Angiotensin II Type 1 Receptor Blocker Combined with Calcium Channel Blocker for the Treatment of Obese Hypertensive Patients

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Angiotensin II (Ang II) receptor blockers (ARBs) are highly selective for the Ang II type 1 (AT1) receptor, which is a member of the G protein-coupled receptor (GPCR) superfamily, and block the diverse effects of Ang II. Hypertension (HT) and diabetes mellitus (DM) frequently coexist, and their association provides an additional increase in the risk of cardiovascular events. Renin-angiotensin system (RAS) blockers, such as ARB or angiotensin-converting enzyme inhibitor (ACEI), have been recommended as the first choice for lowering BP in patients with DM. In addition, clinical trials have shown a reduced incidence of new-onset DM in patients treated with RAS blockers compared with placebo (1, 2). ARBs have been shown to improve insulin sensitivity and decrease cardiovascular morbidity and mortality in patients with hypertensive diabetic nephropathy with proteinuria (3), in addition to their blood pressure-lowering effects in hypertensive patients. The Guidelines for the Management of Hypertension reported by the Japanese Society of Hypertension (2004) recommended blood pressure (BP) goals of <130/80 mmHg for patients with DM (4). Since BP is not adequately controlled in two-thirds of patients, combination therapy is needed to achieve the control of BP. Several combination therapies are now available, including RAS blockers + calcium channel blockers (CCB) or diuretics. When the additional antihypertensive effects of an ACEI, a dihydropyridine CCB and a diuretic were compared in patients whose hypertension was not controlled by ARB monotherapy, the antihypertensive effects of the ARB/CCB and ARB/diuretic combinations were superior to that of the ARB/ACEI combination (5). The negative effect of diuretic on the enhancement of insulin resistance may have counteracted the beneficial effect of the ARB. Fogari et al previously reported in Internal Medicine (6) that the combination ACEI/CCB but not ARB/diuretic significantly decreases insulin resistance, despite similar BP-lowering effects, in obese hypertensive patients. ARB/diuretic combinations can not be used in hypertensive patients with metabolic disorders including obesity. Since CCBs are generally neutral in their effects on insulin sensitivity, the ARB/CCB combination may increase insulin sensitivity and induce a significant depressor effect in hypertensive patients.

More recently, Fogari et al (7) add critical new insights regarding the effects of the ARB/CCB combination on insulin sensitivity in hypertensive patients, because no previous study has examined the effects of this combination on insulin sensitivity in overweight-obese hypertensive patients. The study included 58 overweight-obese patients (body mass index ≥ 25 kg/m^2) with mild to moderate essential hypertension. The patients were treated with the CCB amlodipine 5 mg/day or the ARB valsartan 160 mg/day or amlodipine 5 mg/day + valsartan 160 mg/day for 8 weeks. The ARB/CCB combination induced a significantly greater reduction in BP than ARB or CCB monotherapy. This combination was very useful for the reduction of BP. This is consistent with a previous report (5) and confirms that a combination that targets BP reduction is effective in obese hypertensive patients whose BP is difficult to control. United States Food and Drug Administration has given the commercial go-ahead to a once-daily medication for hypertension (Exforge®) that combines valsartan with amlodipine. In addition, in this study each ARB and CCB significantly increased insulin sensitivity. The CROSS (Candesartan Role on Obesity and on Sympathetic System) study was undertaken to examine the antihypertensive and metabolic effects of ARB candesartan in obese hypertensive individuals (8). Candesartan significantly reduced BP and increased insulin sensitivity. Although it is well known that ARB improves insulin sensitivity, controversial data have been reported about CCB in the literature (9, 10). This study clearly indicated that CCB monotherapy improved insulin sensitivity in obese hyperten-
sive patients. The authors also found a weak but significant positive relationship between insulin sensitivity and the diastolic BP changes with CCB monotherapy. They discussed the mechanisms by which CCB may induce vasodilatation, enhance blood flow in skeletal muscle and decrease the cytosolic free calcium concentration. CCB may be useful in obese but not in lean hypertensive patients due to the effects on insulin sensitivity through the strong effect of vasodilatation.

The most important finding by Fogari et al (7) is that theARB/CCB combination had a greater positive effect on insulin sensitivity than each monotherapy, while no significant relationship was found between BP and the improvement of insulin sensitivity produced by the combination therapy. The mechanisms of ARB and CCB may not overlap because ARB may improve beta-cell function (11), and increase GLUT-4 expression (12), peroxisome proliferative activated receptor-gamma activity and the adiponectin level (13). These mechanisms are vastly different from the previously described mechanisms of CCB.

The present study (7) attempted to elucidate the effectiveness of ARB/CCB combination therapy compared to either medication alone on BP reduction and insulin sensitivity in the treatment of obese hypertensive patients. Previous studies on combination therapies have considered rather small populations and the observation period was relatively short. Large, randomized clinical trials are needed to directly compare ARB/CCB with other combination therapies. Although the effectiveness of CCB on insulin sensitivity is controversial and we may not need to use ARB/CCB combination therapy in every patient with hypertension until more useful data are available, this combination is effective for lowering BP and improving insulin sensitivity, and can be prescribed for obese hypertensive patients.

References


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