Role of Angiotensin II in Renal Prostaglandin E₂ Production After Furosemide Administration

AKIO FUJIMURA AND AKIO EBIHARA

SUMMARY The role of plasma angiotensin II (Ang II) in furosemide-stimulated renal prostaglandin E₂ (PGE₂) production was evaluated in eight healthy subjects. Urine was collected for 60 minutes after furosemide administration (20 mg i.v.) with or without captopril pretreatment, and urinary excretion of PGE₂, sodium, and furosemide was determined. Plasma renin activity (PRA) and Ang II were also measured before and 60 minutes after furosemide administration. Urinary PGE₂ excretion, PRA, and Ang II increased after furosemide administration without captopril pretreatment, and there was a significant correlation between the increment in Ang II and that in urinary PGE₂ excretion. Urinary PGE₂ excretion and Ang II did not increase after furosemide administration with captopril pretreatment. Urine volume and urinary excretion of sodium and furosemide were not influenced by captopril pretreatment. These results suggest that Ang II may play an important role in furosemide-stimulated PGE₂ production. (Hypertension 11: 491-494, 1988)

KEY WORDS • furosemide • prostaglandin E₂ • angiotensin II

Furosemide, a potent loop diuretic, is a widely used therapeutic agent for treatment of hypertension and congestive heart failure. Some effects of furosemide are reported to be partly dependent on renal prostaglandin E₂ (PGE₂) produced by furosemide administration.¹,² This elevation in renal PGE₂ production, as reflected by urinary PGE₂ excretion,³ following furosemide administration could be mediated directly by inhibition of renal 15-hydroxy- prostaglandin dehydrogenase⁴ and 9-ketoreductase⁵ activities. Since furosemide activates the renin-angiotensin system, the elevated levels of angiotensin II (Ang II) may in turn stimulate synthesis of renal PGE₂.⁶

To determine whether the indirect action of Ang II plays an important role in furosemide-induced renal PGE₂ production, we investigated urinary PGE₂ excretion after furosemide administration with or without pretreatment with captopril, an oral converting enzyme inhibitor, in healthy subjects.

Subjects and Methods

Protocol

Eight healthy male subjects, 22 to 28 years old, gave informed consent to the protocol and were studied on three separate occasions. The subjects were requested to refrain from sexual activity and not to take nonsteroidal anti-inflammatory drugs for at least 48 hours before the study. Sodium intake was not restricted until the night before the study. Urine was collected for 24 hours on the day before each study. After fasting overnight, subjects were given 400 ml of water to drink at 0900, 1030, 1200, and 1300 and were asked to void at 1300. The subjects remained supine throughout the study except for 1 to 2 minutes of standing to pass urine. In the first study, urine was collected for 60 minutes after administration of vehicle (10 ml of saline) at 1300. In the second study, 10 ml of saline containing 20 mg of furosemide was injected intravenously after voiding urine at 1300. Urine was collected for 60 minutes after administration of vehicle (10 ml of saline) at 1300. In the second study, 10 ml of saline containing 20 mg of furosemide was injected intravenously after voiding urine at 1300. Urine was collected for 60 minutes after furosemide administration. Blood samples were obtained before and 60 minutes after furosemide administration. In the third study, the procedure of the second study was repeated but a blood sample was also obtained and 50 mg of captopril was given orally at 1200. These three studies were performed at 7-day intervals.

Analytical Procedures

Blood samples for measurement of plasma renin activity (PRA) and Ang II were collected into tubes containing EDTA and kept on ice. After centrifugation at 2000 g at 4°C for 20 minutes, the plasma was separated. Plasma and urine samples were immediately frozen and stored at -20°C in a freezer that had no cyclic system for defrosting and were analyzed within 2 weeks.

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PRA and Ang II were measured by radioimmunoassay. Urinary sodium was determined by a flame photometer (Model 775-A, Hitachi, Tokyo, Japan). Urinary furosemide was measured using high performance liquid chromatography. Urinary PGE2 was measured by radioimmunoassay after extraction according to the method of Jaffe et al. with a slight modification. In brief, after 0.2 N hydrochloric acid was added to 1 ml of urine to adjust to a pH of 3 to 5, the sample was defatted with 3 ml of n-hexane to which 3 ml of acetic acid and ethylisopropanol (1:1, vol/vol) mixture was added and mixed well, then the organic layer was separated with 5 ml of ethylacetic acid and water (2:3, vol/vol) mixture. The upper layer was evaporated, and the residue dissolved with a 1-ml mixture of benzene, ethyl acetate, and methanol (60:40:2, vol/vol). The extract was then applied onto the minicolumn (8 X 160 mm) packed with 1.5 g of silicic acid, and the fraction of PGE2 was collected. The recovery rate of PGE2 was 85.0 ± 5.0% (n = 7). PGE2 was not converted to prostaglandin A in this extraction procedure. PGE2 was measured by radioimmunoassay using a kit (Clinical Assays, Travenol, Deerfield, IL, USA) after conversion to prostaglandin B (PGB) by treating with 0.1 ml of 1 N sodium hydroxide and heating at 100°C for 5 minutes. Greater than 90% of PGE2 was converted in the alkalinizing process to PGB. The cross-reactivity of anti-PGB antibody was 100% with PGB, 22.2% with prostaglandin A1, less than 0.1% with prostaglandin A2, 12.3% with prostaglandin E1, less than 0.1% with PGE2, less than 0.1% prostaglandin F1a (PGF1a), and less than 0.1% prostaglandin F2a. Tritium-labeled PGE2 (1000 cpm) was added to the urine for correction of the recovery rate. The sensitivity of this assay was 20 pg/ml of urine, and the intra-assay and interassay coefficients of variation were 10% (x = 48 pg/ml; n = 15) and 13% (x = 48 pg/ml; n = 15), respectively. Urinary captopril did not interfere with this assay.

**Statistical Analysis**

The results obtained are expressed as means ± SE. Data are analyzed by analysis of variance.

**Results**

There were no significant differences among the three studies in urinary sodium excretion (170-200 mEq/24 hr) on the day before the study. There was a significant increase in urinary PGE2 excretion after furosemide administration (Table 1). This increase disappeared with captopril pretreatment.

After furosemide administration alone, both PRA and Ang II increased (Table 2). Captopril pretreatment in the third study increased basal PRA from 1.1 ± 0.3 to 7.1 ± 2.3 ng angiotensin I/ml/hr (p < 0.05) and decreased basal Ang II from 12.6 ± 1.9 to 8.1 ± 1.1 pg/ml (p < 0.05). Following captopril pretreatment, furosemide produced a greater increase in PRA but produced no significant change in Ang II (see Table 2). There was a high correlation (r = 0.78, p < 0.05) between the increment in Ang II and that of urinary PGE2 after furosemide administration without captopril pretreatment (Figure 1).

Urine volume and urinary excretion of sodium and furosemide after furosemide administration were not influenced by captopril pretreatment (see Table 1). There were significant correlations between urinary

<table>
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<th>Variable</th>
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<th>Study 2 (furosemide)</th>
<th>Study 3 (captopril + furosemide)</th>
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<tr>
<td>Urine volume (ml/hr)</td>
<td>456 ± 36*</td>
<td>1210 ± 42</td>
<td>1049 ± 91</td>
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<td>Urinary PGE2 (ng/hr)</td>
<td>11.4 ± 3.9*</td>
<td>73.5 ± 7.8</td>
<td>10.5 ± 0.9*</td>
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<tr>
<td>Urinary sodium (mEq/hr)</td>
<td>18 ± 4*</td>
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<td>85 ± 9</td>
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<td>Urinary furosemide (mg/hr)</td>
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<td>10.65 ± 0.62</td>
<td>9.71 ± 0.51</td>
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Values are means ± SE of eight subjects.

* p < 0.01, compared with values for Study 2.

<table>
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<tr>
<th>Plasma variable</th>
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<th>Study 3 (captopril + furosemide)</th>
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<tbody>
<tr>
<td>PRA (ng Ang I/ml/hr)</td>
<td>1.7 ± 0.5</td>
<td>3.4 ± 0.7*</td>
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<tr>
<td>Ang II (pg/ml)</td>
<td>13.6 ± 1.8</td>
<td>78.6 ± 5.0*</td>
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<tr>
<td>PRA (ng Ang I/ml/hr)</td>
<td>7.1 ± 2.3</td>
<td>16.5 ± 4.7†</td>
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<tr>
<td>Ang II (pg/ml)</td>
<td>8.1 ± 1.1</td>
<td>8.5 ± 0.6</td>
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Values are means ± SE of eight subjects. ANG I = angiotensin I.

† p < 0.05, compared with values at 0 minutes.

**Figure 1.** Correlation between the increment in plasma Ang II (ΔAng II) and that in urinary PGE2 (ΔU-PGE2) after furosemide administration without captopril pretreatment.
Furosemide and Prostaglandin E₂ Production

Furosemide excretion and the increment in urine volume (n = 16, r = 0.56, p < 0.05) and in urinary sodium excretion (n = 16, r = 0.55, p < 0.05). However, there was no significant correlation between the increment in urinary PGE₂ excretion and that in urine volume or urinary sodium excretion after furosemide administration without captopril pretreatment.

**Discussion**

The present study demonstrates that urinary PGE₂ excretion increases significantly after furosemide administration and this increment is completely inhibited by captopril pretreatment. The present study also reveals a high degree of correlation between changes in plasma Ang II concentration and in urinary PGE₂ excretion during the study without captopril pretreatment. These observations confirm and extend a previous report by Attallah et al., who suggested that the effect of furosemide on renal PGE₂ production is mediated through the action of Ang II. Ang II is reported to stimulate PGE₂ synthesis in the kidney, in cultures of renal medullary interstitial cells, and in isolated glomeruli. On the basis of these observations, the observed increment in furosemide-induced renal PGE₂ production can be entirely accounted for by the concurrent increase in Ang II. The obliteration of this response by captopril pretreatment provides additional support for this thesis. For these reasons, the effect of furosemide on the prostaglandin degrading enzymes appears negligible.

Furosemide increases urinary excretion of several prostaglandins, including PGE₂ and 6-keto-PGF₁α, in humans. Ang II stimulates arachidonic acid release through Ang II-activated phospholipase A₂ and subsequent prostaglandin biosynthesis. Ang II has been shown to stimulate PGE₂ and 6-keto-PGF₁α production by isolated human glomeruli. Therefore, the increase in urinary 6-keto-PGF₁α after furosemide administration also might be decreased by captopril, although this was not examined in the present study.

As the urinary PGE₂ excretion after captopril alone was not determined in the present study, a direct effect of the drug on urinary PGE₂ excretion could not be evaluated. However, since captopril is reported to increase plasma levels of PGE₂, it is not likely that captopril prevents the increment in urinary PGE₂ excretion after furosemide administration by a mechanism other than inhibition of its furosemide-related effect.

The contribution of renal PGE₂ to the mechanism of action of furosemide is still debated. After furosemide was administered intravenously, urinary PGE₂ increased rapidly during the first 15 to 30 minutes and this increase was related to natriuresis in two studies, but not in a third. In the present study, the urine volume and urinary sodium excretion responses to furosemide administration were not influenced by captopril pretreatment, although urinary PGE₂ excretion was remarkably reduced. Moreover, there were no significant correlations between the increment in urinary PGE₂ and that in urine volume or urinary sodium excretion after furosemide administration without captopril pretreatment. Our results agree with the work of Nadler et al., which demonstrated that Ang II by itself stimulates PGE₂ excretion without affecting urine volume and urinary sodium excretion. Therefore, it may be concluded from the present study that renal PGE₂ does not play an important role in the diuretic and natriuretic effects of furosemide.

**Acknowledgments**

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**References**

17. Stanek B, Silberbauer K. Acute and chronic effects of captopril.
on bicyclo-PGE\textsubscript{m}, the stable bicyclic end product of prostaglandin E\textsubscript{2} in essential hypertension. Nephron 1986;44:40–45
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### Brief Summary

**Pharmacological Information**

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**CONTRAINDICATIONS**

CARDIZEM® is contraindicated in (1) patients with sick sinus syndrome unless in the presence of a functioning ventricular pacemaker, (2) patients with a second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with ventricular hypotension less than 50 mm Hg systolic, and (4) patients who have demonstrated hypersensitivity to the drug.

1. **Cardiac Conduction:** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (less than 90 mm Hg systolic) after a single dose of 60 mg of diltiazem.

2. **Concomitant Use:** CARDIZEM concomitantly with any agents known to effect cardiac conduction should be exercised when using the drug in such patients. The relationship to CARDIZEM is uncertain in most cases, but there have been some reductions in the PR interval in man.

### Pharmacological Studies

- Studies in dogs showed that diltiazem did not affect heart rate or blood pressure in normal dogs, but that it decreased blood pressure and reduced the rate of rise of the femoral artery pressure in dogs with hypotension.
- The effect of diltiazem was dose-dependent in dogs and was more pronounced in patients with intact sympathetic nervous system than in patients with intact sympathetic nervous system.
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### Adverse Reactions

- **Cardiovascular:** Arrhythmia, AV block, AV node/AV node recovery time, except in patients with sick sinus syndrome.
- **Respiratory:** hyperventilation, bronchospasm, rhinitis, asthma.
- **Gastrointestinal:** Anorexia, constipation, diarrhea, nausea, vomiting, dyspepsia, melena, dysphagia, dyspepsia.
- **Hematologic:** thrombocytopenia, agranulocytosis, aplastic anemia, pancytopenia, leukopenia, neutropenia, anemia.
- **Renal:** albuminuria, proteinuria, oliguria, acute renal failure.
- **Skin:** pruritus, rash, urticaria, angioneurotic edema, porphyria.
- **Other:** fever, malaise, weight loss, weight gain, edema, anaphylactic reaction, erythematous rash, maculopapular rash, angioneurotic edema, acral erythema, hyperhidrosis.

### Dosage and Administration

- The dosage of diltiazem should be adjusted according to the patient's response and tolerated dosage range.
- The maximum daily dosage of diltiazem should not exceed 120 mg.
- Diltiazem may be administered alone or in combination with other antianginal agents.

### Drug Interactions

- Diltiazem may interact with other antianginal agents, such as beta-blockers, calcium channel blockers, or digoxin.
- Diltiazem may also interact with other medications that affect cardiac conduction or blood pressure.

### Contraindications

- Patients with sick sinus syndrome unless in the presence of a functioning ventricular pacemaker.
- Patients with a second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
- Patients with ventricular hypotension less than 50 mm Hg systolic.
- Patients who have demonstrated hypersensitivity to the drug.

### Precautions

- Patients with impaired liver function or hepatic dysfunction should be monitored for any signs of liver function tests.
- Patients with impaired renal function or renal dysfunction should be monitored for any signs of renal function tests.

### References

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Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with angiotensin-converting-enzyme (ACE) inhibitors, including VASOTEC (0.2% of patients treated with VASOTEC in clinical trials). In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.

Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. In using VASOTEC, consideration should be given to the fact that another ACE inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and the available data are insufficient to show that VASOTEC does not have a similar risk.

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**Warnings:** Angioedema. Angioedema of the face, extremities, lips, tongue, glottis, or larynx has been reported in patients treated with enalapril. In such cases, VASOTEC should be promptly discontinued and the patient observed carefully until the swelling disappears. Swelling of the face, lips, tongue, or glottis may be so severe as to produce obstruction of the airway (see ADVERSE REACTIONS). The potential for fatal airway obstruction has been observed in patients with angioedema associated with angiotensin converting enzyme inhibitors. Therefore, if a patient develops laryngeal edema following the administration of VASOTEC, it is necessary to discontinue the drug until the patient is observed carefully for 48 hours. Patients with a history of angioedema associated with other drug classes should be observed carefully for signs of angioedema during therapy with enalapril. If angioedema occurs, the drug should be discontinued and appropriate therapy initiated immediately (see ADVERSE REACTIONS).

Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema may occur in patients who have not previously had angioedema and who had a normal serum complement level. Angioedema may develop at any time during treatment with ACE inhibitors. In such cases, the drug should be discontinued and appropriate therapy initiated immediately (see ADVERSE REACTIONS).

Other adverse reactions occurring in greater than 1% of patients treated with VASOTEC included hyperkalemia (1.9%), hypokalemia (1.0%), hypocalcemia (0.8%), and orthostatic effects (1.3%).

Concomitant administration of VASOTEC with potassium supplements, potassium-sparing diuretics, potassium-sparing agents, or other drugs that raise serum potassium levels may increase the risk of hyperkalemia. If concomitant use of these agents is unavoidable, serum potassium levels should be monitored regularly (see PRECAUTIONS). Discontinuation of therapy was required in 6.0% of patients in clinical trials. In clinical trials, the overall frequency of adverse experiences was not related to total daily dosage within the range of 10 to 80 mg/day. In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Associated renal insufficiency, excessive hypotension, and/or oliguria have been observed in patients who were treated with enalapril. Therefore, in patients with severe congestive heart failure, renal function should be monitored during therapy with enalapril. If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion. Patients who are dehydrated or salt-depleted as a result of diuretic therapy or volume contraction from any cause should be volume expanded prior to the initiation of enalapril therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pretreatment renal vascular disease have developed increases in blood urea nitrogen and serum creatinine. These increases were usually reversible upon discontinuation of enalapril and/or diuretic therapy.

In clinical trials of enalapril, the most frequent clinical adverse experiences were headache (4.8%), dizziness (3.8%), and fatigue (3.4%). Other adverse reactions occurred in greater than 1% of patients treated with enalapril, including hyperkalemia (1.9%), hypokalemia (1.0%), hypercalcemia (0.8%), hypocalcemia (0.8%), hypoglycemia (0.8%), pruritus (0.8%), nasopharyngitis (0.6%), febrile response (0.6%), cough (0.6%), chest pain (0.6%), lower respiratory tract infection (0.6%), and upper respiratory tract infection (0.6%).

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. This is likely to occur in patients with hypertension, renal disease, and/or with impaired renal function. ACE inhibitors have been associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death in patients with severe renal disease (GFR < 10) prior to the initiation of therapy with ACE inhibitors. In such patients, renal function should be monitored during the first few weeks of therapy. If oliguria and/or sudden decreases in urine output occur in patients treated with enalapril, VASOTEC should be discontinued promptly unless it is considered essential to continue enalapril therapy. Moderate to severe renal disease is associated with hyperkalemia.

Clinical Laboratory Findings

**Hematology**

Leukopenia, eosinophilia, neutropenia, and agranulocytosis have been reported in patients receiving enalapril. Agranulocytosis in which a causal relationship to enalapril cannot be excluded has been reported in association with neutropenia, eosinophilia, or both. Therefore, patients should be observed carefully during therapy with enalapril. Discontinuation of therapy is required in patients who develop neutropenia, eosinophilia, or agranulocytosis (see ADVERSE REACTIONS). Discontinuation of therapy was required in 6.0% of patients in clinical trials. In clinical trials, the overall frequency of adverse experiences was not related to total daily dosage within the range of 10 to 80 mg/day. In patients with severe congestive heart failure, renal function should be monitored during therapy with enalapril. If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion. Patients who are dehydrated or salt-depleted as a result of diuretic therapy or volume contraction from any cause should be volume expanded prior to the initiation of enalapril therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pretreatment renal vascular disease have developed increases in blood urea nitrogen and serum creatinine. These increases were usually reversible upon discontinuation of enalapril and/or diuretic therapy.

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**Chemical Laboratory Test Findings**

**Serum Electrolytes**

Hyperkalemia has been reported (see PRECAUTIONS).

**Blood Urea Nitrogen**

Serum creatinine and blood urea nitrogen may increase in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone increases more in patients receiving concomitant diuretics or in patients with renal artery stenosis (see PRECAUTIONS).

**Other (Causal Relationship Unknown)**

In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

**Dosage and Administration**

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should be discontinued or the dose of diuretic reduced in these patients (see PRECAUTIONS). The diuretic should be discontinued or the dose of diuretic reduced in these patients (see PRECAUTIONS). The diuretic should be discontinued or the dose of diuretic reduced in these patients (see PRECAUTIONS). The diuretic should be discontinued or the dose of diuretic reduced in these patients (see PRECAUTIONS). The diuretic should be discontinued or the dose of diuretic reduced in these patients (see PRECAUTIONS). The diuretic should be discontinued or the dose of diuretic reduced in these patients (see PRECAUTIONS).

**Dosage Adjustment in Renal Impairment**

The usual dose of enalapril is recommended for patients with renal impairment (see PRECAUTIONS). The use of diuretics may be associated with a reduction in the volume of distribution of enalapril and may require a reduction in the starting dose and dosage frequency. The starting dose of 5 mg once daily is recommended in patients with mild to moderate renal impairment (GFR 10-50 ml/min). The starting dose of 5 mg once daily is recommended in patients with mild to moderate renal impairment (GFR 10-50 ml/min). The starting dose of 5 mg once daily is recommended in patients with mild to moderate renal impairment (GFR 10-50 ml/min). The starting dose of 5 mg once daily is recommended in patients with mild to moderate renal impairment (GFR 10-50 ml/min). The starting dose of 5 mg once daily is recommended in patients with mild to moderate renal impairment (GFR 10-50 ml/min).

**Concomitant Administration of VASOTEC with Potassium-Binding Resin Diuretics**

If concomitant use of these agents is unavoidable, serum potassium levels should be monitored regularly (see PRECAUTIONS). Discontinuation of therapy was required in 6.0% of patients in clinical trials. In clinical trials, the overall frequency of adverse experiences was not related to total daily dosage within the range of 10 to 80 mg/day. In patients with severe congestive heart failure, renal function should be monitored during therapy with enalapril. If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion. Patients who are dehydrated or salt-depleted as a result of diuretic therapy or volume contraction from any cause should be volume expanded prior to the initiation of enalapril therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pretreatment renal vascular disease have developed increases in blood urea nitrogen and serum creatinine. These increases were usually reversible upon discontinuation of enalapril and/or diuretic therapy.

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Canada and Mexico $47.50

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A Fujimura and A Ebihara

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