Case Report

Successful Treatment of Severe Hypertension with the Combination of Angiotensin Converting Enzyme Inhibitor and Angiotensin II Receptor Blocker

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Three patients who suffered from congestive heart failure caused by severe hypertension were treated with a combination therapy consisting of angiotensin converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB). Before initiation of treatment, all three patients showed elevations of serum creatinine concentration (sCr), plasma renin activity (PRA), and plasma aldosterone concentration (PAC), which indicated insufficient blood supply to the kidney during exacerbation of hypertension. All three cases successfully recovered from hypertensive heart failure with the combination therapy. sCr gradually decreased during continuation of the therapy, although one patient showed an increase in sCr at an early stage of the combination therapy. Blockade of the renin-angiotensin-aldosterone system (RAAS) by the combination of ACEI and ARB was well tolerated in patients with severe hypertension with renal damage and showed a beneficial effect in protecting against further renal damage. This result suggests that combination therapy with ACEI and ARB should be considered as a candidate treatment in cases of severe hypertension.

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Key Words: renin-angiotensin-aldosterone system, malignant hypertension, angiotensin converting enzyme inhibitor, angiotensin II receptor blocker

Introduction

Severe hypertension (diastolic blood pressure greater than 120 mmHg), including accelerated and malignant hypertension, progressively injures the kidneys and other target organs (1–3). Protection of these target organs from injury is one of the main therapeutic aims in the treatment of hypertension. In severe hypertension, plasma renin activity (PRA) is often elevated and the renin-angiotensin-aldosterone system (RAAS) is thought to play a central role in exacerbating the hypertension. The kidney is a contributor to severe hypertension, as the site of circulating renin secretion (2).

For treatment of severe hypertension, application of calci-

um channel blockers and nitroglycerin derivatives, especially with intravenous continuous infusion, is widely used and has been proven to be effective (1). In the kidney, however, these agents reduce vascular resistance of the afferent arterioles more effectively than that of the efferent arterioles (4). Since activated RAAS increases the vascular resistance of the efferent arterioles in severe hypertension, which in turn increases intra-glomerular pressure and then induces glomerular endothelial damages (5), administration of agents that inhibit RAAS is recommended to preserve renal function. RAAS blocking agents, angiotensin converting enzyme inhibitors (ACEI) and angiotensin II (Ang II) receptor blockers (ARB), have shown renal protective effects in patients with diabetes mellitus and glomerulonephritis (6–9). For treat-

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Fig. 1. Clinical course of Case 1 during treatment. The horizontal bar indicates days after initial admission. Temocapril was added from 0.5 mg/day, and increased stepwise (1, 2, 3, and 4 mg/day). Valsartan was added from 40 mg/day and increased to 80 mg/day. After an initial reduction of blood pressure (BP), intravenous nicardipine was tapered from 1 mg/h and replaced with oral administration of nifedipine (an initial dose of 60 mg/day and then 40 mg/day). Because BP increased after a cessation of furosemide (20 mg/day), bunazosin was added at 3 mg/day and then 6 mg/day. With reduction of BP, PRA, sCr and urinary protein (Pro) decreased gradually to a normal level.

ment of severe hypertension, monotherapy with any of these agents alone has also been reported to be beneficial (3, 10). Recently, combination therapy using ACEI and ARB has been reported to be more effective than monotherapy with either agent alone for preservation of renal function in the patients with renal disease (11). However, combination therapy against severe hypertension has not yet been reported.

In this report, we describe three cases of severe hypertension in which combination therapy with ACEI and ARB showed beneficial effects. All three patients suffered from congestive heart failure accompanied with renal damage, which was indicated by proteinuria and increased levels of serum creatinine (sCr). Initial values of PRA and plasma aldosterone concentration (PAC) were increased in all three cases, indicating activated RAAS. With a combination therapy consisting of ACEI and ARB, all three patients recovered from hypertensive heart failure and renal damage. These results suggest that a combination therapy with ACEI and ARB is an effective therapeutic option for the treatment of severe hypertension.

Case Reports

Case 1

A 30-year-old man was referred to our hospital because of

dyspnea. Three years before the referral, high blood pressure of 150/110 mmHg was noticed during an annual health examination, but the patient declined medical consultation due to the absence of symptoms.

Initial physical examination revealed severe hypertension (210/145 mmHg), tachycardia (120 beats per minute (bpm)), and orthopnea. Bilateral moisture rales by auscultation and slight pretibial pitting edema were detected. The results of blood analysis were as follows: urea nitrogen (BUN) 15 mg/dl, sCr 1.3 mg/dl, uric acid (UA) 9.4 mg/dl, sodium (Na) 143 mEq/l, potassium (K) 3.4 mEq/l, chloride (Cl) 108 mEq/l, and lactate dehydrogenase (LDH) 564 IU/l. No abnormal fragmentation of red blood cells (RBC) was detected. Urinalysis showed proteinuria (1.84 g/g creatinine (Cr)) and decreased Cr clearance (CCr) (68 ml/min). Arterial blood gas (ABG) analysis showed slight hypoxia (P_{O_2} 72.2 mmHg) and respiratory alkalosis (pH 7.465, P_{CO_2} 24.6 mmHg, HCO_3^- 17.7 mmol/l). A chest X-ray film (CXR) showed cardiomegaly (CTR 63%) and bilateral pleural effusion. ECG showed sinus tachycardia and left ventricular hypertrophy. PRA and PAC were increased to 13.4 ng/ml/h (normal: 0.2–2.7) and 17.3 ng/dl (normal: 4.5–10.5), respectively. Brain natriuretic peptide (BNP) was 395.9 pg/ml (normal: ≤ 18.4). Examination of the ocular fundi revealed slight hypertensive change (Keith-Wagener grade 1, Scheie H1S1).

Severe hypertension was thought to be a cause of the heart failure. Without detecting renal artery stenosis by magnetic resonance arteriogram (MRA), an anti-hypertensive treatment with intravenous nicardipine (1 mg/h) and a small dose of temocapril (0.5 mg/day) was initiated. With reduction of blood pressure to 160/100 mmHg, dyspnea improved and intravenous nicardipine infusion was replaced with oral administration of long-acting nifedipine (60 mg/day). The dose of temocapril was increased stepwise to 4 mg/day and administration of valsartan (40 mg/day) was started from the 20th hospital day. The clinical course during treatment is summarized in Fig. 1. PRA decreased to a normal level after 22 days of treatment. Serum Cr improved gradually to 0.9 mg/dl and proteinuria diminished (< 0.15 g/gCr) on the ninth hospital day. Pleural effusion subsided on the seventh hospital day. CCr improved to 74.6 ml/min and CTR decreased to 54% on the 21st hospital day. With reduction of the dose of nifedipine (from 60 to 40 mg/day) the blood pressure increased gradually. Bunazosin was initiated at a dose of 3 mg/day, and then the doses of valsartan and bunazosin were increased to 80 mg/day and 6 mg/day, respectively. The level of serum BNP was normalized to 17.2 pg/ml after two months of treatment.

Case 2

A 30-year-old man who had a 12-year history of hypertension consulted our department because of dyspnea. At the age of 26, a diagnosis of essential hypertension had been made without detecting the apparent causes of the secondary

Fig. 2. Clinical course of Case 2 during treatment. The dose of temocapril was increased as in Case 1. After the initial reduction of blood pressure (BP), intravenous nicardipine (1 mg/h) and furosemide (40 mg/day) were tapered and switched to oral administration of nifedipine (60 mg/day) and bunazosin (3 mg/day). While reducing the dose of nifedipine (40 and then 20 mg/day), valsartan (40 mg/day) and cilnidipine (20 mg/day) were added. Further addition of bunazosin (6 mg/day) and valsartan (80 mg/day and then a stepwise increase to 120 and 160 mg/day) was needed to reduce BP sufficiently. Serum Cr increased at the start of therapy, but then decreased gradually until reaching a level below the pretreatment value. Proteinuria and PRA also decreased, but were not reduced to a normal level during the 40 days of treatment.

hypertension. However, the patient stopped his regular visits and also stopped taking anti-hypertensive medication. He remained asymptomatic until several weeks before revisiting our department, when he noticed worsening cough and dyspnea.

On initial physical examination, tachycardia (93 bpm), prominent hypertension (217/154 mmHg) and bilateral moisture rales were detected. Initial laboratory data were as follows: BUN 42 mg/dl, sCr 6.1 mg/dl, Na 136 mEq/l, K 3.4 mEq/l, Cl 96 mEq/l, LDH 1,533 IU/l, PRA 79.0 ng/ml/h, PAC 49.3 ng/dl, and BNP 395.9 pg/ml. A low level of haptoglobin (8.8 mg/dl) was detected with fragmentation of RBC. Severe proteinuria (5.28 g/gCr) and hematuria (> 100/HPF) were also detected with reduced CCr of 15 ml/min. ABG showed hypoxia (P_{O_2} 58.4 mmHg) and mixed respiratory and metabolic alkalosis (pH 7.501, P_{CO_2} 34 mmHg, HCO_3^- 27.2 mmol/l). CXR showed cardiomegaly (CTR 55%) with pulmonary congestion. ECG showed sinus tachycardia and left ventricular hypertrophy. Examination of the ocular fundi revealed severe hypertensive change (Keith-Wagener grade 3, Scheie H3S1) in both eyes.

We made a diagnosis of accelerated hypertension, and initiated intravenous infusion of nicardipine and oral adminis-

tration of both furosemide (40 mg/day) and temocapril (0.5 mg/day). With reduction of blood pressure to 170/110 mmHg, the dyspnea improved and furosemide was stopped. Serum Cr increased at an early stage of this treatment (peak value: 7.1 mg/dl), and then decreased gradually thereafter. The renal arteries were examined and no stenotic lesions were detected. While tapering the dose of intravenous nicardipine, long-acting nifedipine was administered from a dose of 60 mg/day. The dose of temocapril was increased stepwise to 4 mg/day, and then bunazosin (3 mg/day) was added to counteract a rise of blood pressure in the morning. While reducing the dose of nifedipine, cilnidipine (20 mg/day) and valsartan (40 mg/day) were initiated. In order to attain further reduction of blood pressure, the doses of bunazosin and valsartan were increased stepwise to 6 mg/day and 160 mg/day, respectively. As summarized in Fig. 2, the patient's blood pressure was decreased gradually to within a normal range by these medications. PRA also decreased to 12.6 and 7.1 ng/ml/h after 10 days and 40 days of treatment, respectively. CTR was improved to 43% with normalization of BNP (3.31 pg/ml), and the amount of urinary protein excretion was reduced to ~0.5 g/g Cr three months after the initiation of this therapy. Serum Cr declined gradually, reaching to 3.4 mg/dl and 1.7 mg/dl after three months and after 1 year of therapy, respectively. CCr was improved to 61.5 ml/min at three months after the start of treatment.

Case 3

A 24-year-old man consulted the ophthalmologic department of our hospital because of blurred vision accompanied with general fatigue. Fundoscopic examination revealed hemorrhage and papilledema (Keith-Wagener grade 4, Scheie H4S1) and he was referred to our department.

On initial physical examination, prominent hypertension (269/140 mmHg), tachycardia (123 bpm), slight moisture rales, and pretibial pitting edema were detected. Initial laboratory data were as follows: BUN 34 mg/dl, sCr 3.2 mg/dl, Na 140 mEq/l, K 2.7 mEq/l, Cl 99 mEq/l, LDH 1,216 IU/l, BNP 472 pg/ml, PRA 52.7 ng/ml/h, and PAC 50.2 ng/dl. Low level of haptoglobin (2.8 mg/dl) was detected with RBC fragmentation. Urinary protein excretion was 2.27 g/gCr and CCr was 28 ml/min. ABG showed slight hypoxia (P_{O_2} 85.0 mmHg) and respiratory alkalosis (pH 7.582, P_{CO_2} 24.1 mmHg, HCO_3^- 22.2 mmol/l). CXR showed cardiomegaly (CTR 57%), and ECG showed sinus tachycardia and left ventricular hypertrophy.

We made a diagnosis of malignant hypertension and began a treatment with intravenous infusion of nicardipine. Without detecting renal artery stenosis by MRA, furosemide (10 mg/day) and temocapril (0.5 mg/day) were added. After an initial reduction of blood pressure to 160/110 mmHg, we reduced and then stopped the administration of nicardipine and furosemide, while simultaneously initiating long-acting nifedipine (60 mg/day) and increasing the dose of temocapril

Fig. 3. Clinical course of Case 3 during treatment. Intravenous application of nicardipine was initiated from 0.8 mg/h, increased to 1 mg/h, and then replaced with oral administration of nifedipine (60 mg/day). After the initial reduction of blood pressure (BP), the dose of temocapril was increased as in Case 1. Because of a suspicious side effect of face flush, nifedipine was reduced stepwise (60, 40, 20, and 0 mg/day). Valsartan was started to replace nifedipine, and the dose was increased as in Case 2. Addition of benidipine (8 mg/day) and atenolol (12.5 mg/day) were needed to reduce BP, which increased gradually even with the maximum doses of temocapril (4 mg/day) and valsartan (160 mg/day). PRA was reduced to a normal level with the reduction of BP, and was not elevated even at the maximum doses of temocapril and valsartan. Proteinuria and sCr decreased gradually, but were not reduced to within the normal range over the 80 days of treatment.

stepwise to 4 mg/day. As shown in Fig. 3, the patient's blood pressure and PRA were decreased to within a normal range under this treatment. Because of a suspected side effect (face flush), nifedipine was changed to valsartan and the dose of valsartan was increased stepwise to 160 mg/day. Even with the maximum doses of temocapril (4 mg/day) and valsartan (160 mg/day), blood pressure increased gradually. CCr and BNP improved (44 ml/min and 53.7 pg/ml, respectively), but were not normalized during the first month of treatment. With addition of another calcium channel blocker (benidipine 8 mg/day) and a β -blocker (atenolol 12.5 mg/day), the blood pressure was reduced to 135/90 mmHg. CTR improved to 54% without any apparent side effects. Two months after the initiation of treatment, sCr improved to 1.6 mg/dl and the amount of urinary protein subsided to ~ 0.5 g/gCr.

Discussion

In this report, we described three cases of severe hypertension treated with a combination therapy consisting of ACEI and ARB. For treatment of severe hypertension, use of either

of these agents singly has been reported to show beneficial effects (3, 10), but the safety and efficacy of combination therapy using both agents have not been reported. We clearly demonstrated, for the first time, that severe hypertension with renal impairment could be treated even with a combination of the maximum doses of ACEI and ARB. The combination therapy preserved renal function in all cases. Especially in Case 1, for whom this therapy was initiated at a relatively early stage of severe hypertension, the level of sCr and the amount of urinary protein excretion could be reduced to normal values.

In all three cases, elevated PRA was detected before the initiation of therapy. In many of the previously reported cases of malignant/accelerated hypertension, the initial values of PRA were also found to be elevated (3, 12). In a few cases, PRA was not elevated, and even in such cases, RAAS blockade showed renal-protective effects. In addition, experimental evidence also suggests that RAAS blockade prevents renal damage irrespective of the blood pressure-lowering effect (10, 13, 14). Taken together, these observations indicate that the RAAS activated locally within the kidney contributes to the deterioration of renal function in severe hypertension. Because the Ang II-generation in local tissues is regulated by not only the angiotensin converting enzyme pathway but also other enzymes such as chymase (15, 16), simultaneous use of ACEI and ARB is theoretically more effective for RAAS blockade than either agent alone. Recently, comparative studies between combination therapy and monotherapy of either agent were conducted for the treatment of heart failure and renal disease (11, 17, 18), and combination therapy showed a greater organ-protective effect than monotherapy. In this report, we showed that the combination of ACEI and ARB was also very effective in reducing the amount of urinary protein as well as in improving renal function even for patients with severe hypertension.

We have shown that addition of RAAS blockade to calcium channel blockers was effective to protect renal function in severe hypertension. To attain a sufficient reduction in blood pressure, the addition of low-dose diuretics has been recommended (19). In our cases, however, we discontinued the use of diuretics according to the results of ultrasonographic cardiac examination, which indicated slight dehydration after the initial reduction of blood pressure. To preserve renal function, protection of renal ischemia and reduction of intra-glomerular pressure are essential. For protection against renal ischemia, use of anti-hypertensive agents with a potent vaso-relaxing action on the afferent arterioles, such as calcium channel blockers, is appropriate (4). Although some calcium channel blockers, including benidipine, have been reported to exert a potent vaso-relaxing action on the efferent arterioles (4, 20) without concomitant vaso-relaxation of the efferent arterioles, these agents may nonetheless induce a further increase in intra-glomerular pressure. For protection against intra-glomerular hypertension, potent vaso-relaxants against the efferent arterioles, such as ACEI and ARB, are

appropriate (5). Conversely, however, without sufficient vaso-relaxation of the afferent arterioles, these agents could induce a further decrease of renal perfusion. Taken together, these results indicate that combination treatment including vaso-relaxants of both the afferent and efferent arterioles is appropriate to preserve renal function. Because vaso-relaxants of the afferent arterioles are usually used for the initial treatment of severe hypertension, we emphasized the use of the vaso-relaxants of the efferent arterioles.

Recently, the authors of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study suggested that when blood pressure is sufficiently reduced, the agents used for treatment might not show any significant difference in the protection of target organs in patients without severe renal dysfunction (21). It is uncertain if the renal protective effect of the combination therapy in our cases resulted from a specific therapeutic effect of the RAAS blockade or just from a sufficient reduction in systemic blood pressure (8, 22–24). Previously, the use of RAAS blockers to treat hypertension had been restricted to patients without renal dysfunction, because these agents showed the potential to worsen renal function (1). However, many large-scale clinical studies suggest that RAAS blocking agents would be superior to other anti-hypertensive agents for achieving reno-protection in patients with renal dysfunction (6–9, 25). In these studies, RAAS blockers were used in patients with diabetic nephropathy or chronic glomerulonephritis, and effectively decreased both the amount of urinary protein and the rate of increase in sCr. In some of these patients, a slight decrease in CCr was observed at the initiation of treatment (8). However, with continuation of RAAS blockade, sCr was stabilized over time and reno-protection became more evident than in the absence of RAAS blockade. Our second case also showed an initial increase and then a gradual decrease in sCr during the continuation of combination therapy. Since an initial increase in sCr is a functional consequence of reduced intra-glomerular pressure rather than glomerular tissue damage, this should not be taken as an indicator to stop RAAS inhibition (2, 26). RAAS blockade should be continued with careful monitoring of renal function.

In conclusion, in the present study, a combination therapy with ACEI and ARB successfully prevented the deterioration of renal function in three cases of severe hypertension. Although there might be an initial exacerbation in sCr, combination therapy could be continued and show a renal protective effect. Reduction of intra-glomerular pressure and blockade of intra-renal local RAAS may be the mechanism by which ACEI and ARB confer renal protection. Since the combination of ACEI and ARB is considered to block RAAS and protect renal function more effectively than monotherapy with either agent alone, combination therapy with both ACEI and ARB should be considered as a candidate for initial treatment of severe hypertension.

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