CONSIDERATION OF INVESTIGATION FOR SECONDARY HYPERTENSION

Introduction:

Hypertension is common, reversible causes of hypertension are generally considered to be rare. For this reason attempts to identify a 'cause' in the majority of patients with raised BP would be unproductive (not cost effective). All patients attending the CV risk clinic should already have a routine measurement of 'U & E' and this might give some clues. As we have no formal protocol for looking for specific causes of hypertension, however, it is likely that requests for additional 'tests' are performed as a result of haphazard views as to who should be assessed further. Even if this were not the case there would be some merit in setting down some guidelines for:-

- Whom to investigate? and,
- How to investigate?

Reversible causes of hypertension:

- Renal – Any renal disease can be associated with raised blood pressure but an elevation of plasma creatinine would identify many, non-reversible disease processes. More attention has been paid to the identification of unilateral or bilateral renal artery stenosis in the belief that intervention might improve BP control.
- Adrenal
    - Cortex – Primary aldosterone excess (otherwise known as primary hyperaldosteronism or, more accurately, low renin aldosteronism) can be associated with an aldosterone secreting adenoma (Conn's syndrome), ACTH dependent aldosterone excess (Glucocorticoid Suppressible Hyperaldosteronism) or so-called Idiopathic Hyperplasia, a condition where aldosterone secretion is exquisitively sensitive to circulating angiotensin II. Other rare adrenal enzyme defects such as 17- alpha hydroxylase or 11-ß hydroxylase deficiency are invariably associated with hypokalaemia and should be discovered in the pursuit of this. Cushing's syndrome should be picked up clinically.
    - Medulla – Phaeochromocytoma is characterised by a set of symptoms that ought to direct the clinician to this possibility.
- Other causes – It is always important to consider drug induced hypertension and coarctation of the aorta.

Whom to investigate?

Not everyone who might have secondary hypertension has to be investigated and as long as BP is well controlled there is nothing to suggest that it matters if a secondary cause is not detected. There are some, generally accepted criteria for initiating a search however.

- Patients with a clue from the history (e.g. paroxysmal headaches, palpitations or pallor [*not flushing*] – for phaeochromocytoma), examination (e.g. Cushing's but not necessarily an abdominal bruit which is non specific) or simple blood tests (e.g. unprovoked hypokalaemia is suggestive of mineralocorticoid excess (if sodium high-normal think of primary aldosteronism or other mineralocorticoid excess state, if low-normal think of secondary aldosterone excess).
- Youngpatients – defined as those below 25 years
- Patients with resistant hypertension – defined as hypertension despite 3 or more drugs. There is a problem with this definition however in that it will include a large proportion of the patients attending the CVRC if failure to control means $\geq$ 140/90 mm Hg. It is probably more acceptable to have a cut off level of 160/100 mm Hg. There is literature evidence to suggest that RAS might be present in 20% of such people and some form of low renin aldosteronism in a further 20%.

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 initiate testing?

NB – Do not initiate imaging techniques for endocrine hypertension until/unless biochemical confirmation has been obtained.

- If a phaeochromocytoma is suspected arrange for a 24 hr collection (in an acid bottle) for nor-metanephrine and metanephrine. This can be repeated at intervals if normal but the clinical suspicion remains. Sister Gough will arrange collection, simply request normetadrenalin on the white sheet.

- Investigation for renal artery stenosis is now performed initially using magnetic resonance angiography and this is done by Dr Ian Gillespie or Dr Susan Ingram at the **New** Royal Infirmary. If renal artery stenosis is suspected (reasons as above or the presence of significant vascular disease elsewhere – remember that the use of ACEI or ARA can induce rapid acute renal failure in patients with bilateral functional RAS or RAS to a single functioning kidney) discuss plan of action with a consultant. A letter of referral should then be made to Dr Ian Gillespie or Dr Susan Ingram at the new RIE with a copy to Dr Caroline Whitworth (renal physician, new RIE). If a treatable lesion is seen then angioplasty/stenting may be performed at the same sitting. This will be done on the basis

of an assessment made at that time so it must be made very clear in the referral letter why this investigation is being requested. NB – Do not embark on this procedure without explaining the implications to the patient including a description of what angioplasty/stenting means.

There is no point discovering RAS unless the patient is prepared to undergo angioplasty/stenting (**unless the purpose is simply to establish the safety of initiating ACEI in a patient with extensive vascular disease**).

None of the screening tests for RAS are good enough to predict those individuals whose BP will be corrected or improved by intervention thus the only test to be performed should be an angiogram.
NB Arrange an ABPM prior to angioplasty as this will be a baseline to assess BP pre and post procedure.

- Perhaps the most difficult area for investigations is that of detecting primary aldosterone excess. The first clue remains unprovoked hypokalaemia but it is thought that approximately 50% of patients will be normokalaemic. If a low plasma potassium occurs as a consequence of low dose thiazide therapy, consider this diagnosis again but mostly the question will arise in patients with resistant hypertension. There exists a 'Conn's protocol' which remains our gold standard but should ideally be initiated in **untreated** patients. Patients should normally be off all drugs for 6 weeks at least before actioning a 'Conn's protocol'. Simply put 'Conn's protocol' on the white investigation sheet and direct the patient to Sister Gough. If it is considered unsafe to leave a patient off all therapy for this period then dihydropyridine calcium channel blockers (Amlodipine, Nifedipine) may be used as they have little impact on the R/A/A axis (Debrisoquine, which was previously employed in such circumstances, is no longer available)

After discussion within the unit we do not believe currently that it is worth using the Aldosterone/renin ratio as a screening tool in patients on treatment. If however the plan is to embark on the full Conn's protocol it would be appropriate to perform a seated Aldosterone/renin ratio and a urinary 18 OH cortisol while on treatment so that we can assess, in the fullness of time, whether or not there is concordance between the results of these initial screening tests and those found on full testing. We can call this 'a treated Conn's protocol' and it should only be done prior to the full Conn's protocol.

It is increasingly held that an elevated aldosterone/renin ratio in patients with a normal circulating plasma aldosterone simply identifies patients with 'low-renin' hypertension. There are some uncontrolled studies to suggest that such patients may have a good BP lowering response to the drug spironolactone (a non specific aldosterone antagonist). A pragmatic

strategy in patients with resistant hypertension is to try a 2-month course of this drug at 50 mg per day. The more specific mineralocorticoid antagonist (eplerinone) is now available and is appropriate in patients intolerant of spironolactone. Recent evidence however suggests that increasing the dose of any diuretic may result in similar reductions in BP

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