Coping with ulcers

KATHLEEN A. KUK

The stomach is designed to take a tremendous beating. Stuff it beyond its one-quart capacity, bathe it in irritating substances, deprive it of regularly scheduled meals...and the organ still steadfastly continues its chore of storing and mixing food. Ironically, the stomach is more commonly harmed not by any abuse we dish out, but by the self-destructive forces of its own acidic juices.

Contrary to popular belief, the stomach is not the primary site of digestion. The task of absorbing vital nutrients falls to the small intestine. In order to transform the bite-size chunks of food into a manageable slurry of chyme, the stomach secretes two powerful digestive juices: hydrochloric acid and the enzyme pepsin. The act of chewing—and often the mere whiff of food—is enough to start these juices flowing. To protect itself from these corrosive agents, the stomach has developed a host of defensive mechanisms, such as a mucous membrane barrier and a protective ring of muscles at critical junctures that prevent strong acids from backing up in the digestive process. Yet for unknown reasons, the delicate balance between secretion and protection sometimes fails. The result is a peptic ulcer. This raw spot or open sore can occur anywhere along the gastrointestinal tract. Ulcers may develop at the start of the food's passage through the body (at the base of the esophagus, for example) or near the end of the journey (in the large intestine). However, most ulcers appear at one of two sites: in the stomach itself (a gastric ulcer); or at the junction of the stomach and the first 10 inches of the small

intestine (a duodenal ulcer). (See figure on page 447/120.) Although the two types of ulcers share overlapping similarities, they also display fundamental differences. The chart on page 448/121 highlights these distinctions.

Ulcers are fairly common problems in America today. Over 400,000 new cases of ulcers are diagnosed every year. Although they are more common in adults, they can appear at birth and in childhood and adolescence. One of every 10 men and 1 of every 20 women will develop the digestive disease at some point in their life. This gender gap is beginning to close as more women enter the stress-filled business world—often while juggling all the responsibilities of a home. It only complicates matters that women in greater numbers have also adopted habits of heavy alcohol and tobacco use.

Simple indigestion ... or ulcer?

Concerned about whether last week's heartburn is really the harbinger of a more serious gastrointestinal disorder? Approximately half of ulcer victims exhibit the classic symptoms of a burning, gnawing sensation that lasts 30 minutes to 3 hours. Patients often complain of an empty, hungry soreness that is usually centered upon the upper abdomen but occasionally migrates into the lower chest below the breastbone. The transient pain may linger for weeks, and just suddenly disappear for a brief, pain-free period. The ache is often mistakenly attributed to heartburn, indigestion, or simple hunger pains.

The type of pain may be a clue to the location of the ulcer. The rule of thumb is that "cancers may ulcerate, but ulcers will not 'cancerate.'" Duodenal ulcers are rarely malignant, but 3% to 4% of gastric ulcers are cancerous. Therefore, a physician will keep a special eye on gastric ulcer patients who have recurrent ulcers or ulcers that are slow to heal.

Sites of ulcers in the gastrointestinal tract.

Diagnosing the ulcer

The physician will first gather a careful medical and personal history from the patient who comes to the office complaining of "stomach problems." Since ulcers tend to run in families, the physician will ask if siblings, parents, aunts and uncles, or grandparents had the disease. The doctor will also inquire about lifestyle and well-being; although research studies have shown conflicting results, one theory holds that stress can trigger ulcers. Doctors treating patients during the London Blitz of World War II noticed a dramatic increase in ulcer patients. While we do not have to grapple with nightly bombings, subtle yet constant pressures, such as a death in the family, work-related troubles, or tense interpersonal relationships, may trigger the stomach to produce greater-than-normal amounts of hydrochloric acid. Stress-induced ulcers can strike regardless of one's occupation or income.

A doctor will also query about medication habits. Nonsteroidal anti-inflammatory drugs and other aspirin-containing medications irritate the

sensitive linings of the digestive tract. Although these drugs have brought relief to millions of pain sufferers (particularly arthritic patients), they also carry risks. According to the American Rheumatism Association, long-term use of such pain relievers is associated with a 20% risk of developing peptic ulcers. Some studies suggest that enteric-coated aspirin (which does not dissolve until it reaches the intestine) is less harmful than plain or buffered aspirin. But to be safe, it is best to use aspirin substitutes such as acetaminophen if one is required to take large quantities of pain killers. And be on the look-out for "hidden aspirin." The ingredient lurks in many cold formulas, menstrual cramp relievers, and other over-the-counter drugs.

If your lifestyle and symptoms point to the possibility of an ulcer, the physician will likely order a rectal examination and stool test to check for hemorrhage and hidden (occult) blood. The next step will be a barium x-ray. In this diagnostic examination, the patient is asked to swallow a chalky contrast dye. This barium cocktail coats the digestive tract and highlights any abnormalities a vivid white against a black backdrop. This procedure is not fool-proof, and may miss 20% to 30% of ulcers. However, it is especially useful because of its ability to rule out other structural abnormalities of the esophagus, stomach, and intestine.

Therefore, an endoscopic examination of the stomach and intestine may be necessary. In this painless procedure, a thin scope is threaded down the throat and into the duodenum. (When inserting the tube, the back of the throat may be numbed to eliminate the gag reflex.) A small camera attachment allows the operator to peer into the dark passage. The flexible tube comes equipped with a small snare to snatch tissue samples for culture. Tests on a few cells will help to rule out the possibility of a cancerous growth.

Treating an ulcer

Ulcers are a quirky disorder. Some sores disappear spontaneously; other stubborn ulcers require professional treatment. Either way, half of all ulcers will recur within two years. The options open to

most sufferers are to treat acute attacks when they appear, use available medication as prevention to decrease the frequency of attacks, and amend one's lifestyle to help stave off future attacks. Most patients must attempt trial-and-error methods to discover what relieves the burning ache. Rest, antacids, and milk do the trick for many sufferers. The following treatment approaches all have their benefits and drawbacks. A team approach between patient and physician is necessary to discover the best regimen for each patient.

Antacids

The primary goal of these over-the-counter and prescription concoctions is to neutralize and absorb stomach acids. To be effective, they must be taken consistently and in adequate doses. "Taking a swig" now and again is a waste of time, effort, and money. Formulations on the market come in varying strengths, and cause differing side effects. Products containing magnesium hydroxide tend to cause diarrhea, while aluminum hydroxide-containing preparations cause constipation. Combination products tend to cancel out these unpleasant side effects. Another problem with antacids is that the sodium content in many formulations is too high for patients with co-existing problems of hypertension or congestive heart failure. These patients should read labels carefully and choose an antacid with a low sodium content.

H₂ Receptor antagonists

This new family of drugs has revolutionized ulcer treatment. Cimetidine (Tagamet) and ranitidine (Zantac) help cure ulcers by blocking acid secretion. Symptoms are commonly relieved within the first week, with healing occurring within 2 to 8 weeks. It must be remembered, however, that ulcers are a chronic, recurring disease. No treatment regimen has been successful in curing ulcers completely.

Anticholinergics

These acid-suppressing drugs have generally been superceded by the more successful H₂ receptor antagonists. The side effects of anticholinergics

A comparison of duodenal and gastric ulcers.

Duodenal

Peak occurrence in the 30-50 age bracket
Predominantly male disorder
Greater-than-normal acid secretion
Pain relieved by food and antacids
Diagnosis by UGI series is 70-80%
Rarely cancerous
Responds well to operation in which vagus nerve is cut
High association with blood group type O

Gastric

Peak occurrence in the 50-60 age bracket
Ratio of male:female is less dominant
Normal or less-than-normal acid secretion
Pain worsens with food, less relief with antacids
Diagnosis by UGI series is 90%
Cancer more common
Responds well to operation in which diseased portion of the stomach or intestine is removed
High association with blood group type A

(blurred vision, urinary retention, dry mouth) generally outweigh the benefits of the drugs. However, the drugs may still play a role in some treatment plans.

Barrier medications

A new class of drugs presents a novel approach of protecting the gastrointestinal tract by bolstering the mucosal barrier. The drugs bind to diseased patches of tissue and prevent further penetration of acid and pepsin. Sucralfate (Carafate) and other barrier medications appear beneficial with few side effects.

Surgery

If surgery is necessary, two types are performed: gastrectomy and vagotomy. In the former, the diseased portion of the stomach is removed and the remaining sections of the stomach are rejoined. The smaller stomach gamely takes over the job that was once handled by the larger, complete organ. Ulcerated sections of the intestine can also be removed and reattached by this procedure.

In vagotomy, a different surgical tactic is used.

Rather than excising the site of the disease, the "master controls" are adjusted. Vagus nerves run from the brain to the stomach, and carry messages governing muscular and secretory activity. Severing select nerves regulates the amount of acid entering the stomach. Often, a combination of vagotomy and gastrectomy is used.

Despite its successes, all surgery carries risks. For this reason, surgery is often restricted to stubborn ulcers that have not yielded to conservative methods, and in association with complications of uncontrolled bleeding, unremitting pain, perforation, cancer, and obstruction of the stomach into the duodenum. The decision for surgery, as well as which type of surgery, is unique to each case and should be discussed thoroughly between patient and physician.

Diet

Gone are the days when patients were put on a Spartan diet that banished all spicy foods, caffeine, and alcohol. Today, the school of thought is "all things in moderation." Alcohol seems to have a direct irritating effect on the sensitive tissue linings, but no studies have proven that alcohol "causes" ulcers. Alcoholics, however, do have an increased likelihood of developing an ulcer. Likewise, caffeine is known to stimulate stomach acid secretion. However, it will not "cause" ulcers in the amount consumed by normal eating habits. The best rule of thumb is to avoid these foods if they cause pain, and to eat them sparingly if you do already have an ulcer.

These substances pose an exception: aspirin, nonsteroidal anti-inflammatory drugs (such as ibuprofen), and nicotine. Aspirin definitely aggravates the stomach lining, and all persons with ulcers should choose a nonaspirin substitute for pain relief. And everyone (whether or not they have an ulcer) should refrain from smoking. Studies

show that persons who smoke more than 10 cigarettes a day have more difficulty recovering from an ulcer, and are more likely to have the ulcer recur once it has disappeared.

Prevention

Ulcer prevention is important—just follow the rules for a normal, healthy lifestyle. Eat healthy meals, do not smoke, make moderate use of alcohol, caffeine, and aspirin-containing drugs, and learn to cope with stress. And see your physician about any pertinent stomach complaint—no matter how innocuous it seems.

(All material in the Patient Health Guide is reviewed by JAOA referees.)

References

- Drug therapy for peptic ulcer disease. By J. Voirin. *American Family Physician*, vol. 30, pp. 154-9, Dec 1984
- Drug therapy for preventing peptic ulcer recurrence. By J.E. Sutherland. *American Family Physician*, vol. 34, pp. 141-4, Nov 1986
- NSAID use may result in development of peptic ulcer lesions. *American Family Physician*, vol. 32, pp. 275-7, Oct 1985
- Peptic ulcer. In *The Merck manual of diagnosis and therapy*. Edited by R. Berkow, Merck Sharp & Dohme Research Laboratories, Rahway, NJ, 1982, pp. 724-36
- Peptic ulcer disease. By E.D. Medley. *Journal of Family Practice*, vol. 18, pp. 443-63, Mar 1984
- Peptic ulcer disease: Current management in the elderly. By E. Achkar. *Geriatrics*, vol. 40, pp. 77-83, Sep 1985
- The American Medical Association Family medical guide*. Random House, 1982
- Ulcers*. By M.M. Eisenberg. Random House, New York, 1978

- American Osteopathic Association
1987 Convention, 3
Convention Registration
Form, 15, 16
Hotel Convention Registration
Form, 35, 36
- Beecham Laboratories
Fastin, 28-30
- Fisons Corporation
Nasalcrom, 65
- Lederle Laboratories
Asendin, 48, 49
- Lever Brothers, Inc.
Dove Bar, 11
- Lilly & Company, Eli
Ceclor, 4
- Marion Laboratories
Cardizem, 71-74
- Merck Sharp & Dohme
Vaseretic, 17-21
- Merrell Dow Pharmaceutical, Inc.
Lorelco, 59-62
Seldane, 91-94
- Muro Pharmaceutical Inc.
Bromfed, 77, 78
- Pfizer Laboratories
Diabinese, 52-54
Feldene, 111, 112
Procardia, 12-14
- Riker Laboratories
Norflex, 69, 70
- Roche Laboratories
Medical Director's Page, 51
- Roerig
Glucotrol, 66-68
Sinequan, 33, 34
- Ross Laboratories
Similac, Cover 3
- Sandoz Pharmaceuticals
Tavist, 55, 56
- Schering Laboratories
Normodyne, 6-8
- Smith Kline & French Laboratories
Tagamet, Cover 4
- Squibb & Sons, Inc., E.R.
Capozide, 37-40
- Stuart Pharmaceuticals
Tenoretic, 124-128
- Syntex Laboratories, Inc.
Anaprox, 23, 24
- Upjohn Company
Medrol, 26
Micronase, 44-46
Motrin, 57
Xanax, Cover 2-2
- Vitamin Diagnostics, Inc., 123

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For added blood pressure control,
a major office-based study shows*...

In the elderly regardless of previous therapy

PREVIOUS ANTIHYPERTENSIVE THERAPY	Change in BP [†]		
	n	Systolic	Diastolic
Beta blocker (monotherapy)	1,206	-22.9	-12.43
Diuretic (monotherapy)	820	-24.2	-14.4
Free combination			
• 2 drugs	2,346	-17.8	-10.2
• 3 drugs	517	-17.9	-9.6
• 4 drugs	142	-18.7	-10.8
Fixed combination	1,621	-21.97	-12.6

*TENORETIC Evaluation Program, an open 28-day study of 26,892 hypertensive patients (data on file, Stuart Pharmaceuticals, Wilmington, Delaware); physicians entered those patients needing more control than provided by monotherapy. TENORETIC is not indicated for the initial therapy of hypertension.

[†]Decreases in blood pressure were statistically significant.

**In the elderly
without added side effects**

- ▶ Total number of older patients treated: 9,098.
- ▶ No adverse reactions reported in 89.2%.
- ▶ Patients reported feeling either better than or as good as before: 94.7%.

See last page for brief summary of prescribing information.

ONE TABLET A DAY
Tenoretic[®]

Each tablet contains:

TENORMIN[®] (atenolol) 50 mg or 100 mg
and chlorthalidone 25 mg

**For added control and convenience
...without added side effects.**

STUART PHARMACEUTICALS

For added blood pressure control...

**In black males
regardless of age***

Age	n	Change in BP†	
		Systolic	Diastolic
<40	318	-18.9	-14.1
40-60	828	-20.5	-13.9
>60	322	-23.9	-13.7

*TENORETIC Evaluation Program, an open 28-day study of 26,892 hypertensive patients (data on file, Stuart Pharmaceuticals, Wilmington, Delaware): physicians entered those patients needing more control than provided by monotherapy. TENORETIC is not indicated for the initial therapy of hypertension.

†Decreases in blood pressure were statistically significant.

And in all patients
regardless of age, race, sex*

Type	n	Change in BP [†]	
		Systolic	Diastolic
Overall	26,892	- 20.99	- 13.1
White	19,185	- 20.9	- 12.9
Black	3,701	- 21.2	- 13.5
Other	1,147	- 22.3	- 13.8
Female	12,540	- 21.6	- 13.1
Male	11,844	- 20.3	- 13.1

*TENORETIC Evaluation Program, an open 28-day study of 26,892 hypertensive patients (data on file, Stuart Pharmaceuticals, Wilmington, Delaware); physicians entered those patients needing more control than provided by monotherapy. TENORETIC is not indicated for the initial therapy of hypertension.

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Each tablet contains:

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and chlorthalidone 25 mg

**Added control, added convenience
...without added side effects...
regardless of age, race, or sex.**

**Please consult complete product information before prescribing.
A summary follows:**

TENORETIC (atenolol and chlorthalidone) is for the treatment of hypertension. It combines the antihypertensive activity of two agents: a beta₁ selective (cardioselective) hydrophilic blocking agent (atenolol, TENORMIN) and a monosulfonamide diuretic (chlorthalidone).

INDICATIONS AND USAGE: TENORETIC is indicated for the treatment of hypertension. This fixed-dose combination drug is not indicated for initial therapy of hypertension. If the fixed-dose combination represents the dose appropriate to the individual patient's needs, it may be more convenient than the separate components.

CONTRAINDICATIONS: TENORETIC is contraindicated in patients with: sinus bradycardia, heart block greater than first degree, cardiogenic shock, overt cardiac failure (see WARNINGS), anuria, hypersensitivity to this product or to sulfonamide-derived drugs.

WARNINGS: **Cardiac Failure:** Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORETIC should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients receiving TENORETIC should be digitalized and/or be given additional diuretic therapy. Observe the patient closely. If cardiac failure continues despite adequate digitalization and diuretic therapy, TENORETIC therapy should be withdrawn.

Renal and Hepatic Disease and Electrolyte Disturbances: Since atenolol is excreted via the kidneys, TENORETIC should be used with caution in patients with impaired renal function.

In patients with renal disease, thiazides may precipitate azotemia. Since cumulative effects may develop in the presence of impaired renal function, if progressive renal impairment becomes evident, TENORETIC should be discontinued.

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

Ischemic Heart Disease: Although not yet reported with atenolol following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORETIC is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORETIC should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁-selectivity, however, TENORETIC may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁-selectivity is not absolute, the lowest possible dose of TENORETIC should be used and a beta₂-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs, it may be decided to withdraw TENORETIC before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents because of the risk of further depression of the myocardium.

Beta blockers are competitive inhibitors of beta-receptor agonists and their effects on the heart can be reversed by administration of such agents; eg, dobutamine or isoproterenol with caution (see section on OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg IV).

Metabolic and Endocrine Effects: TENORETIC may be used with caution in diabetic patients. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Atenolol does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest during chlorthalidone administration.

Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis and from whom TENORETIC therapy is to be withdrawn should be monitored closely.

Because calcium excretion is decreased by thiazides, TENORETIC should be discontinued before carrying out tests for parathyroid function. Pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy; however, the common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen.

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

PRECAUTIONS, General—Electrolyte and Fluid Balance Status: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Patients should be observed for clinical signs of fluid or electrolyte imbalance, ie, hyponatremia, hypochloremic alkalosis, 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 include dryness of the mouth, thirst, weakness, lethargy, drowsiness, 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 during concomitant use of corticosteroids or ACTH.

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 (eg, increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements or foods with a high potassium content.

Any chloride deficit during thiazide therapy is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). 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.

Drug Interactions: TENORETIC may potentiate the action of other antihypertensive agents used concomitantly. Patients treated with TENORETIC plus a catecholamine depletor (eg, reserpine) should be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude the therapeutic effectiveness of norepinephrine. Thiazides may increase the responsiveness to tubocurarine.

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such preparations with TENORETIC.

Should it be decided to discontinue therapy in patients receiving TENORETIC and clonidine concurrently, the TENORETIC should be discontinued several days before the gradual withdrawal of clonidine.

Other Precautions: In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. The possible exacerbation or activation of systemic lupus erythematosus has been reported. The antihypertensive effects of thiazides may be enhanced in the postsympathectomy patient.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study with atenolol, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents.

Atenolol was negative in the mouse dominant lethal test, the Chinese hamster in vivo cytogenetic test and the Salmonella typhimurium back mutation test (Ames test), with or without metabolic activation.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Use in Pregnancy: Pregnancy Category C. TENORETIC (atenolol and chlorthalidone) was studied for teratogenic potential in the rat and rabbit. Doses of 10, 100 and 300 mg/kg/day were administered orally to pregnant rats, with no teratologic effects observed. Two studies were conducted in rabbits. In the first study, pregnant rabbits were dosed with 10, 100 or 200 mg/kg/day. No teratologic changes were noted; embryonic resorptions were observed at all dose levels (ranging from approximately 5 times to 100 times the maximum recommended human dose). In a second rabbit study, dosages were 5, 10 and 25 mg/kg/day. No teratogenic or embryotoxic effects were demonstrated. It is concluded that the no-effect level for embryonic resorptions is 25 mg/kg/day (approximately 12.5 times the maximum recommended human dose) or greater. TENORETIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Atenolol—Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women.

Chlorthalidone—Thiazides cross the placental barrier and appear in cord blood. The use of chlorthalidone and related drugs in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving TENORETIC.

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

ADVERSE REACTIONS: TENORETIC is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient. The adverse effects observed for TENORETIC are essentially the same as those seen with the individual components.

Atenolol: The frequency estimates that follow derive from controlled studies in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both atenolol and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for atenolol and placebo is similar, causal relationship to atenolol is uncertain.

The data present these estimates in terms of percentages: first from the US studies (volunteered side effects) and then from both US and foreign studies (volunteered and elicited side effects):

US STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%).

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%).

RESPIRATORY (see WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%).

TOTALS US AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-1%), leg pain (3%-1%).

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%).

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%).

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%).

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

Chlorthalidone: Cardiovascular: orthostatic hypotension; Gastrointestinal: anorexia, gastric irritation, vomiting, cramping, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, CNS: vertigo, paresthesias, xanthopsia; Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; Hypersensitivity: purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis, cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis); Miscellaneous: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness. Clinical trials of TENORETIC conducted in the United States (89 patients treated with TENORETIC) revealed no new or unexpected adverse effects.

Potential Adverse Effects: In addition, a variety of adverse effects not observed in clinical trials with atenolol but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of atenolol. Nervous System: reversible mental depression progressing to cataplexy, hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, decreased performance on neuropsychometric tests; Cardiovascular: intensification of AV block (see CONTRAINDICATIONS); Gastrointestinal: mesenteric arterial thrombosis, ischemic colitis; Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura; Allergic: erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress; Miscellaneous: reversible alopecia, Peyronie's disease.

There have been reports of a syndrome comprising photosensitivity skin rash, conjunctivitis sicca, otitis, and sclerosing serositis attributed to the beta-adrenergic receptor blocking agent, practolol. This syndrome has not been reported with TENORETIC or TENORMIN (atenolol).

Clinical Laboratory Test Findings: Clinically important changes in standard laboratory parameters were rarely associated with the administration of TENORETIC. The changes in laboratory parameters were not progressive and usually were not associated with clinical manifestations. The most common changes were increases in uric acid and decreases in serum potassium.

DOSEAGE AND ADMINISTRATION: Initial dose should be one TENORETIC 50 tablet once a day. If optimal response is not achieved, the dosage should be increased to one TENORETIC 100 tablet once a day. Package insert should be consulted for dosage adjustments in cases of severe impairment of renal function.

HOW SUPPLIED: TENORETIC 50 Tablets (atenolol 50 mg and chlorthalidone 25 mg). NDC 0038-0115 (white, round, biconvex, uncoated tablets with TENORETIC 50 on one side and Stuart 115 on the other side) are supplied in bottles of 100 tablets. TENORETIC 100 Tablets (atenolol 100 mg and chlorthalidone 25 mg). NDC 0038-0117 (white, round, biconvex, uncoated tablets with TENORETIC 100 on one side and Stuart 117 on the other side) are supplied in bottles of 100 tablets.

Protect from heat, light, and moisture. Dispense in well-closed, light-resistant container.

Inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate.

STUART PHARMACEUTICALS

Division of ICI Americas Inc

Wilmington, DE 19897

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STR-2473

1919-2938ms

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All standard infant formulas meet certain criteria, including producing growth similar to that achieved with breast milk.

But one infant formula takes performance a step further and provides metabolic responses closest to those produced by breast milk.

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- ☐ Plasma essential amino acid profiles^{1,2} closer to those of breastfed infants than are those produced by whey-dominant formulas
- ☐ Plasma concentrations of zinc,³ taurine,⁴ serum urea nitrogen¹ and high-density lipoproteins⁵ equivalent* to those of breastfed infants
- ☐ Absorption of fat,⁶ calcium and phosphorus⁷ equivalent* to that of breastfed infants
- ☐ Bone mineralization⁸ equivalent* to that of breastfed infants

*No statistically significant differences between breastfed infants and infants fed SIMILAC® Infant Formulas

SIMILAC®

Infant Formulas

**Providing growth . . .
plus metabolic
response closest to the
breastfed infant**

1. Janas et al: *Pediatrics* 75:775-784, 1985.

2. Nauyok et al: Presented at Third International Symposium on Infant Nutrition and Gastrointestinal Disease, Brussels, Belgium, August 26, 1985.

3. MacLean: *Am J Clin Nutr* 40:1304, 1984.

4. Ross Study CP-AA64: Medical Department, Ross Laboratories, Columbus, Ohio.

5. Stein et al: *Circulation* 68(3):190, 1983.

6. Fomon et al: *Am J Clin Nutr* 23:1299-1313, 1970.

7. Ziegler and Fomon: *Infant Nutrition*, ed 2. WB Saunders Co, 1974, pp 267-297.

8. Roberts et al: *J Pediatr* 99:192-196, 1981.

Safety Highlights

from new research with h.s. dosing

Outstanding CNS safety profile

Based on a large U.S. study with h.s. dosing^{1,2*}

Less potential for theophylline interaction

Based on a pharmacokinetic study with normal subjects receiving Theo-Dur[®]† 300 mg. b.i.d. and Tagamet[®] 800 mg. h.s. vs. Tagamet[®] 300 mg. q.i.d.³

Documentation of safety in older patients

Before prescribing, see complete prescribing information in SK&F LAB CO. literature or PDR. The following is a brief summary.

Based on a large U.S. study with h.s. dosing¹

Indications: Tagamet[®] (brand of cimetidine) is indicated in the short-term treatment of active duodenal ulcer; in maintenance therapy after healing of active duodenal ulcers; in the short-term treatment of active benign gastric ulcer; and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison Syndrome, systemic mastocytosis and multiple endocrine adenomas).

Tagamet[®] HCl (brand of cimetidine hydrochloride) may be administered parenterally to hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or to patients who are unable to take oral medication.

Clinical studies have indicated that suppression of nocturnal acid is the most important factor in duodenal ulcer healing. Tagamet[®] 800 mg. h.s. is the regimen of choice for most patients for acute duodenal ulcer therapy, as it provides a high healing rate, maximal pain relief, a decreased potential for drug interactions, and maximal patient convenience. Other Tagamet[®] regimens in the U.S. shown to be effective are: 300 mg. q.i.d., with meals and at bedtime; and 400 mg. b.i.d., morning and bedtime.

In active duodenal ulcer, concomitant antacids should be given as needed for relief of pain; however, simultaneous administration is not recommended.

Contraindications: There are no known contraindications to the use of Tagamet[®].

Precautions: While a weak antiandrogenic effect has been demonstrated in animals, Tagamet[®] has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity in humans.

In a 24-month toxicity study in rats at dose levels approximately 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving Tagamet[®].

Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of Tagamet[®] HCl (brand of cimetidine hydrochloride) injection by intravenous bolus.

Symptomatic response to Tagamet[®] therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy. Reversible confusional states have been reported on occasion, predominantly in severely ill patients.

Tagamet[®] has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, lidocaine, theophylline and metronidazole. Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when Tagamet[®] is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either Tagamet[®] 300 mg. q.i.d. or 800 mg. h.s. concomitantly with a 300 mg. b.i.d. dosage of theophylline (Theo-Dur[®], Key Pharmaceuticals, Inc.), demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg. h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

*The most commonly reported adverse events were nausea, diarrhea, and headache; incidences were similar to those for placebo. Other adverse effects have been reported with Tagamet[®] therapy. Please see prescribing information for a complete description of precautions, adverse reactions, and drug interactions.

†theophylline anhydrous sustained action tablets/
Key Pharmaceuticals, Inc.

1. Data on file, Smith Kline & French Laboratories.
2. Sabesin, S., et al.: Postgrad. Med. [special report, interim data], pp. 43-46, Nov. 1985.
3. Seaman, J.J., et al.: Postgrad. Med. [special report], pp 47-53, Nov. 1985.

Lack of experience to date precludes recommending Tagamet[®] for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken in patients taking the drug since cimetidine is secreted in human milk.

Adverse Reactions: Diarrhea, dizziness, somnolence, headache, rash, gynecomastia. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported. Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported. Reversible impotence in patients with pathological hypersecretory disorders receiving Tagamet[®], particularly in high doses, for at least 12 months, has been reported. Reversible alopecia has been reported very rarely. Decreased white blood cell counts in Tagamet[®]-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and a few cases of aplastic anemia have also been reported. Increased serum transaminase and creatinine, as well as rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including hypersensitivity vasculitis, have been reported. Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving Tagamet[®] has been reported.

How Supplied: Tablets: 200 mg. tablets in bottles of 100; 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only); 400 mg. tablets in bottles of 60 and Single Unit Packages of 100 (intended for institutional use only); and in 800 mg. Tillab[®] tablets in bottles of 30 and Single Unit Packages of 100 (intended for institutional use only).

Liquid: 300 mg./5 ml., in 8 fl. oz. (237 ml.) amber glass bottles and in single-dose units (300 mg./5 ml.), in packages of 10 (intended for institutional use only).

Injection:

Vials: 300 mg./2 ml. in single-dose vials, in packages of 10 and 30, and in 8 ml. multiple-dose vials, in packages of 10 and 25.

Prefilled Syringes: 300 mg./2 ml. in single-dose prefilled disposable syringes.

Plastic Containers: 300 mg. in 50 ml. of 0.9% Sodium Chloride in single-dose plastic containers, in packages of 4 units. No preservative has been added.

ADD-Vantage[®] Vials: 300 mg./2 ml. in single-dose ADD-Vantage[®] Vials, in packages of 25.

Tagamet[®] HCl (brand of cimetidine hydrochloride) Injection premixed in single-dose plastic containers is manufactured for SK&F Lab Co. by Travenol Laboratories, Inc., Deerfield, IL 60015.

*ADD-Vantage[®] is a trademark of Abbott Laboratories.

BRS-TG-172

Date of issuance Mar. 1987

For acute duodenal ulcer
Tagamet[®]
brand of
cimetidine **800** mg
tablets **hs**