P1–474: HIGH THROUGHPUT ASSAY OF RENIN MASS IN THE DETECTION, TREATMENT-TITRATION OR CURE OF LOW-RENIN PATIENTS WITH SALT-DEPENDENT HYPERTENSION

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Abstract

Renin is one of the oldest but least measured of hormones. We are undertaking a number of studies to demonstrate its use in the recognition and management of patients with salt-dependent hypertension. Previous study suggested that such patients are not optimally treated by low-dose thiazide diuretics but need either K^+-sparing or combination diuretic.

Here we report a double-blind crossover comparison of all the diuretic classes, alone or in combination, in the extreme phenotype of young low-renin hypertension. After 5 weeks on each therapy we found low-dose bendroflumethiazide + amiloride to be more effective than high doses of any single drug. Failure to achieve target BP was associated with failure to de-suppress plasma renin. In two extreme cases, where even combination failed to elevate renin, we found a Conn's adenoma whose removal cured the hypertension.

Background

Automated assay of renin mass now permits its routine use in hypertension. We recently reported that in patients with elevated aldosterone-renin ratio, plasma renin is more useful than either the ratio or plasma aldosterone itself in predicting either the response to K^+-sparing diuretics or the presence of a Conn's adenoma. In a crossover comparison of diuretics, high-dose thiazide was as effective at lowering BP as spironolactone or amiloride, but only half as effective in de-suppressing plasma renin (1). We therefore hypothesized that in hypertension, the epithelial Na^+ channel (ENaC) is the main site of excess Na^+ retention; that K^+-sparing diuretics are better natriuretics than thiazides; and that amiloride + thiazide would cause even greater rise in renin, and BP reduction, than higher doses of either drug alone.

Figure 1

Comparison of blood pressure lowering efficacy.

Amiloride 40 mg was the most effective individual drug. Combination (bfz 2.5 mg + amiloride 20 mg) was the most effective treatment.

Objective

To compare the blood pressure and renin response to four different classes of diuretic, or combination, in the extreme phenotype of young Caucasians with low-renin hypertension.

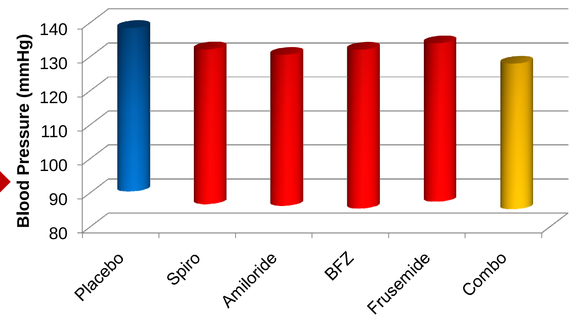
Materials & Methods

The hypothesis was tested in young, low-renin Caucasians. This is a select group, ~5% of young patients, who may be more likely to have discrete causes of Na^+-dependent hypertension than older patients. 30 patients, aged <45, with plasma renin <12 mU/L (≅ 0.65 ng/ml/hr) rotated in random order between spironolactone 100 mg, amiloride 40 mg, bendroflumethiazide (bfz) 5 mg, combination (bfz 2.5 mg + amiloride 20 mg), frusemide 40 mg and placebo, each taken once daily for 5 weeks. The endpoints were home systolic BP (12 readings over 3 days), and plasma renin.

Figure 2:

Comparison of effects on plasma renin and aldosterone

As in our previous rotation, 'SALT', the K^+-sparing diuretics were >2-fold more effective than thiazide or loop in de-suppressing plasma renin.



Results

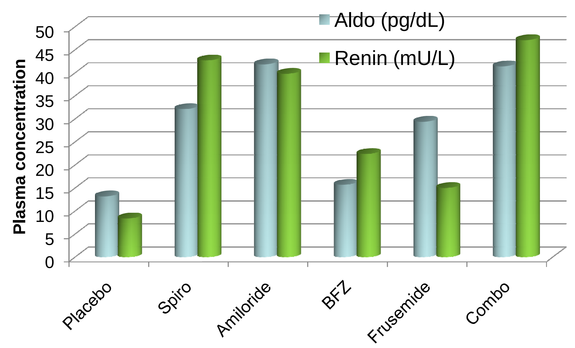
Amiloride was the most effective single drug, but BP on combination (despite half-doses) was lower than on any single drug ($p<0.05$, Figure 1). We confirmed that plasma renin rises twice as much on K^+-sparing diuretics than on thiazide or frusemide, with further increase on combination (Figure 2).

A Conn's adenoma was found in 2 patients, despite normal K^+ and aldosterone at baseline. The clue was a fall in serum K^+ by 1 mmol/L on bfz (Figure 3). These patients differed from the others in having a suppressed plasma renin throughout the rotation. One patient, with poor BP control throughout, was treated pre-operatively with spiro 25 mg + amiloride 10 mg. This elevated renin to 138 mU/L and reduced BP to 124/76 mmHg.

Discussion

Measurement of renin is invaluable in both the initial diagnosis of patients who require atypical diuretics, and thereafter in titration of treatment.

Clues to the presence of a Conn's adenoma are a suppressed plasma renin despite treatment with drugs which normally elevate renin, and an exaggerated fall in K^+ on thiazide.



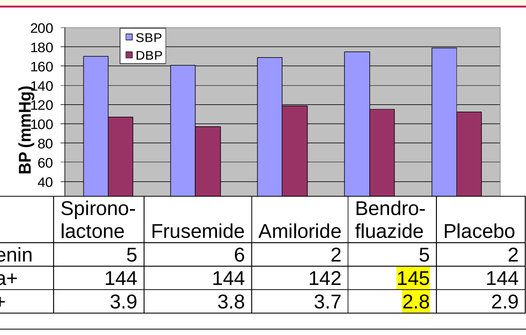
Summary

In patients at the Na^+-dependent extreme of the volume/vasoconstriction spectrum of hypertension, single diuretics can be sub-maximal even when the hypertension is monogenic. Plasma renin measurement can be used to titrate need for combinations, and to recognise patients with Conn's adenomas.

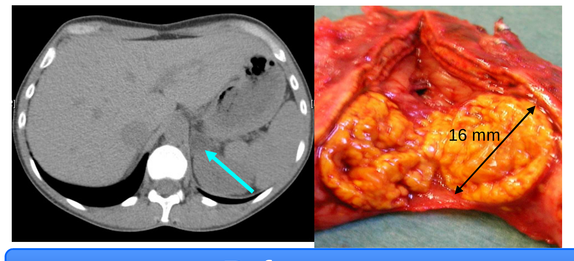
Figure 3:

Normokalemic Conn's Adenoma

One of 2 patients in whom this diagnosis was unmasked by the fall in K^+ during thiazide treatment, and failure of bfz + amiloride to de-suppress renin. BP was, by contrast, completely controlled by spiro+amiloride.



	Spirono-lactone	Frusemide	Amiloride	Bendro-fluazide	Placebo
Renin	5	6	2	5	2
Na+	144	144	142	145	144
K+	3.9	3.8	3.7	2.8	2.9



References

1. Hood SJ et al. Circulation 2007;116: 268-275

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