well as safety reasons. We have developed an outpatient Fludrocortisone Suppression Test protocol and report on 29 consecutive cases.

Aim

Possible confirmatory tests for primary aldosteronsim include Oral Sodium Loading, Saline Infusion Test (SIT), Fludrocortisone Suppression Test (FST), and Captopril Challenge Test[1]. In Australasia, SST and FST are most commonly used. Stowasser's Unit in Brisbane has favoured FST based on their extensive clinical experience and research[2], although a recent study from them suggests that technical refinements to SIT may improve results with that test[3].

The basis of the FST is that in individuals with PA, aldosterone level will not suppress below 165pmol/l despite 3-5 days oral fludrocortisone supplemented by high sodium intake, and potassium supplementation, with the proviso that simultaneously measured serum potassium is >= 3.5mmol/l and plasma renin < 8.4mu/l [1,2,6]. (Hypokalaemia at the end of he test is only important however if aldosterone is < 165pmol/l when the result becomes uninterpretable. If aldosterone is > 165pmol/l despite hypokalaemia PA diagnosis is secure). Possible refinements to the test include, dietitian assistance with dietary modification, daily monitoring of serum potassium, morning and evening plasma cortisol measurement on the final day, 24-hour urine collection for sodium to ensure compliance with high sodium intake, and also clinical monitoring of the patient for excessive hypertension and signs of heart failure[2,7]

FST was originally envisaged as an outpatient procedure[6], but due to complexity, and perhaps perceived clinical risk, virtually all reports suggest that it should be conducted as an inpatient procedure. This includes academic units like Brisbane[1,2], and also those British and American units who publish their clinical protocols on-line and elsewhere [8,9.10]. In fact it is difficult to find reports of units who routinely

perform this as an outpatient procedure. The Endocrine Society Clinical Guidelines[1] reference two articles on outpatient-testing [11,12], but scrutinising the papers reveals that they are both from the same unit in Chile, and it is specified in neither paper the tests are conducted as an outpatient.

The Waitemata Hypertension Clinic (established 2009) initially used SIT, but in early 2013 changed to FST because of a perceived unreliability of SIT in a number or cases [4,5]. When the Waitemata Hypertension Service transitioned from SIT to FST, the logistics of inpatient FST were reviewed, and a couple of attempts made to admit patients to the renal ward for this procedure. It became clear that pressure on acute medical beds would often result in postponement or cancellation of FST admissions. Additionally, from the management point of view, the costs of an elective 4-5 day hospital admission proved a significant obstacle, and from the patient point of view, 4-5 days off work, in hospital ,was generally greeted as an unattractive proposition. For these reasons, we developed a somewhat simplified outpatient protocol, as follows:

Waitemata Outpatient FST Protocol

Spironolactone is always discontinued at least a month prior to FST, and other drugs known to importantly affect renin and aldosterone measurements[1,2] are withdrawn as safety and practicality permits. To maintain adequate blood pressure control, these are replaced, as required, with doxazosin, verapamil and hydralazine.

Patients regarded as high risk for malignant hypertension, stroke, coronary ischaemia or heart failure are excluded.

Patients are counselled about the potential risks of the test by the hypertension nurse specialist and are asked to measure their blood pressure at home daily (with their own monitor or a loaner) and to call the nurse (day or night) if a prespecified maximum safe level is exceeded, or if they experience breathlessness, chest pain, or any other concerning symptoms.

Lunch Day 1 commence

- Fludrocortisone 0.1mg QID (lunch, dinner, bed, breakfast)
- Sodium Chloride 10mmol tablets 3 TDS (lunch, dinner, breakfast)
- Potassium Chloride tablets 8mmol 2-3 TDS (lunch, dinner, breakfast)
- High dietary sodium intake (diet sheet and education by nurse)

Breakfast Day 6

- Last doses of fludrocortisone, sodium and potassium tablets

10 am Day 6

- Bloods drawn at community laboratory (after 5 minutes seated having been upright or ambulant for at least an hour prior) for electrolytes, renin and aldosterone

PA diagnosis confirmed if aldosterone > 165pmol (6ng/dl) , providing potassium >= 3.5 mmol/l and renin <= 8.4miu/l (1ng/ml/hr).

(Daily measurements of potassium were dispensed with along with cortisol measurements at the end of the test, 24-hour urine sodium collection, and dietitian input).

Method

All relevant clinical, pharmacological and laboratory data in patients attending the Waitemata DHB Hypertension Clinic is collated on a *Microsoft Access* relational database (M*icrosoft Corporation, Redmond WA USA*). Information on all patients subjected to FST for possible PA from January 2013 was extracted, and supplemented with data from the electronic clinical record.

Results

29 consecutive FST's were conducted between January 2013 and June 2014 in hypertensive patients with suspected PA.

The results are summarised in Table 1. 26 of the tests were interpreted as positive for PA and 3 negative. The three patients interpreted as negative for PA were:

- Patients 19 and 29: Unsuppressed aldosterone, but renin significantly higher than 8.4miu/l, without and other strong clues to PA (hypokalaemia, adenoma etc)
- Patient 28: Clear aldosterone suppression below 165pmol/l

Among the patients interpreted as positive for PA, three patients had a plasma renin > 8.4miu/l

- Patients 10. and 12: Both had strong clues to PA with hypokalaemia and adenoma, and were both subsequently cured with laparoscopic adrenalectomy
- Patient 17: Renin 10iu/l which was interpreted as a borderline result, but unprovoked hypokalaemia supported a diagnosis of PA. She subsequently had adrenal vein sampling which demonstrated bilateral aldosterone secretion. She was labelled bilateral adrenal hyperplasia and treated successfully with spironolactone.

Average potassium supplementation during the FST was 6 x 8mmol potassium chloride tablets per patient per day, and mean serum potassium at the end of the test was 3.6mmol/l. In 11 patients end serum

potassium was < 3.5mmol/l (3.2 – 3.4 mmol/l). This did not affect the interpretation of the FST result in any case because in all instances simultaneous plasma aldosterone was > 165pmol/l.

The outpatient test was extremely well-tolerated and there were no serious medical complications. Some patients felt non-specifically unwell during the test and a number reported mild puffiness of the face and hands. In two cases (patents 19 and 27), the test was shortened by one day because of concern about rising blood pressures but this did not affect interpretation of the results.

Not all patients were able to have their antihypertensive drug regimens optimised (for diagnostic purposes) prior to FST. In particular, 7 remained on regimens which included a beta blocker (which tends to suppress renin secretion without significantly affecting aldosterone level[1,2]). One would nevertheless expect volume expansion with sodium loading and fludrocortisone in these patients to suppress aldosterone below 165pmol/l in patients without PA;- this did not occur in any instance.

Discussion

We have conducted outpatient Fludrocortisone Suppression Tests, using a simplified protocol, on 29 patients with suspected primary aldosteronsim. 26 were interpreted as confirming the diagnosis, and 3 refuting it. Among the patients with a positive FST, 11 went on to have a diagnosis of unilateral aldosterone-producing adenoma and had curative laparoscopic adrenalectomies. The remainder had a diagnosis of bilateral aldosterone secretion made (with adrenal vein sampling) and were treated with long-term spironolactone. Clinical outcome in all was excellent apart from patient 2 in whom ongoing difficulties achieving blood pressure control were experienced despite high doses of spironolactone in combination with conventional antihypertensives;- this was partly a result of adherence issues.

There is no perfect diagnostic test for PA, but FST is at least as good as the alternatives and regarded by some as the best test. FST is our favoured test but the logistics, and cost, of providing is as an inpatient procedure make inpatient testing impractical in our organisation. Our (simplified) outpatient protocol has been used safely in 29 consecutive individuals with excellent diagnostic results.

FST does not always produce an unequivocal answer, and (as in patients 7,12,17,19,28 and 29, discussed above) in which case other clinical and laboratory data need to be used to assist with interpretation. This is similar to the experience of others. From a diagnostic point of view, the need to ensure a normal serum potassium at the end of the test is probably the strongest argument for inpatient testing (daily checking of serum potassium and increasing supplementation as required to maintain serum potassium around 4mmol/l). Although a few patients in our series were mildly hypokalaemic at the end of the test, this did not materially affect interpretation of the results. It is acknowledged that significant hypokalaemia at the end of the test in conjunction with a plasma aldosterone < 165pmol/l would render that result uninterpretable, but we saw no cases of this.

In summary, our preliminary data suggest that FST can be conducted safely and effectively on an outpatient basis with associated advantages for cost as well as patient convenience.

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Table 1. Demographic and Clinical Details

Patient number	Age	Sex	Ethnicity	Resistant hypertenson	Hypokalaemia	Radiological adenoma	BP Drugs during FST	KCl dose (8mmol tablets)	End K^+ mmol/l	End Renin (miu/l) + Aldosterone (pmol/l)	Final Diagnosis
1.	58	M	European	Y	Y	N	Metoprolol Cilazapril Felodipine Doxazosin	4	3.7	2/493	APA*
2.	29	M	Chinese	Y	Y	N	Atenolol Doxazosin Lisinopril Amlodipine	4	3.7	2/369	BAH**
3.	65	M	European	N	Y	N	Felodipine Cilazapril Celiprolol	4	4	5/1065	BAH
4.	65	M	Middle-East	Y	Y	Y	Doxazosin Losartan Chlorthal Atenolol	6	3.2	5/320	APA
5.	38	F	European	N	Y	Y	Amlodipine	6	3.6	6/818	APA
6.	37	F	Maori	Y	Y	Y	Verapamil Doxazosin	9	3.4	<2/276	APA
7.	47	F	Chinese	N	Y	Y	Cilazapril Amlodipine	6	3.4	3/1031	APA
8.	40	F	European	N	N	N	Verapamil Doxazosin	6	4	6/674	BAH
9.	59	F	Indian	Y	N	N	Bisoprolol Losartan	9	3.9	4/185	BAH
10.	36	F	European	N	Y	Y	Cilazapril Amlodipine	9	3.6	12/503	APA
11.	56	F	Maori	Y	Y	Y	Verapamil Candesartn Doxazosin	9	3.4	3/1870	APA
12.	54	M	European	Y	Y	Y	Verapamil Doxazosin Hydralazine	9	3.3	15/470	APA
13.	43	M	African	Y	N	N	Verapamil Doxazosin Hydralazine	9	4.1	6/227	BAH

14.	47	F	European	Y	Y	N	Verapamil Doxazosin	6	3.3	2/352	BAH
15.	32	F	Chinese	Y	Y	Y	Cilazapril	6	3.3	2/293	APA
16.	30	F	European	N	N	N	Quinapril Labetolol	4	4.2	2/196	BAH
17.	45	F	Maori	N	Y	N	Verapamil Doxazosin	6	3.5	10/362	BAH
18.	46	F	Filipino	Y	N	N	Doxazosin Lisinopril Atenolol Chlorthal	6	3.2	<2/282	BAH
19.	57	F	European	N	N	N	Verapamil Doxazosin	9	3.7	36/238	**Not PA**
20.	47	M	Middle-East	Y	N	N	Verapamil Doxazosin Hydralazine	9	3.3	6/596	BAH
21.	65	M	Pacific	Y	N	N	Verapamil Doxazosin Hydralazine	6	3.2	<2/299	APA
22.	52	M	Filipino	Y	N	Y	Verapamil Doxazosin Hydralazine	6	3.2	44/764 (un sup renin CKD)	BAH
23.	60	F	European	N	N	N	Hydralazine	6	3.6	3/1076	BAH
24.	40	M	Chinese	Y	N	N	Verapamil Doxazosin Hydralazine	6	4.4	10/589	BAH
25.	60	F	European	Y	N	N	Verapamil Doxazosin	-	4.2	8/368	BAH
26.	48	F	European	N	N	N	Verapamil Doxazosin	6	3.6	2/196	BAH
27.	50	F	Chinese	Y	Y	N	Verapamil Doxazosin	6	3.7	3/260	BAH
28.	50	F	European	N	N	N	Nil	Nil	4.1	2/135	**Not PA**
29.	34	F	Chinese	N	N	N	Verapamil Doxazosin	6	3.6	22/478	**Not PA**

(* APA = aldosterone producing adenoma. **BAH = bilateral adrenal hyperplasia)