Case Report

Effects of Losartan on Blood Pressure and Humoral Factors in a Patient Who Suffered from Anaphylactoid Reactions When Treated with ACE Inhibitors during LDL Apheresis

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In a patient who was taking an angiotensin-converting-enzyme inhibitor, low-density lipoprotein (LDL) apheresis with dextran-sulfate cellulose provoked hypotension accompanied by lacrimation and blurred vision. Hypotension was eliminated by changing the anticoagulant from heparin to a protease inhibitor, nafamostat mesilate. A study was undertaken to clarify whether an antagonist of angiotensin type 1-receptor, losartan, could be safely used in the same patient during LDL apheresis treatment. Blood pressure and humoral factors were compared between the apheresis sessions with losartan and those without. Although angiotensin II and bradykinin plasma levels during LDL apheresis were significantly greater with losartan than without, blood pressure reduction by losartan was mild and unpleasant symptoms were not induced. Losartan was thus safely used for this patient during treatment by LDL apheresis. The greater rise in bradykinin levels during apheresis with losartan might be ascribable to angiotensin type 2-receptor stimulation. (*Hypertens Res* 2001; 24: 595–598)

Key Words: LDL apheresis, bradykinin, angiotensin converting enzyme inhibitors, angiotensin receptors

Introduction

Several randomized controlled trials (1, 2) have demonstrated that angiotensin-converting-enzyme (ACE) inhibitors reduce morbidity and mortality in patients with heart failure and myocardial infarction. One of the major risk factors of myocardial infarction is hypercholesterolemia. Severe hypercholesterolemia resistant to anti-lipidemic drugs can be corrected using low-density lipoprotein (LDL) apheresis (3). The negative charges of dextran-sulfate cellulose (DSC) used for selective adsorption of LDL activate the intrinsic coagulation pathway (4). In the activation of the intrinsic coagulation pathway by DSC-LDL apheresis, plasma kallikrein, converted from plasma prekallikrein, catalyzes

high-molecular-weight kininogen to produce a large amount of bradykinin (5). Olbricht *et al.* (6) reported episodes of anaphylactoid reactions during DSC-LDL apheresis in two patients who were taking angiotensin-converting-enzyme (ACE) inhibitors. They proposed that the anaphylactoid reaction and hypotension occurring during DSC-LDL apheresis could be attributed to accumulated bradykinin. Bradykinin accumulation appears to result from the synergistic effect of bradykinin production by LDL apheresis and inhibition of bradykinin breakdown by ACE inhibitors. Bradykinin production during LDL apheresis is prohibited by a change in anticoagulant from heparin to nafamostat mesilate that inhibits the kallikrein activity (5). Recently, angiotensin II type 1 (AT₁)-receptor antagonists instead of ACE inhibitors have been used in the treatment of hyperten-

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This work was supported by a Research Grant for Cardiovascular Diseases (11C-5) from the Ministry of Health and Welfare of Japan.

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Received December 18, 2000; Accepted in revised form March 12, 2001.

Fig. 1. Changes in blood pressure and pulse rate during dextran-sulfate cellulose (DSC)-LDL apheresis in a patient who had been treated with an ACE inhibitor, imidapril hydrochloride (5 mg/day). SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; NM, nafamostat mesilate.

sion (7) and congestive heart failure (8). While ACE inhibitors suppress the degradation of bradykinin, antagonists of AT₁ receptor lack such action. This study was undertaken to clarify whether an AT₁-receptor antagonist, losartan, could be safely used during DSC-LDL apheresis in a patient who experienced hypotension when treated with an ACE inhibitor during DSC-LDL apheresis. Blood pressure and the plasma levels of bradykinin, renin, angiotensin II, and aldosterone were compared between apheresis sessions with losartan and those without.

Case Report

On November 6, 1985, a 48-year-old man with heterozygous familial hypercholesterolemia was admitted to our hospital due to acute myocardial infarction of the inferior wall. Coronary angiography showed triple-vessel disease, and saphenous vein bypass grafts were placed between the aorta and the two coronary arteries. Five years later, the recurrence of angina pectoris led us to repeat coronary angiography, which showed obstruction of the bypass grafts. In addition, he showed severe hypercholesterolemia (serum total cholesterol > 300 mg/dl), which could be barely controlled by anti-lipidemic drugs. He has therefore been treated using DSC-LDL apheresis fortnightly since June 1992.

For the procedure of LDL apheresis, we used an automated machine (MA01, Kanegafuchi Chemical Industry, Osaka, Japan) equipped with one plasma hollow fiber filter and two DSC columns. Plasma separated by the hollow fiber filter was passed through the DSC column for selective adsorption of LDL. Figure 1 shows the changes in blood pressure during DSC-LDL apheresis on May 21, 1998. Beginning at 2 weeks prior to this date, the patient had been inadvertently administered an ACE inhibitor, imidapril hydrochloride 5 mg (Tanatoril, Tanabe Co., Osaka) daily for the control of hypertension. About 10 min after starting plasma adsorption,

he complained of blurred vision and lacrimation, and these symptoms were accompanied by a blood pressure reduction from 128/68 mmHg to 96/53 mmHg. Soon after the plasma adsorption was interrupted (shown as first "off" in Fig. 1), his symptoms disappeared and his blood pressure returned to 123/64 mmHg. Two minutes after resumption of plasma adsorption, he complained of the same symptoms again. After his symptoms had disappeared by interruption of plasma adsorption (shown as second "off" in Fig. 1), the anticoagulant for apheresis was changed from heparin to nafamostat mesilate (Futhan, Torii & Co., Ltd., Tokyo) and then plasma adsorption was resumed. LDL apheresis was continued without blood pressure reduction or unpleasant symptoms until the end of apheresis.

Effects of Losartan on Blood Pressure and Humoral Factors

The following study was designed to clarify the safety of losartan for use in treating a patient during DSC-LDL apheresis. The study was carried out according to the principles of the Declaration of Helsinki and approved by our institutional review board; informed consent was obtained from the patient. Blood pressure and plasma levels of bradykinin, renin, angiotensin II, and aldosterone during the LDL apheresis session were compared between the session with losartan and that without (control session). In the losartan session, a 50 mg-tablet of losartan was administered at 7 AM daily. LDL apheresis was started at 10 AM and finished at about 12 AM, after processing 3,500 ml of plasma. The measurements were averaged from each of four control and losartan sessions. For measurement of bradykinin, renin, angiotensin II, and aldosterone, blood samples were taken at the 0 ml-, 1,000 ml-, 2,000 ml-, and 3,000 ml-stages of plasma treatment. At each stage, blood pressure was measured at the brachial artery using an automated manometer (BP-103N, Nippon Colin Co., Ltd., Komaki, Japan). All separated plasma samples were stored in a freezer at -80°C until used for measurement. Bradykinin, renin, and aldosterone were measured by radioimmunoassay as shown previously (9, 10). Angiotensin II levels were also measured with radioimmunoassay using a commercial kit (11). Values were presented as the mean $\pm$ SE. Statistical analyses were performed by repeated measures of analysis of variance (ANOVA) with post hoc Fisher's PLSD test. Levels of $p < 0.05$ were taken to indicate statistical significance.

Figure 2 shows the changes in the average of bradykinin plasma levels during the control and losartan sessions in the patient. At the 0 ml-, 1,000 ml-, 2,000 ml-, and 3,000 ml-stages of the control session, bradykinin levels were 17.9 ± 2.6 , $1,048 \pm 654$, 529 ± 121 , and 470 ± 175 pg/ml, respectively. In the losartan session, they were 6.4 ± 0.6 , $1,486 \pm 253$, $1,058 \pm 49$, and 952 ± 162 pg/ml, respectively. The bradykinin levels increased markedly during apheresis in both the control and losartan sessions. The bradykinin levels

at the 2,000 ml-stage were significantly ($p < 0.05$) greater in the losartan session than in the control session. Figure 3 shows the changes in mean blood pressure, plasma renin activity, and plasma levels of angiotensin II and aldosterone. There was a small but significant difference in blood pressure between the control session and losartan session. While blood pressure tended to increase in the control session, it

tended to decrease in the losartan session (control vs. losartan at the 2,000 ml-stage: 109.5% vs. 93% of the respective 0 ml-stage, $p < 0.01$). Angiotensin II levels were similar at the start of apheresis (control vs. losartan: 13.0 ± 2.4 pg/ml vs. 13.0 ± 1.4 pg/ml), but the levels at the 2,000 ml-stage were significantly ($p < 0.05$) greater in the losartan session (95.8 ± 18.5 pg/ml) than in the control session (24.3 ± 9.3 pg/ml). Plasma renin activity rose significantly only in the losartan session and was higher than in the control session. Aldosterone levels were lower in the losartan session and tended to decrease towards the end of apheresis.

Discussion

ACE inhibitors cause anaphylactoid reactions in patients under the treatment of DSC-LDL apheresis (6). We presented a patient who was inadvertently given an ACE inhibitor and complained of hypotension accompanied by lacrimation and blurred vision. The reaction was terminated when the anticoagulant was changed from heparin to nafamostat mesilate. We previously demonstrated that nafamostat mesilate, in contrast to heparin, inhibits bradykinin generation during LDL apheresis (5). Hypotension and the accompanied symptoms in the patient during LDL apheresis with heparin could be accounted for by bradykinin accumulation due to the concomitant treatment by ACE inhibitors.

Fig. 2. Changes in bradykinin plasma levels during dextran-sulfate cellulose (DSC)-LDL apheresis with (closed circles) and without (open circles) losartan. Control indicates the apheresis session without losartan. Values are shown as the mean $\pm$ SEM ($n=4$). * $p < 0.01$: significantly different from the corresponding value of 0 ml. # $p < 0.01$: significantly different from the corresponding value of the control session.

Fig. 3. Changes in mean blood pressure (MBP), plasma renin activity (PRA), and plasma levels of aldosterone (PAC) and angiotensin II during LDL apheresis with (closed column) and without (dotted column) losartan. Control indicates the session without losartan. Values are shown as the mean $\pm$ SEM ($n=4$). * $p < 0.05$; ** $p < 0.01$: significantly different from the corresponding value of 0 ml. # $p < 0.05$; ## $p < 0.01$: significantly different from the corresponding value of the control session.

Several randomized controlled trials demonstrated that the use of ACE inhibitors improved the prognosis of patients with myocardial infarction (1, 2). The favorable effects of ACE inhibitors have been ascribed to suppression of the renin-angiotensin system, and/or accumulation of bradykinin via its inhibitory effect on bradykinin degradation. However, AT₁ antagonists suppress the renin-angiotensin system without effects on the kallikrein-kinin system. Theoretically, AT₁ antagonists should be safe for use in patients under DSC-LDL apheresis. Two studies (12, 13) have already confirmed the safety of an AT₁ antagonist, losartan, in DSC-LDL apheresis. However, these studies did not measure blood pressure or bradykinin levels, both of which were measured here. Our results showed that DSC-LDL apheresis could be continued without noticeable side effects, despite the tendency of blood pressure to decrease slightly.

Since the effects of losartan on the humoral factors were examined in only one patient, the findings may not be applicable to other patients. In the current patient, however, bradykinin plasma levels were higher in the losartan session than in the control session. While the increase by the ACE inhibitors, alacepril and lisinopril, was respectively 4- and 2.5-fold (14, 15), the increase in bradykinin levels by losartan was only 1.5-fold. Inhibition of bradykinin degradation is the cause of the increase in bradykinin levels due to ACE inhibitors. Augmentation of bradykinin generation via the effect on non-AT₁ receptor may be the cause of the increase due to AT₁ receptor antagonists. Angiotensin receptors are classified into two subtypes, AT₁ and AT₂ (16). While AT₁ receptor mediates major physiological actions of angiotensin II, such as vasoconstriction, the physiological roles of AT₂ receptor are elusive, though one plausible role is bradykinin production (17, 18). By administration of AT₁ antagonists, plasma renin activity is increased through dissolution of the tonic inhibitory effect of angiotensin II on renin release. The increase in angiotensin II plasma levels due to renin release might have stimulated bradykinin production via the AT₂ receptor. Although blood pressure reduction during the losartan session is mainly attributed to losartan's antagonistic effect on AT₁ receptor, bradykinin production may also participate in blood pressure reduction. In the present case, however, blood pressure reduction was only 7% and was not accompanied by any unpleasant symptoms. In conclusion, losartan appears to be safe for patients under treatment by LDL apheresis despite the increase in bradykinin levels and a slight lowering of blood pressure.

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