Effects on Insulin Action of Adding Low-Dose Thiazide to Angiotensin-Converting Enzyme Inhibitor in Essential Hypertension

Claire M. McHenry, A. Brew Atkinson, Steven J. Hunter, Jonathan N. Browne, Cieran N. Ennis, John S. Henry, Brian Sheridan, Patrick M. Bell

Abstract—Concern exists regarding adverse metabolic effects of antihypertensive agents. In the United States, diuretics are recommended first-line but additional agents, usually angiotensin-converting enzyme (ACE) inhibitors, are often required to meet blood pressure targets. We have previously shown that the combination of low-dose diuretic with an ACE inhibitor has detrimental effects on insulin action compared with ACE inhibitor alone in hypertensive type 2 diabetic patients. Our aim was to establish whether similar effects occur in nondiabetic hypertensive patients using this combination. A randomized double-blind placebo-controlled crossover design was used. After a 6-week run-in, when regular antihypertensive medications were withdrawn and placebo substituted, patients received captopril 50 mg twice daily with either bendroflumethiazide 1.25 mg (CB) or placebo (CP) for 12 weeks with a 6-week wash-out between treatments. Insulin action was assessed by hyperinsulinemic euglycemic clamp after the 6-week run-in and at the end of each treatment period. There were no differences between treatments in fasting glucose or insulin concentrations. Glucose infusion rates required to maintain euglycemia were the same with each treatment (CP 22.1 ±2.2 vs CB 22.2±2.2 μmol/kg per minute). There was no difference in endogenous glucose production in the basal state (CP 8.9±0.5 vs CB 9.5±0.7 μmol/kg per minute; P=0.23) or during hyperinsulinemia (CP 2.2±0.6 vs CB 1.5±0.3 μmol/kg per minute; P=0.30). In contrast to the situation in type 2 diabetes mellitus, ACE inhibitor combined with low-dose thiazide diuretic does not adversely affect insulin action when compared with ACE inhibitor alone in nondiabetic hypertensive patients. (Hypertension. 2013;61:800-805.)

Key Words: antihypertensives ■ essential hypertension ■ insulin action

Reduction of blood pressure using antihypertensive drugs decreases risk of vascular events; however, in a large meta-analysis of 17 studies that used β-blocker therapy and diuretics and indicated that lowering blood pressure was associated with a significant fall in coronary heart disease events, the benefit was less than that expected from prospective observational data. One possible explanation is that these drugs adversely affect other cardiovascular risk factors through deleterious effects on insulin action, thereby reducing the overall impact of blood pressure reduction. Despite this, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the largest antihypertensive study to date, has shown diuretics to be superior to other agents in lowering some cardiovascular outcomes. There was, however, an increase in new onset type 2 diabetes mellitus in ALLHAT in those on diuretics compared with angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers.

We have previously examined effects on insulin action of ACE inhibitors and diuretics in essential hypertension. In agreement with others, we found that ACE inhibitors are at least neutral in effect on insulin action. More than 1 agent is usually required to meet strict blood pressure targets, and we have also examined the effect of combination treatment on insulin action in essential hypertension. The combination of high-dose diuretic (bendroflumethiazide 5 mg) and ACE inhibitor compared with an ACE inhibitor alone reduced insulin sensitivity suggesting that low-dose diuretic should be used in combination with ACE inhibitor. In both nondiabetic and diabetic patients with essential hypertension, low-dose diuretic (bendroflumethiazide 1.25 mg once daily) compared with conventional dose (5 mg once daily) is as effective in lowering blood pressure but has fewer adverse metabolic effects. Even compared with bendroflumethiazide 5 mg or 10 mg once daily, blood pressure lowering effects of 1.25 to 2.5 mg were the same but, again, adverse metabolic effects were greater with higher doses. Our most recent data, however, indicate that low-dose diuretic combined with an ACE inhibitor in type 2 diabetes mellitus

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adversely affects insulin sensitivity compared with ACE inhibitor alone.\textsuperscript{15} Given these results, the aim of the present study was to establish whether a similar metabolic effect using the same combination will occur in nondiabetic patients with essential hypertension.

Methods

Patients

Patients aged <70 years with essential hypertension well controlled on no more than 2 antihypertensive agents were recruited from general practices within the greater Belfast area. All were of white western European origin. Patients were excluded if they were known to have had type 2 diabetes mellitus, secondary hypertension, body mass index >40 kg/m$^2$, a history of cardiovascular, cerebrovascular, hepatic, or renal disease (ie, an estimated glomerular filtration rate of <60 mL/min), gout, or epilepsy. Females with childbearing potential were not permitted to take part because of complexities of ensuring they were not exposed to ionizing radiation. All patients gave written informed consent to participate. The study protocol, participant information sheet, and consent form were approved by the Research and Ethics Committee for Northern Ireland, the Research and Development Governance Committee for the Royal Group of Hospitals Trust, and the Administration of Radioactive Substances Advisory Committee of the United Kingdom.

Study Design

A randomized double-blind crossover design was used. All antihypertensive agents were withdrawn and replaced with placebo during a 6-week run-in. During this period, blood pressure was measured every 2 weeks and, if, during the study, diastolic blood pressure rose >100 mm Hg at any time, or >95 mm Hg diastolic or 160 mm Hg systolic on 2 occasions, doxazosin XL was added. Doxazosin has been shown to have no effect on insulin action.\textsuperscript{16} Blood pressure targets during the study were <130 mm Hg systolic and 80 mm Hg diastolic.

After placebo run-in, patients received captopril, which started at 12.5 mg twice daily and was titrated up over 6 days to 50 mg twice daily, and were randomly assigned either bendroflumethiazide 1.25 mg or placebo. Both drugs were identically encapsulated. After 12 weeks on this treatment, the capsules containing bendroflumethiazide or placebo were stopped. Captopril was continued during a 6-week wash-out period, after which the alternate randomly allocated placebo or bendroflumethiazide was given for a further 12 weeks. Throughout the trials, patients were seen by the same investigator. Subsequent to placebo run-in, patients were seen at 2-week intervals by the investigator for measurement of blood pressure. At this visit, medications were also checked and if necessary adjusted by the investigator. None of the patients were reviewed with regard to hyperuricemia, which could not be adequately controlled with doxazosin XL alone. Two had fluid retention after withdrawal of regular diuretic, and a further 2 patients complained of palpitation off β-blocker therapy. One other developed chest pain during run-in and was diagnosed with ischemic heart disease on exercise stress testing. Despite tolerating captopril during the first treatment period, 3 patients developed cough.

Assessment of Insulin Action

Insulin action was assessed after the 6-week placebo run-in and at the end of each 12-week study period. A 1-step euglycemic clamp was performed\textsuperscript{10,15} using a 1 mU/kg insulin infusion. On the morning of the clamp, study medications were taken at 7:00 AM after a 12-hour overnight fast. Patients reported to the Regional Center for Endocrinology and Diabetes of the Royal Victoria Hospital in Belfast at 7:45 AM. A large antecubital vein was cannulated and used for all subsequent infusions. A second cannula was inserted retrogradely into a dorsal vein and used for sampling as described previously.\textsuperscript{10,15}

An adjusted primed-continuous infusion of high-performance liquid chromatography purified [3-3H] glucose (New England Nuclear Research Products Division, Dupont Ltd., Stevenage, United Kingdom [Catalogue number: NET 100C]) was administered during a basal equilibration period (~120 minutes to zero time), after which insulin was infused at 1 mU/kg per minute for further 2 hours. The exogenous infusion of 20% glucose maintained plasma glucose at fasting concentration. This was prelabeled with [3-3H] glucose to match the plasma glucose-specific activity as described.\textsuperscript{15} The primed-continuous tracer infusion was reduced to 50% of the basal rate at 20 minutes and to 25% at 40 minutes to maintain tracer steady state and was kept at this rate throughout the remainder of the hyperinsulinemic period. Normal saline was continued throughout with potassium chloride (14 mmol) added to prevent hypokalemia during insulin infusion.

Analytical Techniques

Arterialized venous blood, as described above, was used for all analyses. Glucose-specific activity was measured after deproteinization with barium hydroxide and zinc sulfate. After centrifugation, the supernatant was transferred to a plastic scintillation vial, frozen in liquid nitrogen, and lyophilized before reconstitution to original volume in water. After addition of Ultima Gold (PerkinElmer, Catalogue No: 6013329), samples were counted for 10 minutes on a liquid scintillation spectrometer (Wallac 1410 Liquid Scintillation Counter). Aliquots of tracer infusate were spiked into nonradioactive plasma before storage at −20°C and were processed in parallel to plasma samples to allow calculation of [3-3H]-glucose infusion rates. Nonradioactive samples of plasma were also processed in parallel to permit measurement of background radioactivity.

Calculations

The nonsteady-state equations of Steele et al\textsuperscript{16} as modified by De Bodo et al\textsuperscript{15} were used to calculate rates of glucose turnover during these periods −30 minutes to time zero and 90 to 120 minutes, assuming a pool fraction value of 0.65 and an extracellular volume of 190 mL/kg. Rates of infusion of [3-3H] glucose were calculated as the sum of the tracer infused continuously and the tracer in the labeled exogenous glucose infusion. Rates of endogenous (hepatic) glucose production were then calculated by subtraction of the exogenous glucose infusion rates required to maintain euglycemia from the isotopically determined rates of glucose appearance.

Statistical Methods

The power of the study was calculated from previous clamp data.\textsuperscript{11,15} Twelve patients were required to give a 90% chance of detecting a 10% change in insulin action at the 5% level of significance. End-of-period results for normally distributed variables were analyzed as recommended by Hills and Armitage\textsuperscript{17,12} for 2-period crossover studies. This method allows comparison of both treatments to be adjusted for any period effects. The method also supplies a test for treatment period interaction. Comparison of treatments was derived from the differences in response between the 2 periods. Significance was assessed using a t statistic. Where baseline values were available for each period, analysis was change of parameter from baseline.

Results

Twenty-three patients were enrolled for the study. Seven patients withdrew during placebo run-in; 2 had unacceptably high blood pressure after withdrawal of antihypertensive medication, which could not be adequately controlled with doxazosin XL alone. Two had fluid retention after withdrawal of regular diuretic, and a further 2 patients complained of palpitation off β-blocker therapy. One other developed chest pain during run-in and was diagnosed with ischemic heart disease on exercise stress testing. Despite tolerating captopril during the first treatment period, 3 patients developed cough.
which settled after withdrawal of the ACE inhibitor and they also withdrew. Finally, 1 other subject left in the final study period because he developed depression. Twelve patients completed the study. Baseline characteristics after placebo run-in and prestudy medications are summarized in Tables 1 and 2. No carryover effect was detected for any variable, and there was, therefore, no necessity to analyze any variable as a parallel study. Results are presented as mean and SEM, unless otherwise stated.

Blood pressure results are shown in Table 3. Captopril alone significantly reduced systolic blood pressure compared with baseline. There were no differences in blood pressure between treatments; however, it should be noted that doxazosin XL was required to meet targets in 8 of the 12 subjects. This was started during placebo run-in in all 8 patients. Three of these 8 patients then required dose adjustment during the treatment periods; 2 in the first treatment period and 1 in the second all corresponding to the captopril/placebo arm.

The effects of treatment on various biochemical parameters are shown in Table 4. There were no significant differences in measures of glycemia (fasting glucose, hemoglobin A1c, fasting insulin, fasting C peptide) or lipid profile. The triglyceride concentration was higher after captopril/bendroflumethiazide compared with captopril alone but this did not reach statistical significance. There was no difference in serum potassium concentration was higher after captopril/bendroflumethiazide compared with captopril alone.

Results from the euglycemic hyperinsulinemic clamp are summarized in Figure 1 and Table 5. Infusion of insulin 1 mU/kg per minute led to comparable steady-state plasma concentrations of insulin. Exogenous glucose infusion rates required to maintain euglycemia during the final 30 minutes of the glucose clamp were identical after both treatments (Figure 1). Endogenous glucose production in the basal state (an index of hepatic insulin sensitivity) was not significantly different after both treatments and during hyperinsulinemia was suppressed to a similar extent (Figure 2). Total rates of appearance and disappearance of glucose during the insulin infusion did not differ significantly between treatments.

**Discussion**

Essential hypertension is characterized by peripheral resistance to insulin with reduced insulin-mediated uptake of glucose in skeletal muscle, whereas hepatic sensitivity to insulin is normal. In this study, we have shown that exogenous glucose infusion rates during hyperinsulinemia were no different after treatment with captopril/bendroflumethiazide compared with captopril alone. Hepatic sensitivity to insulin, a good indicator of drug-induced changes, was assessed in detail. There were no differences in fasting endogenous glucose production or in endogenous glucose production during hyperinsulinemia. Furthermore, there were no significant differences in fasting insulin concentrations or indices of glycemic control.

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>7:5</td>
</tr>
<tr>
<td>Age, y*</td>
<td>59 (39–69)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.2 (1.0)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>140 (4)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>88 (2)</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>5.6 (0.1)</td>
</tr>
<tr>
<td>Fasting insulin, mU/L</td>
<td>9.0 (2.0)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.4 (0.1)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.84 (0.31)</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mmol/L</td>
<td>2.54 (0.23)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mmol/L</td>
<td>1.25 (0.10)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.17 (0.43)</td>
</tr>
</tbody>
</table>

HbA1c indicates hemoglobin A1c.

*Expressed as median (range).

### Table 2. Number of Patients on Antihypertensive Medications

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Blocker</td>
<td>0</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>6</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>2</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>2</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>5</td>
</tr>
<tr>
<td>sDiuretic</td>
<td>6</td>
</tr>
<tr>
<td>Statin</td>
<td>4</td>
</tr>
<tr>
<td>Fibrate</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 3. Effects of Treatment on Blood Pressure (mm Hg)

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>Captopril/Placebo</th>
<th>Captopril/Bendroflumethiazide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>End</td>
<td>Pre-treatment</td>
</tr>
<tr>
<td>Systolic</td>
<td>141 (4)</td>
<td>131 (4)†</td>
</tr>
<tr>
<td>Diastolic</td>
<td>85 (2)</td>
<td>83 (2)</td>
</tr>
</tbody>
</table>

P values denote P value for comparison between changes in blood pressure from baseline.

†P<0.05 systolic.

### Table 4. Effects on Measures of Glycemia and Lipid Parameters

<table>
<thead>
<tr>
<th>Metabolic Variables</th>
<th>CP</th>
<th>CB</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>5.6 (0.1)</td>
<td>5.6 (0.1)</td>
<td>0.9</td>
</tr>
<tr>
<td>Fasting serum insulin, mU/L</td>
<td>9.5 (1.7)</td>
<td>8.6 (1.2)</td>
<td>0.6</td>
</tr>
<tr>
<td>C peptide, ng/mL</td>
<td>2.0 (0.4)</td>
<td>1.4 (0.4)</td>
<td>0.5</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.6 (0.1)</td>
<td>5.6 (0.1)</td>
<td>0.4</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.77 (0.31)</td>
<td>4.82 (0.43)</td>
<td>0.8</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.07 (0.42)</td>
<td>2.59 (1.11)</td>
<td>0.6</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.31 (0.11)</td>
<td>1.32 (0.10)</td>
<td>0.8</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2.45 (0.23)</td>
<td>2.40 (0.23)</td>
<td>0.7</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio</td>
<td>3.95 (0.46)</td>
<td>3.99 (0.57)</td>
<td>0.9</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.28 (0.08)</td>
<td>4.23 (0.08)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

P values denote P value for comparison between end of period values.
Subjects were carefully selected from a group of primary care patients with blood pressure well controlled at baseline on no more than 2 antihypertensive agents. During the study, captopril alone significantly reduced blood pressure compared with baseline, but there were no differences observed between treatments. Two thirds of these subjects required the addition of doxazosin XL to keep blood pressure at target and, of these 8, 3 needed the dose titrated up subsequent to placebo run-in. Therefore, we must interpret comparative blood pressure data with caution. There were also no differences in effects on lipid profile but, as with other studies in which diuretics are combined with ACE inhibitors, there was a tendency for triglyceride concentrations to be higher after treatment with captopril/bendroflumethiazide, although this was not statistically significant.

Adverse metabolic effects of antihypertensive therapy have been suggested as an explanation for the less-than-expected reduction in cardiovascular events after lowering of blood pressure. Traditional antihypertensive agents, β-blockers and diuretics in conventional dose, worsen preexisting insulin resistance in hypertension. Such an effect occurs after short-term exposure and is more common in those with abdominal obesity. This has created a dilemma when choosing appropriate therapy. Although clinicians rely heavily on the results of long-term clinical outcome studies, inevitably these do not cover all situations where a decision about drug choice is required. Furthermore, evidence in support of guideline recommendations regarding the extent to which blood pressure should be lowered and resultant benefits is scanty. Stringent targets mean that several drugs are needed to control blood pressure adequately, and those with adverse effects on insulin action are often needed.

Our previous work in patients with essential hypertension has shown the ACE inhibitor captopril to have a neutral effect on insulin action. This is in agreement with findings by Petrie et al., whereas others have shown a beneficial impact. ACE inhibitors are recommended first-line treatment for many patients, and the combination of ACE inhibitor and calcium channel blocker now has the support of large-scale outcome trials. It has been suggested that because of the potential positive impact of ACE inhibition on insulin action, combining diuretics with ACE inhibitor may in part ameliorate adverse effects of thiazides; however, in patients with essential hypertension, there was still a negative effect when high-dose bendroflumethiazide was combined with captopril. In hypertensive type 2 diabetic patients, both conventional (2.5 mg) and low-dose (1.25 mg) bendroflumethiazide combined with captopril, when compared with captopril alone, resulted in increased insulin resistance. The current study aimed to establish whether these negative effects were also present when low-dose thiazide in combination with ACE inhibitor was given to nondiabetic patients with essential hypertension.

Overall our results are reassuring and add to the body of evidence supporting the use of diuretics in essential hypertension. We accept that this is a small study but, based on previous clamp data, it was adequately powered and there is no doubt that peripheral insulin sensitivity is the same after captopril/bendroflumethiazide compared with captopril/placebo. We note with interest the apparent difference in fasting endogenous glucose production. However, the $P$ value was far from reaching statistical significance, and the observation that fasting insulin was if anything slightly lower after the bendroflumethiazide combination is additional evidence tending against an adverse effect on insulin resistance.

Thiazides were superior in preventing major forms of cardiovascular disease in ALLHAT (2002), although a higher percentage of these patients developed diabetes mellitus. ALLHAT subjects were given chlorthalidone 12.5 mg once daily. Up titration to chlorthalidone 25 mg once daily was required in 40% and 56.9% at year 1 and 5, respectively. Recent meta-analysis shows doses of bendroflumethiazide equivalent to those of chlorthalidone are...
much more potent in blood pressure lowering effects.\textsuperscript{31} The dose of chlorthalidone (12.5–25 mg) used in ALLHAT is approximately equal to bendroflumethiazide 2 to 4 mg once daily. Cardiovascular outcomes have been achieved in ALLHAT using a slightly higher equivalent dose than that which we propose using to achieve neutral effects on insulin action; however, our previous studies have shown clearly that blood pressure lowering effects of bendroflumethiazide are the same with low (1.25 mg) and conventional doses (5 mg).\textsuperscript{10} In a large prospective study of 12,555 adults, patients on diuretics, calcium channel blockers, and ACE inhibitors were not at greater risk for the subsequent development of diabetes mellitus than those with hypertension not receiving any treatment. Patients on $\beta$-blockers had a higher incidence of diabetes mellitus.\textsuperscript{32} ACE inhibitors generally are associated with a lower incidence of diabetes mellitus compared with other agents.\textsuperscript{22,33,34}

Detrimental effects on insulin action of low-dose bendroflumethiazide combined with captopril\textsuperscript{13} compared with ACE inhibitor alone have been shown in hypertensive type 2 diabetic patients. By contrast, in this study of nondiabetic subjects with mild essential hypertension, which used an identical protocol, no such effect was observed and there was no difference in insulin action between treatments. It is difficult to explain why these changes occurred in hypertensive type 2 diabetic patients and not in patients with essential hypertension. One possible explanation that may account for the difference is the change in potassium concentrations. Previously, it has been shown that hypokalemia results in impaired insulin action, and it has been postulated that this could account for the glucose intolerance associated with thiazide diuretic usage.\textsuperscript{35} In this study, there were no differences in potassium concentrations after the bendroflumethiazide/captopril combination compared with captopril alone. When the same comparison was made in type 2 diabetic patients, the potassium levels were slightly but significantly lower after thiazide and ACE inhibitor. The actual difference was very small, so it is difficult to attribute the contrasting results to this alone.

A second explanation for the discrepancy between our results in diabetic and nondiabetic hypertensive patients relates to the fact that baseline insulin sensitivity and body mass index in our previous study of type 2 hypertensive diabetic patients were both higher than in the hypertensive patients in the present study. Although this difference is a little surprising, it is possible that if a less insulin-resistant group of hypertensive patients had been studied, there may have been more potential for an adverse effect on insulin action after low-dose thiazide diuretic.

Overall, these results are reassuring and should encourage physicians to continue to use low-dose diuretics in patients with essential hypertension who require combination therapy.

**Perspectives**

Thiazide diuretics are an effective and inexpensive treatment for hypertension and can reduce cardiovascular morbidity and mortality. Controversy over their use has arisen because of the potential detrimental effects on glucose metabolism, the mechanism of which is likely related to changes in insulin action. Most patients need combination therapy to lower their blood pressure to target. Diuretics are often used first line and then combined with ACE inhibitors. We have shown that, in patients with essential hypertension, when a low dose of thiazide is combined with an ACE inhibitor, there is no such adverse effect on glucose metabolism when compared with ACE inhibitor alone. Based on our results, physicians should be encouraged to continue to prescribe these effective drugs.

**Acknowledgments**

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**Disclosures**

None.

**References**

Diuretics are cheap and effective means of lowering blood pressure. No negative effect of low-dose diuretic has been shown.


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