Avoiding the risk of aspiration in intubated infants

JOSEPH M. BRAND, DO
NANCY L. BRODSKY, PHD
HALLAM HURT, MD

Aspiration is a potential problem in intubated infants who are fed enterally. In this prospective study,¹⁰ intubated preterm infants were fed orogastrically or oroduodenally. Aspiration was assessed by examining endotracheal aspirates for evidence of blue-colored dye. None of the babies had blue-colored endotracheal secretions when fed by either route. Heart and respiratory rates, blood pressure, and transcutaneous oxygen and carbon dioxide measurements were recorded at each interval of the study. There were no significant differences from baseline for these measurements. These findings indicate that there is no significant aspiration in intubated preterm infants who are fed by the orogastric or the oroduodenal route.

Achievement of adequate caloric intake in sick neonates who require assisted ventilation is difficult, and the most effective manner of feeding remains controversial.¹⁻⁶ Although total parenteral nutrition can be used, its attendant complications⁷ have led most nurseries to initiate enteral feedings in infants who need long-term ventilator support. Some authors advocate duodenal feedings,⁶ whereas others recommend the gastric⁵ approach. In clinical practice, nasoduodenal, oroduodenal, nasogastric and orogastric methods all are used.

Aspiration is one of the hazards of feeding infants who are intubated with uncuffed endotracheal tubes, with previous studies^{8,9} showing an incidence of 75% to 80%. Specifically, Goodwin and associates⁹ reported that 16 of 20 intubated premature infants had evidence of aspiration.

Concerned that our ventilator-dependent infants could be having episodes of silent aspiration, we decided to evaluate the incidence of aspiration in our own nursery. The purpose of this study was twofold: (1) to evaluate the incidence of aspiration

in intubated infants by instilling a dye-colored formula directly into the stomach or duodenum; and (2) to compare the incidences of aspiration in intubated infants fed by the orogastric versus the oroduodenal route.

Materials and methods

In a prospective, crossover study, the incidence of aspiration was evaluated in 10 preterm infants (six boys, 4 girls) who were fed by both orogastric and oroduodenal routes. All infants were intubated with an uncuffed endotracheal tube, were on mechanical ventilation for longer than 72 hours, and were given enteral feedings of 100 cc/kg/day for at least 24 hours.

The mean birthweight was 889 ± 325 (range, 600 g to 1670 g), and the mean gestational age was 27.5 ± 2.5 weeks (range, 25 weeks to 33 weeks). Mean weight and age at initiation of the study were 1203 ± 339 g (range, 740 g to 1940 g) and 35.9 ± 22.3 days (range, 10 days to 74 days), respectively.

To achieve a distinguishable color, one drop of sterile Food, Drugs & Cosmetics [Act] #1 blue dye was mixed with 30 cc of infant formula. To assess the effect of dilution with gastric or duodenal contents, sterile water was mixed with the solution; color was still distinguishable at a dilution of 1:64.

All infants were placed in the 30-degree elevated prone position while being fed to minimize any gastroesophageal reflux.¹⁰ Infants fed by the bolus and continuous feeding methods were kept in this position 2 and 3 hours, respectively. Initially, nine infants were fed dye-colored formula by the oroduodenal route, and one was fed orogastrically. After at least a 24-hour washout period, the same infants were fed by the alternate route. Nine babies were fed by bolus and one by the continuous method through the orogastric tube; all were fed by the continuous method through the oroduodenal tube. Placement of the oroduodenal tube was verified by roentgenography.

To test for aspiration after a bolus feeding, the infant's endotracheal tube was suctioned 10, 30, 60, and 120 minutes post-feeding. For continuous feedings, the formula was infused for at least 60

minutes prior to obtaining aspirates at study intervals. At each interval, endotracheal secretions were collected in a separate mucous trap. Heart and respiratory rates, blood pressure, and transcutaneous oxygen and carbon dioxide measurements were recorded at each time interval.

Aspiration was assessed by examining endotracheal aspirates for evidence of blue-colored dye. The infant's nurse and a physician observed and recorded the color of the secretions at study intervals. In addition, at the end of the study, one of the investigators (JMB) reviewed all specimens for evidence of blue color.

The protocol for this study was approved by the Institutional Review Board, and informed, written parental consent was obtained prior to study in all cases. Statistical analysis included the two-tailed Student's t-test; a difference of $P < 0.05$ was considered to be significant. Data are presented as the mean $\pm$ SD.

Results

No infant had evidence of formula aspiration; all collected secretions were clear. In addition, there were no significant differences from baseline for respiratory rate, blood pressure, and transcutaneous oxygen and carbon dioxide measurements with either orogastric or oroduodenal feeding.

Discussion

In our study, no infant had evidence of aspiration when fed oroduodenally or orogastrically. This finding is in marked contrast to that of Goodwin and associates,⁹ who reported aspiration in 80% of intubated preterm infants. Their high incidence of aspiration may be related to their testing method, which was instillation of a solution of Evans' blue dye directly onto the tongue rather than into the stomach. It is possible that some dye mixed with saliva and was aspirated.

Although reflux has been shown to be dependent on volume in the stomach at any given time,¹¹ this variable was minimized, because nine of 10 infants were fed by bolus through the orogastric tube. By placing our dye-colored formula directly into the stomach or duodenum, we specifically addressed the issue of formula aspiration.

Conclusion

From our data, we conclude that the risk of aspiration of formula is low in intubated preterm infants who are fed in the 30-degree prone position via the orogastric or the oroduodenal route.

Supported in part by grant F-85-02 from Burroughs-Wellcome Osteopathic Research Fellowship and by research funds from the National Osteopathic Foundation Mead Johnson Fellowship Grant Program.

1. Beddis J, McKenzie S: Transpyloric feeding in the very low birth-weight (1500 g and below) infant. *Arch Dis Child* 1979;54:213-217.
2. Benda GIM: Modes of feeding low-birth-weight infants. *Semin Perinatol* 1979;3:407-415.
3. Dryburgh E: Transpyloric feeding in 49 infants undergoing intensive care. *Arch Dis Child* 1980;55:879-882.
4. Minoli I, Moro G, Ovadia MF: Nasoduodenal feeding in high-risk newborns. *Acta Paediatr Scand* 1978;67:161-168.
5. Pereira GR, Lemons JA: Controlled study of transpyloric and intermittent gavage feeding in the small preterm infant. *Pediatrics* 1981;67:68-72.
6. VanCaillie M, Powell GK: Nasoduodenal versus nasogastric feedings in the very low birthweight infant. *Pediatrics* 1975;56:1065-1072.
7. Postuma R, Trevenen CL: Liver diseases in infants receiving total parenteral nutrition. *Pediatrics* 1979;63:110-115.
8. Browning DH, Graves SA: Incidence of aspiration with endotracheal tubes in children. *J Pediatr* 1983;102:582-584.
9. Goodwin SR, Graves SA, and Haberkern CM: Aspiration in intubated premature infants. *Pediatrics* 1985;75:85-88.
10. Meyers WF, Herbst JJ: Effectiveness of positioning therapy for gastroesophageal reflux. *Pediatrics* 1982;69:768-772.
11. Herbst JJ: Gastroesophageal reflux. *J Pediatr* 1981;98:859-870.

From Albert Einstein Medical Center, Northern Division, Temple University School of Medicine, Philadelphia.

Reprint requests to Joseph Brand, DO, St. Vincent's Hospital, Perinatal Center, PO Box 13508, Green Bay, WI 54307-3508.

THE NEWLY
DIAGNOSED HYPERTENSIVE

THERAPY SHOULD NOT CHANGE
THE WAY HE FEELS

For a Brief Summary of Prescribing Information, please see the last page of this advertisement.

LOWER HIS BLOOD PRESSURE,
NOT HIS PERFORMANCE

FOR MANY HYPERTENSIVE PATIENTS
START WITH ONCE-A-DAY

VASOTEC[®]
(ENALAPRIL MALEATE | MSD)

VASOTEC is generally well tolerated and not characterized by certain undesirable effects associated with selected agents in other antihypertensive classes. Thus, VASOTEC is being prescribed as initial therapy for hypertension by an increasing number of physicians.

VASOTEC generally has little or no effect on a patient's physical or mental activity, since it is not characterized by certain subjective symptoms (such as malaise or drowsiness) which may interfere with such activity. This highly favorable tolerability profile may be related to the specificity of action of VASOTEC on the renin-angiotensin-aldosterone system.

VASOTEC is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in heart failure patients), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. In patients at risk for excessive hypotension, therapy should be started under very close medical supervision, and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased.

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.

If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx develops, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. Angioedema associated with laryngeal edema may be fatal.

For more details, including information on treatment, see the Brief Summary of Prescribing Information on the last page of this advertisement.

VASOTEC® (ENALAPRIL MALEATE) MSD

VASOTEC is available in 2.5-mg, 5-mg, 10-mg, and 20-mg tablet strengths.

Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings: **Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. 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.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Heart failure patients given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in heart failure patients), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE 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 also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: **General:** **Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (> 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See Drug Interactions.)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that caution be exercised when lithium is used concomitantly with VASOTEC and serum lithium levels should be monitored frequently.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters. There are no adequate and well-controlled studies in pregnant women. VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of ¹⁴C enalapril maleate. It is known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 2,000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

Hypertension: The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

Heart Failure: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic tension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within the category:

Cardiovascular: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension; high-risk patients (see WARNINGS, Hypotension); cardiac arrest; pulmonary embolism and infarction; rhythm disturbances; atrial fibrillation; palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), late hypertrophy.

Respiratory: Bronchospasm, rhinorrhea, asthma, upper respiratory infection.

Skin: Herpes zoster, pruritus, alopecia, flushing, photosensitivity.

Other: Muscle cramps, hyperhidrosis, impotence, blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include fever, myalgia, and arthralgia; an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have appeared after discontinuation of therapy.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 1.9% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings:

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases 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 are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC. Rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: **Hypertension:** In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed. If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Interactions.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended in patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with a creatinine clearance < 30 mL/min (serum creatinine > 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and CAUTIONS, Drug Interactions.) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects.) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Heart Failure Patients with Renal Impairment or Hyponatremia: In heart failure patients with hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine > 1.6 mg/dL, therapy should be initiated at 2.5 mg once daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, Heart Failure, WARNINGS, and CAUTIONS, Drug Interactions.) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19386.

JVS36(815)

MS
MERCK
SHARP
DOHME