Effect of Valsartan Addition to Amlodipine on Insulin Sensitivity in Overweight-Obese Hypertensive Patients

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Abstract

Objective The aim of the study was to evaluate the effect of valsartan/amlodipine combination on insulin sensitivity in overweight-obese hypertensive patients.

Methods After a 4-week placebo period, 58 overweight-obese (BMI ≥25 kg/m²) patients, with mild to moderate essential hypertension (DBP >95 and <110 mmHg, SBP >140 mmHg) were treated with amlodipine 5 mg od or valsartan 160 mg od or amlodipine 5 mg plus valsartan 160 mg od for 8 weeks according to a randomized, open-label, blinded end-point, cross-over study. At the end of the placebo period and each treatment period, blood pressure (BP) and insulin sensitivity (IS) (by euglycemic hyperinsulinemic clamp technique) were evaluated. IS was expressed as the amount of glucose infused during the last 30 min (glucose infusion rate, GIR) in mg/kg/min.

Results Valsartan/amlodipine combination produced a significantly greater decrease in SBP/DBP values (-22.3/16.7 mmHg, p<0.001 vs baseline) than valsartan (-15.2/11.7 mmHg, p<0.01 vs baseline) and amlodipine monotherapy (-16.1/12.6 mmHg, p<0.01 vs baseline). Both valsartan and amlodipine provided a significant increase in GIR (+1.24 mg/kg/min, p=0.036 vs baseline and +1.02 mg/kg/min, p=0.047, respectively), but such an increase was significantly greater with their combination (+1.82 mg/kg/min, p<0.01 vs baseline). These greater changes in IS were not related to BP changes.

Conclusion Valsartan/amlodipine combination improved IS more than respective monotherapy beyond affording greater BP reductions. This strengthens the rationale to use valsartan/amlodipine combination in the treatment of overweight-obese hypertensives.

Key words: valsartan, amlodipine, insulin-sensitivity, overweight, obesity, hypertension

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Introduction

It is widely accepted that excess weight and hypertension are closely related; the prevalence of elevated blood pressure increases progressively with increasing body mass index (BMI) and hypertension is about 6 times more frequent in obese than in lean subjects (1, 2). One possible pathogenetic link between obesity and hypertension is insulin resistance with consequent hyperinsulinemia (3, 4). Insulin resistance is commonly associated with obesity and is considered to increase blood pressure through renin-angiotensin system activation, sympathetic nervous system stimulation and vascular muscle cell proliferation (5, 6). The clustering of insulin resistance, obesity and hypertension, which frequently coexist with other metabolic risk factors, is associated with an increase in cardiovascular morbidity and mortality (3).

Although the current guidelines do not give specific recommendations for antihypertensive therapy of obese hypertensive patients, the need to improve the global risk profile in these high risk patients involves optimal pharmacological treatment of obesity hypertension that requires antihypertensive drugs that do not worsen and possibly improve insulin resistance and associated metabolic disturbances, beyond
lowering blood pressure (BP) levels (7, 8). Furthermore, since the response rates to antihypertensive drug therapy are notoriously low in overweight-obese patients (9, 10), two or more antihypertensive agents are requested to reach the BP goal of <140/90 mmHg in these patients.

Most data from the literature indicate that diuretics and beta-blockers reduce insulin sensitivity and increase lipid levels (11, 12); calcium channel blockers (CCB) are generally considered to be metabolically neutral (13), although some studies have indicated a positive impact on insulin sensitivity (14, 15). Blockade of the renin-angiotensin system (RAS) with angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) increases insulin sensitivity and decreases the risk for developing type 2 diabetes (11, 12, 16-18). Taking these effects into consideration, a combination of a RAS blocker and a CCB may be particularly appropriate in patients with obese hypertension. While the combination of an ACE-I plus a CCB is well established in antihypertensive strategy (19), the ARB plus CCB combination represents a new addition to the available antihypertensive treatment options. To our knowledge, no study has previously evaluated the effects of such a combination on insulin sensitivity in overweight-obese hypertensive patients.

Given this background, the present study was undertaken to assess the effects on insulin sensitivity of the ARB valsartan plus the CCB amlodipine combination as compared to either drug alone in the treatment of hypertension in overweight-obese patients.

Study Protocol

At the end of an initial 4-week wash-out placebo period, during which any eventual antihypertensive drug was discontinued and placebo was administered, patients fulfilling the inclusion criteria were randomly treated with amlodipine 5 mg od or valsartan 160 mg od or amlodipine 5 mg plus valsartan 160 mg od, each given once daily at the same hour in the morning (approximately between 08:00 and 09:00) for 8 weeks in three crossover periods each separated by a 2-week placebo period.

Patients were checked at the end of the placebo wash-out period and at the end of each active treatment period. At each visit, clinic BP, heart rate (HR), and insulin sensitivity (IS) were evaluated. BP was measured in the morning before daily drug intake (i.e. 24 hour after dosing, at trough) by using a standard mercury sphygmomanometer (Korotkoff I and V), with a cuff of appropriate size, after the patient was seated for 5 minutes in a quiet room. Three consecutive measurements taken at 1 minutes interval were averaged and used as the clinic BP value. HR was measured by pulse palpation at the level of the radial artery.

Insulin-sensitivity evaluation

On the same day, 1 hour after the subjects had received their medication, insulin sensitivity was assessed by the euglycemic hyperinsulinemic clamp, according to the technique of De Fronzo et al (21). At 9 a.m., after the subjects had fasted 12 hour overnight, an intravenous catheter was placed in an antecubital vein for infusion of insulin and 20% glucose. A second catheter was inserted into a brachial artery for blood sampling. A 10-min priming infusion of insulin (Actrapid HM, Novo Industries, Copenhagen, Denmark), calculated as the amount required to increase plasma insulin concentration to 100 U/mL during the insulin clamp, was followed by a constant infusion of 40 mU/min/m² of body surface area for 110 minutes. During insulin infusion, normal fasting blood glucose levels were maintained by adjustment of the infusion of a 20% glucose solution. The amount of glucose taken up (milligram per kilogram of body weight per minute) was calculated for each 10-min interval after the first 20 minutes of the clamp. Insulin sensitivity was calculated from the mean glucose uptake rate for the last 30 minutes of the clamp and expressed as the amount of glucose infused during that time (glucose infusion rate: GIR) in mg/kg/min.

The total amount of exogenous glucose required to maintain a steady-state blood glucose level in response to a defined increase in plasma insulin concentration (total glucose requirement: TGR) was also evaluated.

Blood glucose in the fasting state and during glucose clamp studies was measured by the glucose oxidase method (Beckman Auto-Analyzer, Fullerton, CA, USA). Plasma insulin concentrations were determined by radioimmunoassay (RIA).
The main results of the study are shown in Table 1. Both amlodipine and valsartan monotherapy significantly reduced BP values: the mean decrease in SBP/DBP values was 16.1/12.6 mmHg with amlodipine (p<0.01 vs baseline) and 12.6/11.7 mmHg with valsartan (p<0.01 vs baseline). Combination therapy with valsartan plus amlodipine produced a significant greater reduction in BP values than either drug alone. The mean decrease was 22.3 mmHg for SBP (p<0.001 vs baseline and <0.01 vs valsartan or amlodipine) and 16.7 mmHg for DBP (p<0.001 baseline and p<0.01 vs valsartan, p<0.05 vs amloidipine).

During the euglycemic hyperinsulinemic clamp, plasma insulin levels increased acutely and remained at steady state plateau (mean value 102.8 U/mL during placebo, 103.1 U/mL during amlodipine, 102.9 U/mL during valsartan and 102.5 U/mL during combination). The mean rate of glucose uptake for the last 30 min of the clamp (GIR), considered as an index of insulin sensitivity, was significantly increased by both valsartan and amlodipine monotherapy: the mean increase in GIR was 1.02 mg/kg/min (p=0.047 vs baseline) with amlodipine and 1.24 mg/kg/min (p=0.036 vs baseline) with valsartan. With the valsartan/amlodipine combination GIR increase was of 1.82 mg/kg/min (p<0.01 vs baseline, p<0.05 vs amlodipine) (Fig. 1).

Also the total amount of exogenous glucose required to hold glucose level constant during the clamp (TGR) was significantly increased by total monotherapy (+2.1 g with amlodipine, p<0.041 vs baseline and +3.1 g with valsartan, p=0.02 vs baseline), but the increase was greater with the combination (+4.4 g, p<0.01 vs baseline, p<0.05 vs both monotherapies) (Fig. 2). Plasma insulin was significantly reduced by valsartan/amlodipine combination (by a mean of 12.8 pmol/L, p=0.044 vs placebo), but not by the two monotherapies. There was no significant change in BMI, body weigh and fasting blood glucose during the 3 different treatments. GIR changes showed a weak relationship with DBP changes with amlodipine alone (r=0.44, p<0.05), but not by the two monotherapies.

### Discussion

The results of this study showed that in overweight-obese hypertensive patients treatment with valsartan/amlodipine combination afforded greater BP reductions compared with the monotherapy components. This is in agreement with previous observations (22, 23) and confirms that combination of these two agents, targeting multiple mechanisms involved in BP regulation, is effective in patients whose BP is often considered difficult to control (24).
The most interesting findings, however, regard the effects of the study medications on insulin sensitivity as assessed by the glucose clamp technique, which is considered to be the gold standard for evaluating insulin sensitivity (21, 25). In the present study we found that both valsartan and amlodipine monotherapy improved insulin sensitivity in terms of both GIR and TGR increase, but such an increase was significantly greater with their combination. Further, the plasma insulin levels were significantly reduced by valsartan/amlodipine combination but not by the two monotherapies. Since no significant relationship was found between GIR and SBP/DBP changes produced by combination therapy, the more positive effect of valsartan/amlodipine combination on insulin sensitivity probably resulted from the combined action of the CCB and the ARB with mechanisms other than the greater BP reduction.

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CCB are generally reported to be neutral in their effects on glucose homeostasis (13), but some studies have shown their positive effect on insulin sensitivity (14, 15) and a meta-analysis suggested that antihypertensive treatment with CCB is associated with lower rates of new-onset diabetes mellitus compared to diuretics and beta-blockers (26). Two main mechanisms have been proposed for the increase of insulin sensitivity with CCB. First, these agents produce vasodilation and enhance blood flow to skeletal muscle; this may increase insulin and glucose delivery and enhance the non-oxidative pathways of glucose utilization (27). Secondly, CCB may increase insulin sensitivity at the cellular level, by decreasing the cytosolic free calcium concentrations (28). In the present study a weak but significant positive relationship between the GIR and the DBP changes was found with amlodipine monotherapy, which suggests a role of BP lowering in amlodipine mediated increase in insulin sensitivity.

Although some controversial data have been initially reported in the literature, with some studies showing no effect on insulin sensitivity (29-31), current opinion is that ARB exert a positive influence on insulin sensitivity, particularly in patients with insulin resistance (32, 33). Mechanisms by
which ARB improve insulin sensitivity are still debated. They may include increased glucose uptake in skeletal muscle via increased glucose and insulin delivery due to their vasodilatory effect. However, valsartan has been shown to be associated with lower rates of new onset diabetes mellitus compared to amlodipine in the VALUE study (34), which suggested that blockade of the RAS affected glucose metabolism through mechanisms other than the vascular vasodilating and BP lowering effects alone. Possible alternative explanations include the following:

a) enhancement of insulin release by the pancreatic beta-cells through increased local blood supply (35); in addition to reducing the vasoconstrictive effect of angiotensin II on the vasculature of the endocrine pancreas, ARB may also prevent angiotensin II mediated fibrotic or other degenerative changes that could compromise beta-cell function (36);

b) stimulation of the insulin signal cascade: the molecular basis of insulin resistance involves defects in several steps of the signalling pathway, including serine phosphorylation of the insulin receptor (IRS), degradation of IRS protein and altered activity of phosphoprotein phosphatases. In obese Zucker rats, an animal model of the human metabolic syndrome, an administration of an ARB enhances insulin signalling through a reduction in insulin receptor Ser994 phosphorylation (37) and increased GLUT4 protein expression (38);

c) improvement of glucose homeostasis at the cellular level through agonistic interaction with peroxisome proliferator activated receptor (PPR)-gamma (39);

d) increase in plasma adiponectin levels: adiponectin is an adipocyte derived insulin sensitizer with anti-inflammatory and antiatherogenic functions whose levels are negatively correlated with insulin resistance (40). In some clinical studies with ARB, adiponectin levels, which are typically low in obese patients, increased in parallel to the improvement in insulin resistance (41, 42). RAS blockade might increase adiponectin levels by suppressing tumor necrosis factor (TNF)-alfa synthesis (43), by preventing oxidative stress (44) or by increasing adipogenesis and adipocyte differentiation resulting in greater adiponectin production (45);

e) increase in serum levels of insulin-like growth factor (IGF)-1, which plays an important role in the regulation of glucose metabolism by increasing peripheral glucose uptake and decreasing hepatic glucose production (46); in both experimental and clinical studies treatment with ARB raised serum levels of IGF-1, which paralleled the improvement of insulin resistance (47, 48);

f) reduction in plasma leptin levels: this adipocyte-derived hormone, whose levels have been found elevated in obese hypertension, is involved not only in the control of body fat and energy metabolism but also in cardio-renal regulation and in atherogenesis (49). Some animal and human studies showed that ARB decreased leptin levels together with insulin resistance (50, 51), perhaps by inhibiting the expression of adipocyte genes that regulate leptin production (52);

g) prevention of hypokalemia: this may preserve the insulin secretory response of pancreatic beta-cells to glucose, which is decreased during hypokalemia (53).

Whether the greater improvement of insulin sensitivity obtained with valsartan/amlodipine combination may result in a greater degree of protection from cardiovascular complication of hypertension remains to be demonstrated. However, in high risk patients like overweight-obese hypertensive patients use of drugs that decrease insulin resistance beyond assuring better BP control should be preferable.

Conclusions

The results of this study indicate that in overweight/obese hypertensive patients valsartan/amlodipine combination improved insulin sensitivity more than monotherapy with either component beyond affording greater BP reduction. This strengthens the rationale to use this type of combination therapy in these high risk patients.

References


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