hydrolyzed to enalaprilat, which is a more potent angiotensin converting enzyme inhibitor. As with all vasodilators, enalapril should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

Impaired Renal Function:

In using VASOTEC consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they are on diuretics. The possible implications of these findings in patients on VASOTEC therapy are unclear, but monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Neutropenia/Agranulocytosis

Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they are on diuretics. The possible implications of these findings in patients on VASOTEC therapy are unclear, but monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

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Heart Failure, Mortality Trials

In both CONSENSUS and SOLVD-Treatment trials, patients were also usually receiving digitalis, diuretics or both. In the SOLVD-Prevention trial (every 4 months at the time of follow-up), data from patients who were hospitalized for heart failure had no prior symptoms recorded which would have signaled initiation of treatment. In the CONSENSUS trial, 20 percent of patients died whilst receiving placebo and 14 percent of patients died whilst receiving VASOTEC. The results of these studies and of the SOLVD-Prevention trial are consistent with the findings of the Digitalis Investigation Group study and the SOLVD-Treatment trial (see CLINICAL PHARMACOLOGY).

Additional Information:

The addition of a thiazide diuretic may be useful in some patients to further reduce blood pressure and increase compliance. When given concomitantly with a diuretic, the incidence of adverse effects is increased. In patients with concomitant renal impairment the diuretic dose should be reduced. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

In the SOLVD study, digitalis therapy was usually continued throughout the trial, but the incidence of angioedema was lower in patients on digitalis compared to those not on digitalis.

Under certain circumstances, rapidly reversible increases in blood pressure may occur. In patients with severe hypertension, this may require more vigorous management. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, larynx or glottis, immediate intubation may be necessary. Discontinue VASOTEC as soon as possible. These adverse outcomes are sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include those with the following conditions or symptoms: hypertension, heart failure, renal impairment (creatinine >2.5 mg/dL), cerebral vascular disease (e.g., significant carotid artery disease), advanced pulmonary disease, malignancies, active myocarditis and constrictive pericarditis. The potential for development of angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by exclusion other causes. The angioedema was diagnosed following a negative evaluation for other causes. The angioedema was diagnosed following a negative evaluation for other causes. The angioedema was diagnosed following a negative evaluation for other causes. The angioedema was diagnosed following a negative evaluation for other causes.

Concomitant Therapy: ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. This has been observed in patients with heart failure and renal impairment receiving diuretics. It has also been observed in patients with CAD and renovascular hypertension treated with ACE inhibitors. In these patients, serum levels of angiotensin II may be elevated, contributing to increased peripheral vascular resistance and plasma renin activity. The risk of hypotension and renal damage in these patients appears to be greater when ACE inhibitors are given concomitantly with a diuretic. Close monitoring of blood pressure and renal function is recommended when VASOTEC is used concomitantly with diuretics in patients with heart failure and renal impairment or patients with CAD and renovascular hypertension.

In patients with stable heart failure and renal impairment, who are already taking VASOTEC, the rate of development of oliguria and/or acute renal failure is low. However, in patients with heart failure and renal impairment who are receiving concomitant diuretics and VASOTEC, the incidence of oliguria and/or acute renal failure is higher. Close monitoring of renal function is recommended in these patients. In a study of patients with heart failure, a significant increase in serum creatinine and blood urea nitrogen was observed during treatment with VASOTEC. In all of these patients, however, the increases were almost always reversible upon discontinuation of VASOTEC and/or diuretic therapy. These findings suggest that VASOTEC may be associated with exacerbation of renal function in patients with heart failure and renal impairment.

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Preparation of Suspension (for 200 mL of a 1.0 mg/mL suspension)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to the blood pressure response. It is advised to administer the dose in the morning. The dose may be increased to 10 mg once a day or divided doses, after titration as described above. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the day and it may be advantageous to administer a single dose in the morning or a single dose at bedtime. If the morning dose is used, it should be initiated with 2.5 mg once daily and the dosage increased to 5 mg once daily (or divided), if needed, to achieve the desired response. For patients who are older than 65 years, the recommended initial dose is 2.5 mg once daily. Dosage should be increased to 5 mg daily, or divided, as needed.

The usual recommended starting dose is 0.08 mg/kg (up to 5 mg) once daily. Dosage may be increased to 0.12 mg/kg (up to 10 mg) once daily based on blood pressure response and tolerability.

The dose may be increased to 10 mg once a day or divided doses, after titration as described above. If the morning dose is used, it should be initiated with 2.5 mg once daily and the dosage increased to 5 mg daily (or divided), if needed, to achieve the desired response. For patients who are older than 65 years, the recommended initial dose is 2.5 mg once daily. Dosage should be increased to 5 mg daily, or divided, as needed.

Enalaprilat may be removed from general circulation by hemodialysis and has been shown to be promptly removed from the plasma following an intravenous bolus dose in patients on chronic hemodialysis. A dose of 2.5–5 mg should be administered before hemodialysis. Hemodialysis should be performed immediately after administration of the dose. The dose should be increased to 10 mg after the second or third dialysis and should be increased by 5 mg after each subsequent dialysis to prevent hypotension.

If post-dialysis blood pressure is excessively low, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension.

In patients with heart failure who have hyponatremia (serum sodium less than 130 mEq/L) or with serum creatinine greater than 1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision (see PRECAUTIONS).

In the trial that demonstrated efficacy, patients were started on 2.5 mg twice daily and were titrated as tolerated to the targeted daily dose of 20 mg (in divided doses). If possible, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC Placebo was comparable to placebo.

In the trial that demonstrated efficacy, patients were started on 2.5 mg twice daily and were titrated as tolerated to the targeted daily dose of 20 mg (in divided doses). If possible, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC Placebo was comparable to placebo.

In patients with essential hypertension treated with VASOTEC alone. Increases are not likely to be of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients have developed hemolytic anemia. A causal relationship to enalapril cannot be excluded.

Inhibitors of renin or angiotensin II are strong vasodilators and are capable of precipitating angioedema. The risk of angioedema is greater in patients with a history of angioedema or asthma. Angioedema has been reported in patients receiving VASOTEC, with an incidence of 0.003 per patient-year of exposure (see PRECAUTIONS, ADVERSE REACTIONS, and PATIENT INFORMATION).

Dosage on nondialysis days should be adjusted depending on the blood urea nitrogen levels. This is important for patients with normal renal function. In patients with renal impairment, dialysis may be used to remove enalaprilat from the plasma. This may be necessary for patients with normal renal function. In patients with renal impairment, dialysis may be used to remove enalapril from the plasma. This may be necessary for patients with normal renal function. In patients with renal impairment, dialysis may be used to remove enalapril from the plasma. This may be necessary for patients with normal renal function.

The recommended initial dose is 2.5 mg. The recommended dosing range is 2.5 mg to 10 mg/day. The dose should be increased to 10 mg once a day or divided doses, after titration as described above. If the morning dose is used, it should be initiated with 2.5 mg once daily and the dosage increased to 5 mg daily (or divided), if needed, to achieve the desired response. For patients who are older than 65 years, the recommended initial dose is 2.5 mg once daily. Dosage should be increased to 5 mg daily, or divided, as needed. The dose may be increased to 10 mg once a day or divided doses, after titration as described above. If the morning dose is used, it should be initiated with 2.5 mg once daily and the dosage increased to 5 mg daily (or divided), if needed, to achieve the desired response. For patients who are older than 65 years, the recommended initial dose is 2.5 mg once daily. Dosage should be increased to 5 mg daily, or divided, as needed.

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