Jejunal diverticulosis: Report of a case and review of the literature

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A report of a case and review of the literature of jejunal diverticulum are presented. A 45-year-old woman presented with crampy, generalized abdominal pain which had been present intermittently for five years. A complete endoscopic examination of the gastrointestinal tract was precipitated by an acute decrease in hemoglobin level. The diagnosis was made by detailed small bowel study. In a review of the literature, clinical features, difficulties in diagnosis, and complications are emphasized.

The Latin origin of the word diverticulum designates such structures, when found in the intestine, as byways or wayside prolongations of the lumen. Diverticula of the jejunum traditionally have been accorded benign status. However, the increasing number of reports that associate significant abnormalities to jejunal diverticula suggests that they should be regarded more seriously.

Patients with jejunal diverticulosis may be labeled psychoneurotic because most investigative studies fail to demonstrate organic disease.^{1,2} A typical patient complains of intermittent, frequently cramping abdominal pain, which usually is brought on or aggravated by eating. The pain is associated with nausea, vomiting, belching, flatulence, diarrhea, or constipation. Anemia and malnutrition may develop. Frequently, because of chronic gastrointestinal symptoms, the patient has had repeated roentgenographic examinations and has been seen by several physicians over a period of years. Although usually asymptomatic, diverticula can be associated with massive gastrointestinal

bleeding, perforation, obstruction, abscess formation, and malabsorption. The case described below illustrates some of the difficulties in the diagnosis of jejunal diverticulosis. The literature describing the features of the condition is then summarized.

Report of case

A 45-year-old white woman was first seen in the clinic on January 25, 1986, because of periodic stomach ache of five years' duration. Her abdominal discomfort was described as crampy and generalized, but worse in the right upper quadrant and epigastric regions. Onset was approximately 60 to 90 minutes after eating. Bloating, marked borborygmi, and flatus were always associated with pain. The patient stated that she had noted foul-smelling watery stools on and off for the past six months; dark red blood mixed with the stool had been noted for three months. There was no history of weight loss. The patient emphasized the intermittent nature of the pain, stating that she could sometimes eat without difficulty, while there were other times when eating resulted in severe cramping or vomiting.

She had a past medical history of appendicitis, bronchitis, and vaginitis, and a surgical history of appendectomy, tonsillectomy, and right ovarian cystectomy. The family history was positive for peptic ulcer disease, diabetes mellitus, rheumatic fever, and cancer of the colon, uterus, and vulva. She had no known allergies and did not use tobacco or ethanol. She had taken Bentyl and Mylanta in the past, which had resulted in minimal to moderate relief of her abdominal symptoms.

The physical examination was essentially negative, with the exception of mild epigastric discomfort on palpation. Ultrasonography of the gallbladder was negative for gallstones or signs of infection. Hemoglobin and hematocrit values were 11.4 g/dL and 32.2%, respectively; stool was negative for occult blood. The patient was diagnosed as having irritable bowel syndrome with possible peptic ulcer disease, treated with ranitidine, and asked to return in one week. However, she had a synco-

pal episode within the following 48 hours and was hospitalized. Her hemoglobin level had decreased from 11.4 to 8.4 g/dL within the two-day period.

The patient was given packed red blood cells replacement, and her hemoglobin level subsequently stabilized and slowly increased. Upper gastrointestinal endoscopy, sigmoidoscopy, and colonoscopy failed to demonstrate any active bleeding sites. A detailed small-bowel study demonstrated two small hernial diverticula in the proximal jejunum. She was discharged on the eighth hospital day in stable condition and has been followed as an outpatient on a weekly basis with no evidence of recurrent bleeding or anemia, or complaints of abdominal pain or discomfort. She was given a two-week course of oral antibiotic treatment, (metronidazole, 500 mg., 3 times a day). The patient declined further antibiotic treatment.

Discussion

Pathologic anatomy and physiology

Hernial diverticula of the small intestine appear as rounded or elliptic, single or multiloculated out-pouchings of the intestinal wall. The sac wall is thin and is composed largely of mucosal and adventitious submucosal fibrous tissue. It lacks the well-developed smooth muscle layers that are characteristic of the normal, adjacent small intestine. Hernial diverticula is the type that often becomes pathologic. The terms acquired, pseudo, false, or pulsion diverticula are used interchangeably to denote these structures, in contradistinction to the other form of intestinal diverticulum, which is known as congenital or true diverticulum.^{2,3}

The pathogenesis of these false diverticula is unclear, but they may result from an abnormal increase in intraluminal pressure in the small intestine.^{3,4} Relative weakness of the bowel at the sites of neurovascular entry plus high intraluminal pressure allow protrusion of the mucosa and submucosa.²

Devoid of muscle and composed only of mucosa and submucosa, the atonic diverticula empty poorly. The absence of normal peristalsis may be important in the etiology of malabsorption, which is secondary to bacterial overgrowth.

Incidence, age and sex distribution

Jejunal diverticulosis is an infrequent radiologic or surgical finding. The reported frequency at autopsy approximates 0.2%.⁴ Because these diverticula are acquired structures, they are seen increasingly with aging; the highest incidence is in the sixth and seventh decades of life.^{5,6} Although the disorder is rarely seen before the age of 40, one case in a 10-year-old child has been reported.⁶ In a total of 48 cases studied by Taylor⁵ and Nobles,⁶ 31 patients were male and 17 were female (1.8:1 male predominance).

Clinical features and symptoms

It is estimated^{2,5} that only a small percentage of patients have symptoms that are clearly attributable to small-bowel diverticula. Because gastrointestinal workup may not demonstrate an organic problem, the patient may be thought to be neurotic.^{1,2} Typically, the patient reports periodic abdominal pain (usually cramping), which follows or is made worse by ingestion. Nausea and vomiting, flatulence and belching, and diarrhea or constipation often accompany the pain.

As in the present case, patients frequently are diagnosed as having irritable bowel syndrome and are treated accordingly. However, over a period of years, complications may occur.

Complications

Although rare, complications of the condition may be the presenting features of jejunal diverticula. Acute complications include massive hemorrhage, perforation, and obstruction, while anemia, malabsorption, and hypoproteinemia are chronic complications.⁷

Hemorrhage from jejunal diverticula occurs infrequently.⁴ The patient may present with vomiting of bright red blood or coffee grounds material; however, melena is the most common presenting complaint.⁵ In most cases, the bleeding is massive (decrease in hemoglobin level of 3-4 g/dL, but stops spontaneously). Following an initial hemorrhage, the probability of further bleeding increases.^{1,4}

Of the 48 patients in the studies of Taylor and Nobles, nine were in their 40s. Of these, five had massive hemorrhage, one had nonmassive melena, and one vomited blood. There has been no report of hemorrhage in patients under the age of 40. Twenty-seven of the 48 total cases occurred after the age of 60. With an increasing population of older persons, jejunal diverticula may prove to be of greater importance as a cause of gastrointestinal bleeding.

Perforation has been reported in less than 50 cases of jejunal diverticula. Perforation can present as spontaneous asymptomatic pneumoperitonitis or as diverticulitis with localized or generalized peritonitis.⁸ Fecal contamination may enter the peritoneal cavity through minute perforations in the wall of the diverticula as a result of hyperactive peristaltic activity.

Obstruction, an uncommon complication, is attributed¹ to thickened hypertrophied walls of the jejunum associated with a large number of thin-walled diverticula. This results in jejunal dysfunction or dyskinesia, the more severe type of which would present with obstruction. Most often, mild

partial obstruction is associated with the symptoms of pain, distention, flatulence, and borborygmus, which become more severe as the diverticula enlarge.⁴ Hypoproteinemia is a frequent manifestation of the blind loop syndrome and may be severe enough to cause edema. Jejunal diverticulosis is one of many lesions that may cause the blind loop syndrome—vitamin B₁₂ malabsorption, megaloblastic anemia, and steatorrhea. This triad is rare, however, with only 24 cases having been recorded in the literature.⁹

Bacterial overgrowth is the common factor in all malabsorption problems stemming from intestinal stasis.¹⁰ Multiple factors may be responsible for bacterial overgrowth: the emptying ability of small-bowel diverticula, which are usually deficient of small-bowel muscle layers; the absence of normal peristalsis; and the less acid pH of the proximal small bowel. Bacterial utilization of vitamin B₁₂ in a competitive manner, as well as bacterial product interference with its absorption, have been postulated as mechanisms by which vitamin B₁₂ deficiency occurs.⁹

Diagnosis

The diagnosis of jejunal diverticula can be difficult. Physical examination usually is noncontributory. The syndrome of vague abdominal pain, anemia of obscure origin, and slightly dilated loops of jejunum points to jejunal diverticulosis.⁴ The diagnosis usually is made by abdominal roentgenograms demonstrating air-fluid levels or barium in the diverticula. The frequency of diagnosis depends on the skill and awareness of the radiologist. Diagnosis may be confirmed at surgery, but diverticula hidden by loops of adherent jejunum or buried in the mesentery may be overlooked.² Of course, if the patient presents with active gastrointestinal bleeding, angiography will identify the site if blood loss is ≥ 5 mL/min.

Treatment

Medical therapy for symptomatic jejunal diverticulosis involves management of complications such as diverticulitis, small-bowel bacterial overgrowth, and vitamin B₁₂ deficiency. Broad-spectrum antibiotics are used in episodic courses of one to two weeks per month to suppress bacterial overgrowth. Symptoms of diarrhea, bloating, and significant weight loss often will improve with this therapy.⁷ Parenteral B₁₂ can be given to replete losses of this vitamin.

There is little information on the use of motility-promoting agents, such as metoclopramide, in the treatment of pseudo-obstruction associated with jejunal diverticulosis. However, an empiric trial in

an attempt to enhance upper gastrointestinal motility may be considered.

Surgical resection generally is reserved for patients with serious complications, such as hemorrhage, perforation, and complete small bowel obstruction.

Summary

The jejunum is one of the least likely sites of the gastrointestinal tract to be affected by diverticulosis. The condition is almost twice as common in men, and it occurs most frequently in the sixth and seventh decades of life. Abdominal complaints are present in only 10% to 20% of affected individuals; in most cases these consist of postprandial abdominal pain, distention, flatulence, nausea, and vomiting. Rarely are acute symptoms, such as massive gastrointestinal hemorrhage, obstruction, or perforation, the initial presenting complaint.

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This fixed-dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated or given a diuretic and enalapril simultaneously can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, to begin enalapril at a low initial dose (2.5 mg; see DOSAGE AND ADMINISTRATION). This fixed-dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

VASERETIC, containing 10 mg enalapril maleate and 25 mg hydrochlorothiazide, is contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Evaluation of the hypertensive patient should always include assessment of renal function.

*Although enalapril was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalapril maleate monotherapy than non-black patients. In contrast, hydrochlorothiazide was more effective in black patients than enalapril. Concomitant administration of enalapril maleate and hydrochlorothiazide was equally effective in black and non-black patients.

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CONTRAINDICATIONS

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WARNINGS

Hypotension: 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. Syncope has been reported in 1.3% of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5%. The overall incidence of syncope may be reduced by proper titration of the individual components (see PRECAUTIONS, Drug Interactions, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION in complete Prescribing Information). 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. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased.

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.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with angiotensin-converting enzyme inhibitors, including enalapril. In such cases, VASERETIC 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).**

Neutropenia/Agranulocytosis: Another angiotensin-converting enzyme inhibitor 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.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, Drug Interactions: Hydrochlorothiazide).

PRECAUTIONS

General: Enalapril Maleate: 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 congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors, including enalapril, 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 hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function.**

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials treated with enalapril alone. In most cases, these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1%) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia (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.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid and electrolyte imbalance, namely hypokalemia, hyponatremia, hypochloremia, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving

parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see Drug Interactions: Agents Increasing Serum Potassium).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus, latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathetic patient.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

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 and/or difficulty in 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, 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 VASERETIC® (Enalapril Maleate-Hydrochlorothiazide, MSD) 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: Enalapril Maleate: 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 medical supervision for at least one hour after the initial dose (see WARNINGS and DOSAGE AND ADMINISTRATION). **Agents Causing Renin Release:** The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics). **Other Cardiovascular Agents:** Enalapril has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-channel blockers, hydralazine, and prazosin without evidence of clinically significant adverse interactions. **Agents Increasing Serum Potassium:** Enalapril attenuates diuretic-induced potassium loss. 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, they should be used with caution and with frequent monitoring of serum potassium.

Hydrochlorothiazide: When administered concurrently, the following drugs may interact with thiazide diuretics. **Alcohol, barbiturates, or narcotics:** potentiation of orthostatic hypotension may occur. **Antidiabetic drugs (oral agents and insulin):** dosage adjustment of the antidiabetic drug may be required. **Other antihypertensive drugs:** additive effect or potentiation. **Corticosteroids, ACTH—**intensified electrolyte depletion, particularly hypokalemia. **Pressor amines (e.g., norepinephrine)—**possible decreased response to pressor amines but not sufficient to preclude their use. **Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—**possible increased responsiveness to the muscle relaxant. **Lithium—**should not generally be given with thiazides. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC. **Nonsteroidal anti-inflammatory drugs—**In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when VASERETIC and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is maintained.

Pregnancy: Enalapril Maleate-Hydrochlorothiazide: Pregnancy Category C. There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2-1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2-1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight was observed in both species. No fetotoxicity occurred at lower doses; 30 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

There are no adequate and well-controlled studies in pregnant women. VASERETIC® (Enalapril Maleate-Hydrochlorothiazide, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. **Nonteratogenic Effects:** These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: It is not known whether enalapril is secreted in human milk, however, thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from hydrochlorothiazide, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

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

ADVERSE REACTIONS

VASERETIC has been evaluated for safety in more than 1,500 patients, including over 300 patients treated for one year or more.

In clinical trials with VASERETIC, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6%), headache (5.5%), fatigue (3.9%), and cough (3.5%). Generally, adverse experiences were mild and transient in nature.

Adverse experiences occurring in greater than 2% of patients treated with VASERETIC in controlled clinical trials are shown below:

	Percent of Patients in Controlled Studies VASERETIC (n = 1,500)	Placebo (n = 230)
Incidence (discontinuation)		Incidence
Dizziness	8.6 (0.7)	4.3
Headache	5.5 (0.4)	9.1
Fatigue	3.9 (0.8)	2.6
Cough	3.5 (0.4)	0.9
Muscle Cramps	2.7 (0.2)	1.7
Nausea	2.5 (0.4)	0.9
Asthenia	2.4 (0.3)	0.9
Orthostatic Effects	2.3 (<0.1)	0.0
Impotence	2.2 (0.5)	0.5
Diarrhea	2.1 (<0.1)	1.7

Clinical adverse experiences occurring in 0.5% to 2.0% of patients in controlled trials included: **Cardiovascular:** Syncope, orthostatic hypotension, palpitations, chest pain, tachycardia. **Nervous System:** Insomnia, nervousness, paresthesia, somnolence, vertigo. **Gastrointestinal System:** Abdominal pain, vomiting, dyspepsia, constipation, flatulence, dry mouth. **Other:** Dyspnea, gout, back pain, arthralgia, hyperhidrosis, pruritus, decreased libido, rash, tinnitus, urinary tract infection. **Angioedema:** Angioedema has been reported in patients receiving VASERETIC (0.6%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately (see WARNINGS). **Hypotension:** In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9%), orthostatic hypotension (1.5%), other orthostatic effects (2.3%). In addition, syncope occurred in 1.3% of patients (see WARNINGS).

Clinical Laboratory Test Findings: Serum Electrolytes: See PRECAUTIONS, 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 0.6% of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis (see PRECAUTIONS). **Serum Uric Acid, Glucose, Magnesium, and Calcium:** See PRECAUTIONS, Hemoglobin and Hematocrit. Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g and 1.0 vol %, respectively) occur frequently in hypertensive patients treated with VASERETIC but are 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):** Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below. **Enalapril Maleate:**—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials, adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: **Renal:** Renal dysfunction, renal failure, oliguria. **Hematologic:** Rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported in which a causal relationship to enalapril cannot be excluded. **Hydrochlorothiazide—Body as a Whole:** Weakness. **Digestive:** Anorexia, gastric irritation, cramping, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. **Hematologic:** Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia, **Mucosclerotic:** Musculoskeletal: Myositis, **Nervous System/Psychiatric:** Restlessness. **Special Senses:** Transient blurred vision, xanthopsia. **Hypersensitivity:** Purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.

HOW SUPPLIED

No. 3418—Tablets VASERETIC 10-25 are red, square capsule-shaped, compressed tablets, coded MSD 720 on one side and VASERETIC on the other. Each tablet contains 10 mg enalapril maleate and 25 mg hydrochlorothiazide. They are supplied as follows:

NDC 0006-0720-68 bottles of 100 (with desiccant).

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For more information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc. West Point, PA 19380 JVT04(302)