Amiloride has a More Favourable Effect on Glucose Tolerance than Hydrochlorothiazide in the Treatment of Essential Hypertension - Results of a Double Blind, Placebo Controlled, Randomised Cross Over Study

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In recent years, the dose of thiazide diuretics has been limited, and their combination with β-blockade discouraged, because of a perceived risk of diabetes. Having validated use of the oral glucose tolerance test (OGTT) in crossover studies to detect early glycaemic effects of drugs, we have now tested whether the rise in 2 hour glucose on hydrochlorothiazide (HCZ) is avoided by switching to amiloride, and/or by combining HCZ with a highly β₁-selective antagonist, nebivolol. 38 patients with essential hypertension, mean age 64, 17M, 21F, participated in a double-blind, cross-over study. They received, in random order, 4 weeks of once-daily treatment with each of HCZ 25-50mg, nebivolol 5-10mg, combination (HCZ 25-50mg + nebivolol 5-10mg), amiloride (10-20mg) and placebo. Each drug was force-titrated at 2 weeks and separated by a 4-week placebo washout. At each visit, we measured BP and plasma electrolytes, and a 75g OGTT was performed.

Data (mean (sd)) was analysed by repeated measures between drugs. For a similar reduction in BP, there were contrary changes between diuretics on OGTT (p=0.006). The 2-week OGTT on HCZ 25 mg (not shown) was similar to the 4-week on HCZ 50 mg. Nebivolol did not exacerbate the effect of HCZ, and on its own improved OGTT. No drug caused significant changes to the 30’ insulin. We conclude that the solution to HCZ-induced hyperglycaemia is not to reduce the dose but to switch to – or, combine with, amiloride; and that the addition of β-blockade is neutral providing a β₁-selective drug/dose is used. These conclusions should be confirmed by the BHS’s BHF-funded PATHWAY-3 trial.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Week</th>
<th>Glucose (mmol/l)</th>
<th>K</th>
<th>BP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fasting (mmol/L)</td>
<td>2 hours (mmol/L)</td>
<td>(SD)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
<td>5.30 (0.72)</td>
<td>7.40 (2.42)</td>
<td>4.2(0.3)</td>
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<tr>
<td></td>
<td>4</td>
<td>5.20 (0.53)</td>
<td>6.60 (2.11)</td>
<td>4.1(0.2)</td>
</tr>
<tr>
<td>HCZ</td>
<td>0</td>
<td>5.20 (0.52)</td>
<td>7.00 (2.36)</td>
<td>4.1(0.2)</td>
</tr>
<tr>
<td></td>
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<td>5.45 (0.56)</td>
<td>7.49 (2.24)</td>
<td>3.7(0.3)</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>0</td>
<td>5.20 (0.53)</td>
<td>7.18 (2.07)</td>
<td>4.1(0.3)</td>
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<td>4</td>
<td>5.22 (0.59)</td>
<td>6.77 (2.18)</td>
<td>4.2(0.3)</td>
</tr>
<tr>
<td>Combination</td>
<td>0</td>
<td>5.23 (0.64)</td>
<td>7.33 (2.43)</td>
<td>4.0 (0.3)</td>
</tr>
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<td>4</td>
<td>5.47 (0.64)</td>
<td>7.65 (2.13)</td>
<td>3.7(0.3)</td>
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<td>Amiloride</td>
<td>0</td>
<td>5.19 (0.47)</td>
<td>7.07 (2.17)</td>
<td>4.1(0.2)</td>
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<td>5.23 (0.55)</td>
<td>6.70 (1.88)</td>
<td>4.5(0.3)</td>
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