Angiotensin II Type 1 Receptor Blocker Combined with Hydrochlorothiazide for the Treatment of Hypertension

Shin-ichiro Miura and Keijiro Saku

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Hypertension is a critical risk factor for cardiovascular disease that affects an estimated 35 million people in Japan. According to the Japanese Society of Hypertension 2004 Guidelines for the Management of Hypertension, recommended BP goals are <130/85 mmHg, or <130/80 mmHg for patients with diabetes mellitus (DM) or chronic kidney disease (CKD) (1). Since two-thirds of patients do not have blood pressure (BP) adequately controlled, combination therapy is needed to achieve the control of BP.

Renin-angiotensin system (RAS) blockers, such as angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II (Ang II) type 1 (AT1) receptor blocker (ARB), have been recommended as the first choice for lowering BP in patients with DM or CKD (1). ARBs are highly selective for the AT1 receptor, which is a member of the G protein-coupled receptor superfamily, and can block the diverse effects by Ang II. In addition to their beneficial effects for the treatment of hypertension, ARBs as well as ACEI have also been associated with a decrease in cardiovascular morbidity and mortality. Although RAS blockers are useful for lowering BP, 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. Several studies have shown evidence that the combination of ARB and thiazide is an effective antihypertensive therapy. More recently, Preminent was released in Japan. The combination of losartan with hydrochlorothiazide (HCTZ) may reduce BP more effectively than monotherapy with either compound (2). Thiazide diuretics promote sodium excretion, and lead to a reduction in plasma volume and peripheral resistance. Diuretics may also activate the RAS, and BP is more dependent on Ang II. The counter-regulatory mechanism may help to explain why the combination of an ARB with HCTZ is effective.

The combination of ARB/thiazide diuretic has been compared to other combinations. Recently, Shimosawa et al (3) compared the efficacy and safety of combination therapy with losartan/HCTZ and candesartan (ARB)/amlodipine (CCB) in hypertensive patients. The two combination therapies were equally effective at reducing BP. The combination of losartan/HCTZ had no adverse effects on uric acid, lipid profile or hemoglobin A1c, and was more cost-effective than the combination ARB/CCB. More recently, an interesting study was performed on the efficacy and safety of ARB/HCTZ compared with ACEI/CCB. Fogari et al reported in Internal Medicine (4) that the combination delapril (ACEI)/manidipine (CCB) but not ARB/HCTZ significantly decreased insulin resistance and plasma fibrinogen, despite similar BP-lowering effects, in obese hypertensive patients. In their study, 88 obese, hypertensive patients were randomized to receive delapril 30 mg/manidipine 10 mg or olmesartan (ARB) 20 mg/HCTZ 12.5 mg for 24 weeks. The glucose infusion rate after treatment was significantly increased and plasma insulin or fibrinogen was significantly decreased only with delapril/manidipine. There are at least two possible reasons why they reported that delapril/manidipine significantly decreased insulin resistance compared to olmesartan/HCTZ. First, they enrolled 88 obese hypertensive patients, and the body mass index (BMI) was more than 30 (33.5±0.9 kg/m², mean ± standard deviation). In contrast, the mean BMI in the study of Shimosawa et al (3) was 24.9 kg/m². This difference is critical because obese patients have greater insulin resistance. Second, there are some differences in the pharmacological effects of ACEI and ARB. ACEI decreases the degradation of bradykinin which mediates vasodilation with increased capillary area and vascular permeability, and increases glucose and insulin delivery to tissue (5). On the other hand, a double-blind study investigated the efficacy of delapril 30 mg/manidipine 10 mg compared to losartan 50 mg/HCTZ 12.5 mg in patients with hypertension and controlled type 2 DM for 12 weeks (6). Decreases in mean BP were seen with both combinations, and compliance and adverse events were comparable in both groups.

Department of Cardiology, Fukuoka University School of Medicine, Fukuoka
Correspondence to Dr. Keijiro Saku, saku-k@cis.fukuoka-u.ac.jp
Further investigations are needed to confirm whether ACEI/CCB is more effective than ARB/HCTZ with regard to adverse events including insulin resistance.

Fogari et al (4) also observed that there were no adverse effects on insulin resistance, lipid profile or fibrinogen with olmesartan/HCTZ. The CROSS (Candesartan Role on Obesity and on Sympathetic System) study was undertaken to examine the antihypertensive, neuroadrenergic, and metabolic effects of candesartan in comparison with HCTZ in obese hypertensive individuals (7). Candesartan significantly reduced BP and increased insulin sensitivity. In contrast, HCTZ significantly worsened insulin sensitivity. Thus, the negative effect of HCTZ on the enhancement of insulin resistance may have counteracted the beneficial effect of the ARB. If a low dose of HCTZ is used in ARB/HCTZ combination therapy, the combination would not influence insulin resistance.

Present and future direction of the use of an ARB combined with HCTZ

HCTZ monotherapy was approved at recommended doses of 25 to 100 mg/day to induce effective BP lowering, while such doses also show a higher incidence of side effects (8). In this regard, it is important to determine the optimal dose of HCTZ in ARB/HCTZ combination therapy. Several clinical reports have indicated that HCTZ at 12.5 mg with 50 mg losartan has a greater antihypertensive effect than losartan monotherapy without adverse effects (2, 9, 10). Fixed-dose combination therapy was well-tolerated and more efficient at lowering BP than monotherapy, and is therefore an excellent choice for hypertensive patients in whom combination therapy is necessary to achieve additional reductions in blood pressure. In addition to ARB/HCTZ, the ACEI/CCB combination is also an option for effectively lowering BP and insulin sensitivity. Although the ARB/HCTZ combination is clearly more cost-effective than the ARB/CCB combination, ACEI/CCB has a cost performance similar to ARB/HCTZ. Previous studies on combination therapies have considered rather small populations and the observation periods have been relatively short. Large, randomized clinical trials are needed to directly compare ARB/HCTZ with other combination therapies.

Conclusion

Although we do not need to use ARB/HCTZ in every patient with hypertension until more useful data are available, this combination is effective and safe for lowering BP, and can be prescribed at least for non-obese hypertensive patients.

References


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