Effect of Temocapril Hydrochloride on Serum Lipid Levels in Patients with Hypertensive Type 2 Diabetes Mellitus

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The effect of angiotensin converting enzyme inhibitor, temocapril hydrochloride on the serum lipoproteins, and especially on the size of low density lipoproteins (LDL) of hypertensive diabetic patients, were studied. Temocapril hydrochloride (5 mg/day) was administered to 32 hypertensive type 2 diabetes patients for 16 weeks. During treatment, systolic and diastolic blood pressures decreased significantly from 162/95 mmHg to 138/76 mmHg at 16 weeks (p < 0.001), and serum levels of total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) showed significant reduction, but those of HbAlc, triglycerides (TG) and high density lipoprotein cholesterol (HDL-C) showed no significant changes. LDL particle size evaluated by polyacrylamide gel disc electrophoresis was normalized from small size. It is concluded that temocapril hydrochloride favorably affects the serum lipoprotein metabolism of hypertensive type 2 dependent diabetes mellitus patients. J Atheroscler Thromb, 2001; 8 : 25-29.

Key words: Temocapril hydrochloride, Hypertensive diabetic patient, LDL particle size

Introduction

Both diabetes and hypertension are independent risk factors of atherosclerosis and the combination of these factors further increases the risk (1). In particular, diabetes mellitus sometimes associates with lipoprotein metabolism disorders, such as hypertriglyceridemia, HDL-hypcholesterolemia, and reduction in the LDL particle size (2), and these lipoprotein disorders themselves are risk factors for macroangiopathy (3). Therefore, when an antihypertensive agent is administered to diabetes mellitus patients complicated with hypertension, it is preferable for the drugs to not deteriorate the lipid metabolism.

Temocapril hydrochloride, which is an inhibitor of angiotensin converting enzyme that converts angiotensin I into angiotensin II, has been shown to have a hypertensive effect in clinical studies (4). However, there are few detailed reports concerning the influence of this drug on the serum lipoprotein metabolism.

In the present study, we administered temocapril hydrochloride to patients with hypertensive type 2 diabetes mellitus (type 2 DM) and examined the serum lipid levels and particle size of LDL.

Subjects and Methods

Subjects and methods

Thirty two type 2 DM patients (11 males and 21 females) complicated with hypertension in our hospital were enrolled in this study. The diagnosis of diabetes was made in accordance with the standards of diagnosis of the Japan Diabetes Society (5). The diagnosis of hypertension was made, when systolic blood pressure exceeding 150 mmHg and diastolic blood pressure exceeding 90 mmHg were observed at least twice in a sitting position. A tablet containing 2 mg of temocapril hydrochloride was administered once a day in the morning, and the monitoring term was for 16 weeks. During this period, no other hypotensive agent nor lipid-lowering agent was adminis-
tered. Type 2 DM was treated by diet therapy in 24 patients and by administration of sulfonyl urea in 8 patients. Neither the therapeutic method nor the dose of the sulfonyl urea was changed. No changes in body weight were recognized during the administration of temocapril hydrochloride. The clinical features of patients receiving temocapril hydrochloride are shown in Table 1.

**Parameters measured**

Blood pressure and HbA1c were measured once a month. The TC, TG and HDL-C levels were measured once a month. LDL particle size was evaluated using the Rm ratio (Fig. 1) obtained from a densitometric pattern of polyacrylamide gel (PAG) disc electrophoresis of serum lipoproteins (6). Determination of LDL size was performed before and after 16-week administration of temocapril hydrochloride. A decrease in Rm ratio means an increase in LDL particle size on PAG disc electrophoresis. Blood was collected in the morning, following fasting since lunch time on the previous day before. TC and TG were assayed by an autoanalyzer (HITACHI 1500), and HDL-C was assayed by direct assay method using polymers (7). LDL cholesterol was calculated by Friedewald’s equation (8). Statistical analysis was performed using the Student’s t-test.

### Results

**Changes in blood pressure after administration of temocapril hydrochloride**

The mean systolic blood pressure was 162 ± 8 (mean ± SD) mmHg and the mean diastolic blood pressure was 95 ± 4 mmHg before the administration of temocapril hydrochloride. After 4 weeks of administration, the diastolic blood pressure decreased significantly to 80 ± 3. After 16 weeks of administration, the systolic blood pressure and diastolic blood pressure decreased significantly to 138 ± 6 and 76 ± 4, respectively (Fig. 2).

**Changes in HbA1c after administration of temocapril hydrochloride**

Mean HbA1c was 8.4 ± 0.4% before the administration of temocapril hydrochloride. It decreased to 7.8 ± 0.5% after 16 weeks of administration, but the difference was not significant (Fig. 3).

**Changes in TC and TG levels after administration of temocapril hydrochloride**

The mean TC levels decreased to the level of 5.5 ± 2.2% after 16 weeks of administration (Fig. 4). In the patients with TC levels higher than 220 mg/dl, a more remarkable decrease was observed (8.6 ± 4.7%, p < 0.05) (Fig. 4).

TG levels decreased to the level of 5.5 ± 2.2% after 16 weeks of administration. The statistical analysis was performed using the Student’s t-test.
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weeks of administration (Fig. 5). In patients with TG levels higher than 150 mg/dl, a similar change was observed (Fig. 5).

Changes in HDL-C after administration of temocapril hydrochloride

The HDL-C levels decreased to 5.1±2.4% after 4 weeks of administration of temocapril hydrochloride in all patients (Fig. 6). However, HDL-C levels then increased to 3.3±2.2% after 16 weeks of administration (Fig. 6). Similar changes were observed in the patients with HDL-C levels lower than 40 mg/dl (Fig. 6).

Changes in LDL-C after administration of temocapril hydrochloride

The LDL-C levels decreased to 6.3±3.1% (Fig. 7) in all patients, and decreased to 6.1±3.1% (Fig. 7) in the patients with LDL-C levels higher than 150 mg/dl with a significant difference.

Changes in Rm ratio after administration of temocapril hydrochloride

The Rm ratio decreased significantly from 0.383±0.05 to 0.371±0.06 after 16 weeks of administration of temocapril hydrochloride (Fig. 8).

Discussion

Temocapril hydrochloride was administered at a dose of 5 mg/day to type 2 diabetes mellitus patients with hypertension, and the patients were followed for 16 weeks. Significant decreases in blood pressure, TC level, and LDL-C level, decreases in TG level and HbA1c, and a significant decrease in Rm ratio were observed. No influence was observed on HDL-C.
Concerning the influence of angiotensin converting enzyme inhibitors on the lipid metabolism, it was reported that captopril showed a decrease effect on TC and TG levels and an increase effect on HDL-C (9). In the present study on temocapril hydrochloride, although TC and TG levels were reduced, no HDL-C increase effect was observed. This result can be attributed to the fact that patients with diabetes were selected as subjects in our study, and HDL-C elevation was considered to be disease-specific. Although HDL-C level showed an initial tendency toward decrease, it was then elevated to almost the preadministration level. Generally, this drug is not considered to adversely affect HDL-C levels. The results suggested that temocapril hydrochloride may favorably affect serum lipid levels in type 2 diabetes patients with hypertension.

Recently, the appearance of small-density LDL was reported as one of the abnormalities of the lipoprotein metabolism due to diabetes mellitus, and attracted attention as a cause of ischemic heart disease (2). We evaluated the effect of temocapril hydrochloride on LDL particle size using the Rm ratio calculated from densitometric analysis of PAG disc electrophoresis. Since separation of lipoprotein by PAG disc electrophoresis depends on the particle size rather than on the electric charge, a decrease in Rm ratio indicates an increase in particle size. In this study, the Rm ratio was decreased by the administration of temocapril hydrochloride, indicating that the drug acts to normalize LDL particle size. Small-density LDL is reported to appear in patients with hypertriglyceridemia (10). The LDL particle normalizing effect of temocapril hydrochloride is suggested to accompany a decrease of triglyceride level.

Although the present study showed that temocapril
hydrochloride had a favorable effect on the lipid metabolism in hypertensive diabetic patients, the details of its mechanism have not been clarified. A triglyceride lowering effect was recognized in drugs acting to reduce peripheral vessel resistance and to improve peripheral vessel circulation (11). Since temocapril hydrochloride inhibits angiotensin converting enzyme and dilates the vessels to exert its hypotensive effect, it is suggested that temocapril hydrochloride act to reduce the peripheral vascular resistance and increase the peripheral vessel circulation, and might promote the catabolism of VLDL. Accordingly, the mechanism of temocapril hydrochloride on lipid metabolism is considered to be indirect.

In this study, a reduction in HbA1c was also observed. Since the therapy for diabetes mellitus was not changed during the observation period, it is suggested that the improving effect of temocapril hydrochloride on peripheral vessel hemodynamics might improve insulin-sensitivity. It is also considered to be a factor of normalization of LDL particle size. Further investigation is required for clarification.

References