Clinical Efficacy and Safety of Losartan/Hydrochlorothiazide Combination Therapy

Shin-ichiro Miura and Keijiro Saku

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Hypertension (HT) is a potent risk factor for cardiovascular and cerebral events. HT is estimated to be insufficiently managed in about two-thirds of patients, and most hypertensive patients require two or more drugs to achieve the target blood pressure (BP) control (1).

Thiazide diuretics such as hydrochlorothiazide (HCTZ) have been considered the first-line treatment for hypertension, and several fixed-dose combinations with other classes of antihypertensive agents such as calcium channel blockers (CCBs) and angiotensin II type 1 receptor blockers (ARBs) are now available. The antihypertensive effect of combination therapy is additive or synergistic, and the prevalence of adverse events is less than would be expected with additive effects (2).

Maeda et al. reported in Internal Medicine (3) that the combination of losartan (50 mg/day)/HCTZ (12.5 mg/day) had an early depressor effect, good tolerability, and stable long-term benefits in 614 patients with HT that was not controlled by ARB monotherapy or combination therapy with a CCB (ARCH study). The mean change in systolic BP (SBP)/diastolic BP (DBP), the primary endpoint, was -19.7/-9.7 mmHg at month 3. Moreover, they sought to identify the patient subgroups in which losartan/HCTZ was the most effective. It would be very important if we could anticipate what patients will show a strong antihypertensive response to the use of ARB/HCTZ. They showed that only alcohol consumption had a significant negative effect on changes in both SBP and DBP. The mean daily alcohol consumption was equivalent to 300 mL of sake. They suggested that patients who drink more alcohol generally have a more disordered diet and lifestyle than those who do not drink alcohol. Japanese Society of Hypertension Guideline 2009 recommends that drinking, in terms of ethanol intake, should be restricted to 20-30 mL (equivalent to 180 mL of sake) (1). Patients who are receiving ARB/HCTZ combination therapy should be instructed not to drink more than 180 mL (of sake) per day. In addition, they identified that elderly and female patients have clinical features of salt-sensitive hypertension, which might contribute to the greater reduction of SBP using losartan/HCTZ.

Thiazide diuretics can produce adverse effects, such as hyperuricemia, dyslipidemia, glucose intolerance and hypokalemia (4). The ARCH study (3) demonstrated that the long-term (1 year) use of losartan/HCTZ was safe. Only 5.2% of the patients (32/614) experienced adverse events (total 35) over the entire observation period. There are several reasons why the long-term use of losartan/HCTZ was safe. First, the dose of HCTZ was only 12.5 mg/day (half of the standard dose). The metabolic effects of thiazides are dose-dependent (4). For example, the increase in serum cholesterol has been shown to be 1% at half the standard dose, 3% at the standard dose, and 5% at twice the standard dose. Thiazides at half the standard dose were also less effective at decreasing serum potassium (K), increasing blood glucose, and increasing serum UA (4). Second, ARBs improve insulin resistance and induce hyperkalemia. When administered in combination with HCTZ, losartan can attenuate the increase in insulin resistance caused by HCTZ and HCTZ can attenuate the increase in serum K levels caused by losartan. Third, most ARBs have class (or common) effects, although recent clinical studies have demonstrated that not all ARBs have the same effects and some benefits conferred by ARBs may not be class effects, but rather molecular (or differential) effects (5). For example, losartan has a molecular effect, which is its uricosuric action. On the other hand, antihypertensive therapy with add-on low-dose valsartan significantly increased serum UA levels (6).
Conclusion

Losartan/HCTZ combination therapy provided a significant reduction in BP and patients were able to achieve their target BP. Patients who receive ARB/HCTZ combination therapy should be instructed to reduce their daily alcohol consumption. Moreover, elderly and female patients have clinical features of salt-sensitive hypertension, which might contribute to the greater depressor effect of this combination therapy.

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References