Cerebral Amyloid Angiopathy, Recurrent Intracerebral Hemorrhage, and Dementia in the Elderly

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DR FRANK S. CELESTINO (*Assistant Professor, Department of Family Medicine*): We begin today's Grand Rounds with the relatively common story of an older patient presenting with acute mental status changes. We could not realize at the time that this patient's evolving illness over the next 8 months would introduce us to a "new" threat to the aging cerebrum and would improve our understanding of emerging concepts relating dementia, cerebrovascular insufficiency, and normal brain aging.

CASE PRESENTATION

DR JOSEPH C. KONEN (*Assistant Professor, Department of Family Medicine*): Ms F.M., a 60-year-old woman, was admitted to the hospital in January 1988 for acute mental status changes, having been found at home lethargic, mumbling, incontinent of urine, and poorly responsive to family attempts at arousal. During the month preceding admission, Ms M.'s job performance as a bookkeeper had deteriorated markedly. Her employer had noticed increasing difficulty with even simple mathematics, while her family had noted unsteadiness of gait, difficulty focusing vision, and complaints of headache. For symptom relief she took alprazolam and a butalbital-aspirin combination.

Past medical history was most significant for a 20-year history of moderately well controlled hypertension with a negative radiologic and metabolic workup for secondary causes. Over the years there had been several episodes of symptomatic accelerated hypertension. On two occasions, brief complaints of facial and arm numbness were labeled as possible transient ischemic attacks. In 1985, type II diabetes mellitus was diagnosed. Ms M. denied smoking, rarely drank alcohol, and had no known allergies. No occupational exposures were evident. Family history was positive only for Ms M.'s father dying of atherosclerotic heart disease, two sisters and a child with hypertension, and one brother with a stroke. Medications included 0.5 mg of alprazolam, 1 to 2 tablets of a butalbital-aspirin combination, and 40 mg of propranalol, all taken three times a day, as well as 20 mg of furosemide and 5 mg of glyburide taken once daily.

At admission, her blood pressure was 170/100 mm Hg, her heart rate was 52 beats a minute and regular, her respirations were 20 per minute and unlabored, and her temperature was 36.9°C (98.2°F). The initial examination revealed an obtunded, mildly obese woman who was barely arousable by loud noises, name calling, or sternal rub. She was in no apparent distress and moved extremities purposefully to painful stimuli. The complete physical examination was otherwise normal except for mild bilateral papilledema as the only focal neurologic finding.

The following admission laboratory tests were either normal or negative: complete blood count, automated (SMAC 20) chemistry panel (excluding glucose of 17.4 mmol/L [313 mg/dL]), coagulation studies, thyroid function tests, serum iron, creatine kinase, sedimentation rate, arterial blood gases, ammonia level, rapid plasma reagin test, and ethanol level. Urine drug screening was positive only for barbiturates. Serum alprazolam level was therapeutic. Urine for heavy metals initially indicated mild arsenic elevation, but hair analysis and repeat urine tests were negative. Abdominal films were normal. Chest x-ray examination showed only borderline cardiomegaly. Electrocardiogram (ECG) showed mild sinus bradycardia, left anterior hemiblock, and left atrial dilatation. Cerebrospinal fluid (CSF) studies (including full cultures) were unre-

Submitted September 26, 1990.

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markable. The opening pressure was modestly elevated at 28.5 cm but no xanthochromia was noted. An electroencephalogram showed only nonspecific bifrontal intermittent rhythmic delta activity. An ophthalmology consultant verified mild optic disc edema without signs of neuritis or field cut.

Dr Williams will now review the results of the cerebral imaging procedures used to investigate Ms M.'s problem.

DR DANIEL WILLIAMS (*Neuroradiology Fellow, Department of Radiology*): An unenhanced cranial computed tomography (CT) scan done at admission demonstrated a possible subarachnoid hemorrhage, diffuse deep white matter radiolucencies, and poor delineation of the basilar cisterns and cerebral sulci (felt to be secondary to either cerebral edema or the presence of subarachnoid blood). A repeat CT scan 48 hours later revealed decreasing edema but no new findings.

Because of the clinical and radiologic suspicion of subarachnoid hemorrhage, a four-vessel cerebral arteriogram was performed. No abnormalities were detected. The patient did have prominent infundibula associated with the posterior communicating arteries, but there was no radiographic evidence that either of these had bled. Because of the difficulty in establishing a definitive diagnosis, a cranial magnetic resonance imaging (MRI) scan was performed. This study revealed extensive areas of increased T_2 signal involving the periventricular and subcortical white matter and brain stem, but failed to further clarify the clinical and CT findings.

DR KONEN: Because of the possibility of pseudotumor cerebri, the patient had been started on acetazolamide. The consulting neurologist believed, however, that the clinical picture was perhaps more compatible with "some unknown post-infectious demyelinating encephalitis or encephalopathy than pseudotumor." He recommended conservative, supportive management. The patient's hospital course was punctuated by marked fluctuations in mental status with days of clear sensorium, alertness, and full orientation interspersed with ones of confusion and agitation.

Having been lucid and oriented for nearly 3 days with normal blood pressure, Ms M. was discharged 13 days after admission with tentative diagnoses of nonspecific encephalitis, subarachnoid hemorrhage, possible pseudotumor cerebri, diabetes, and hypertensive vascular disease. She was sent home on acetazolamide, 250 mg daily, and her usual medications. Formal neuropsychological testing at the time of discharge documented persistent cognitive deficits with acquired intellectual impairment and abnormally low scores on receptive vocabulary, attention, and visual and verbal recall.

Three months after discharge, during an emergency department visit for severe headache and moderately elevated blood pressure, Ms M. had another enhanced cranial CT scan showing resolution of edema but persistent deep white matter lucencies.

In September of 1988, Ms M. presented, alert and talkative, to the emergency department with severe bifrontal headache and blood pressure of 160/110 mm Hg. While in the emergency department, she suddenly became unresponsive except to deep pain. Admission vital signs were normal except for a blood pressure of 160/110 mm Hg. As in January, Ms M. was obtunded yet moved extremities purposefully to painful stimuli. Complete physical and neurologic examinations were otherwise unremarkable except for a nonreactive, mid-position (4 to 5 mm) right pupil, mild right ptosis, and inability to adduct the right eye from the midline. This third nerve palsy was thought by a consulting neurologist to be secondary to edema or possible aneurysm.

As before, a complete laboratory evaluation was unrevealing. A rheumatology panel was negative. Serum and urine heavy metals were normal. CSF analysis was once again normal with an opening pressure of 16 cm and no xanthochromia. ECG was unchanged. As before, several cranial imaging modalities were used.

DR WILLIAMS: During the second hospitalization, an initial uninfused CT scan demonstrated unequivocal subarachnoid hemorrhage, cerebral edema with mild brain stem compression, obliteration of the basilar cisterns and sulci, and unchanged white matter lesions. A repeat CT scan 6 days later showed resolving edema and subarachnoid hemorrhage but also a new small lacunar infarct in the right caudate nucleus. After a second cerebral arteriogram failed to show any intracranial abnormalities, a gadolineum-enhanced MRI scan once again revealed the extensive deep white matter abnormalities and a hemorrhagic infarct of the head of the right caudate nucleus.

In retrospect it is interesting to reexamine the CT scan done during the emergency department visit between hospitalizations. It may, in fact, show a small subarachnoid hemorrhage.

DR KONEN: By the second hospital day, Ms M. was more alert with clear speech. A mental status examination showed loose associations, tangential thinking, flights of ideas, thought perseveration, poor orientation except to person, and deficits in judgment, calculation, and abstraction. Her memory was intact. Optic fundi and visual fields were normal. She was felt to have possible hypertensive encephalopathy and recurrent subarachnoid hemorrhage. Ms M. received corticosteroids, antihypertensive therapy, and increased acetazolamide.

Because of the patient's fluctuating mental status and confusing array of clinical, laboratory, and radiologic findings, an open biopsy of the right frontal lobe was performed to investigate the underlying pathology.

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NEUROPATHOLOGY

DR JEAN N. ANGELO (*Professor Emeritus, Department of Pathology*): A wedge of cerebral cortex and subcortical white matter was submitted. There were no gross abnormalities. Several special stains (silver, myelin, fungal, and Congo red for amyloid) were used to supplement the standard hematoxylin-eosin technique. Many capillary-sized vessels, arterioles, and intermediate vessels showed strong congophilia, which had green birefringence with polarized light. Smaller vessels were markedly thickened. In addition to several intracortical glial scars, there were two small subacute infarcts associated with hemosiderin macrophages and mineralization or calcification of small vessels centrally. Only two immature neuritic plaques were noted, but no neurofibrillary degeneration was seen. Subcortical white matter showed a slight increase in astrocytes, but myelin was not significantly altered. Stains other than for amyloid were negative. Electron microscopy, primarily of subcortical white matter, demonstrated thickened small vessels with split laminae and fibrils consistent with amyloid. These findings amply support a neuropathologic diagnosis of cerebral congophilic (amyloid) angiopathy.

CLINICAL FEATURES

DR CELESTINO: Although the pathologic entity of cerebral amyloid angiopathy (CAA) has been recognized since the first decade of this century,[1] only during the last 10 to 15 years has it attracted increasingly intense interest from the research community. This "rediscovery" has been fueled by two observations: (1) that CAA is the probable cause of nontraumatic primary cerebral hemorrhage in a significant portion of elderly patients, especially those who are normotensive or who suffer recurrent episodes of bleeding[1–3]; and (2) that CAA is closely associated with the microscopic hallmarks of Alzheimer's disease and may in fact be causally related to this dementing disease.[4–7] Several recent reviews[1–13] have summarized our current understanding of CAA as well as its relationship to dementia and brain aging in general.

CAA, also known as cerebrovascular amyloidosis, microvascular amyloid, and cerebral congophilic angiopathy, is seldom, if ever, associated with systemic amyloidosis. It is characterized by the deposition of homogeneous (amorphous) eosinophilic material in the walls of arterioles, small arteries, and capillaries of the cortex and leptomeninges.[1,2,11] These deposits, which stain with Congo red and show characteristic yellow-green birefringence under polarized light, are by definition amyloid. The media and adventitia can become replaced by this amyloid, and the elastic lamina may be fragmented, split, or destroyed. The presence of amyloid deposits weakens the vessel wall, which may undergo spontaneous or traumatic rupture or develop microaneurysmal dilatation with subsequent hemorrhage.[1,2]

The incidence of CAA is clearly age related.[1,2,9] It has been estimated that 8% of individuals at age 60 years, 37% at age 80 years, and nearly 60% by the tenth decade are affected.[9] Men and women are equally susceptible. Likewise, the mean age of 72 years for onset of CAA-related brain hemorrhage shows no sex predilection.[1]

CAA predominantly affects the neocortex, relatively sparing the vessels of the basal ganglia, cerebellum, and brain stem.[14] This distribution explains the cortical and subcortical location of the associated hemorrhages, which frequently rupture through the cortical surface to extend into the subarachnoid space. This pattern differs distinctly from hypertensive hemorrhage, which typically involves the basal ganglia, thalamus, cerebellum, and pons, and rarely reaches the subarachnoid space. As in our case, however, hypertension exists concomitantly in up to one third of patients with CAA and may contribute to the occurrence, size, and extent of CAA-related hemorrhages.[1,4,8,10]

DR WILLIAMS: Radiographically, hemorrhages secondary to CAA are usually large and may be multiple or recurrent.[1–3,11,15–20] They occur in superficial, subcortical, or lobar locations. Episodes of lobar bleeding are most common in the frontal and parietal regions, with a somewhat lesser incidence in the temporal and occipital areas. CAA uncomplicated by intracerebral hemorrhage appears most severe in the parieto-occipital region.[1,14] The actual site of bleeding from an amyloid-infiltrated microvessel is rarely identified even after angiography or surgery. Our case well illustrates this point.

DR CELESTINO: It is estimated that CAA now accounts for 5% to 15% of all primary nontraumatic brain hemorrhages, which in turn account for approximately 10% of all strokes.[1] The risk of recurrent hemorrhage is 10% to 30%.[8] Thus, CAA must be accepted as an increasingly important cause of nontraumatic intracerebral hemorrhage and can be strongly suspected in the setting of an elderly normotensive patient with recurrent or multiple simultaneous cerebral hemorrhages, particularly lobar ones. The burgeoning numbers of older individuals, especially those aged over 80 years, will bring this pathologic entity further into the clinical limelight in the years ahead.

CAA is unrelated to atherosclerosis of cerebral vessels but may of itself cause multiple small cortical and subcortical infarcts in severely affected regions.[1,9,11] These usually asymptomatic microinfarctions occur in about one fifth of patients and are attributed to occlusion of vessels by amyloid deposition and fibrinoid degeneration. Large infarcts should never be attributed to CAA.

CAA most often occurs in isolation as a single entity but may also be associated with other pathologic states.[1,2] It has been recognized in dementia pugilistica, Creutzfeldt-Jakob disease, cerebellar ataxia, granulomatous angiitis, rheumatoid vasculitis, giant cell arteritis, post-irradiation necrosis, vascular malformations, spongiform encephalopathy, other rare degenerative dementias, and in adults with Down's syndrome. There are also familial forms of autosomal-dominant cerebrovascular amyloid reported from Iceland and the Netherlands causing premature intracerebral hemorrhage in the fourth and fifth decades.[1,2,4]

Interestingly, parenchymal brain hemorrhages from CAA are very rare in middle-aged patients with Down's syndrome who otherwise have brain abnormalities, including extensive CAA, identical to those seen in Alzheimer's disease.[4] Given this observation, some have proposed that the degenerative microvascular changes leading to rupture of brittle, amyloid-laden vessels may need to be abetted by hypertensive or atherosclerotic vascular disease occurring in the elderly before hemorrhage becomes likely. Clearly, the entire pathogenesis of CAA-related bleeding is not understood.

Recovery from a single episode of CAA-associated bleeding can be surprisingly good,[1,4,21] although overall long-term prognosis is often poor. Most authors[1–3,8–12] advocate conservative, nonsurgical supportive management of intracerebral hemorrhage related to CAA including aggressive management of intracranial hypertension. Because amyloid replaces the contractile elements of vascular walls, the first step in hemostasis is impaired. Surgery plays a limited role because of excessive intraoperative bleeding and recurrent hemorrhage in the early or late postoperative phase. Brain and meningeal biopsy, the only definitive means of establishing a diagnosis of CAA, may in itself cause fatal cerebral hemorrhage.

RELATIONSHIP TO DEMENTIA

Besides intracerebral hemorrhage, the other major association of CAA is with dementia.[1,2,4,8,9,13] Forty to fifty percent of patients with proven CAA exhibit dementia, and a similar proportion show Alzheimer's disease changes at autopsy. Interestingly, although CAA is found in a variety of dementing diseases, as mentioned earlier, it is most severe in patients with Alzheimer's disease, occurring in 90% to 100% of affected brains. The amount of vascular amyloid, however, has failed to correlate with the severity of dementia. Also, severe CAA with associated intracerebral hemorrhage clearly may occur without any of the microscopic or clinical features of Alzheimer's disease. Likewise, Alzheimer's disease probably can occur in the absence of CAA.

Nonetheless, because the incidence of both CAA and Alzheimer's disease increase strikingly with age, and because the senile plaques and neurofibrillary tangles of Alzheimer's disease both contain amyloid, researchers have wondered whether there might be more than a casual relationship between amyloid deposition and the development of dementia in Alzheimer's disease.[4–7] Further interest was engendered by the observation that senile plaques with amyloid cores are often in close proximity to CAA-affected microvessels. In an exciting development, recent immunochemical and biochemical evidence suggests that senile plaque amyloid, CAA deposits, and neurofibrillary tangle amyloid (in both Alzheimer's disease and Down's syndrome) are identical. Additionally, the gene markers for Alzheimer's disease and for the amyloid precursor protein are both located on chromosome 21 in very close proximity. The above findings have prompted some to designate Alzheimer's disease as a form of cerebral amyloidosis.[6]

An attractive current hypothesis,[1,4–7] increasingly supported by recent work at the molecular level, proposes that the amyloid protein gene on chromosome 21 encodes a normal precursor that is subsequently (posttranslationally) abnormally processed by an aberrant enzyme (protease) encoded by the familial Alzheimer's disease gene also on chromosome 21. In one theory the amyloid precursor, arising in peripheral sites, is disseminated through the blood stream to the central nervous system, where cerebral endothelial cell proteases cleave it to produce amyloid fibrils. These fibrils may disrupt that blood-brain barrier, allowing influx of more amyloid into the central nervous system to accumulate pathologically and destructively in plaques, tangles, and vessel walls. The search is now on to identify the specific abnormal proteases and their location and regulation. Understanding these molecular mechanisms could lead to the development of specific proteolytic inhibitors (drugs) used to halt Alzheimer's disease.

One last set of observations has recently given rise to a novel and certainly heretical hypothesis linking CAA, Alzheimer's disease, and dementia.[21–25] Thirty to sixty percent of patients with Alzheimer's disease exhibit periventricular white matter lucencies on CT scanning compared with only approximately 10% to 20% of age-matched controls. Hachinski et al[24] have coined the term *leukoaraiosis* (LA) for these lesions, although *leukoencephalopathy* has sometimes been used. MRI, with its increased resolution (sensitivity), has demonstrated an even more alarming frequency of LA on T_2-weighted images.[21,23,26] As with CAA and Alzheimer's disease, these findings increase dramatically with age, with over 30% of all patients aged over 60 years demonstrating LA by MRI. CAA is only one of several pathologic entities associated with LA. Other disease correlations include

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TENORETIC® (atenolol and chlorthalidone)

INDICATIONS AND USAGE: TENORETIC® (atenolol and chlorthalidone) is indicated in 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 patients who have congestive heart failure controlled by digitalis and/or 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: 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 beta$_1$-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 beta$_1$-selectivity is not absolute, the lowest possible dose of TENORETIC should be used and a beta$_2$-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: It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as ether, cyclopropane, and trichlorethylene. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

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).

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. At recommended doses 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 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

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, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Measurement of potassium levels is appropriate especially in elderly patients, those receiving digitalis preparations for cardiac failure, patients whose dietary intake of potassium is abnormally low, or those suffering from gastrointestinal complaints.

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, each employing oral dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose,* did not indicate a carcinogenic potential in rodents. A third (24 month) rat study, employing doses of 500 and 1,500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose*) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), in vivo cytogenetics test (Chinese hamster) or Ames test (*S typhimurium*).

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.

Animal Toxicology: Six month oral studies were conducted in rats and dogs using TENORETIC (atenolol and chlorthalidone) doses up to 12.5 mg/kg/day (atenolol/chlorthalidone 10/2.5 mg/kg/day — approximately five times the maximum recommended human antihypertensive dose*). There were no functional or morphological abnormalities resulting from dosing either compound alone or together other than minor changes in heart rate, blood pressure and urine chemistry which were attributed to the known pharmacologic properties of atenolol and/or chlorthalidone.

Chronic studies of atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human antihypertensive dose*, respectively).

Use in Pregnancy: Pregnancy Category C. TENORETIC was studied for teratogenic potential in the rat and rabbit. Doses of atenolol/chlorthalidone of 8/2, 80/20, and 240/60 mg/kg/day were administered orally to pregnant rats with no teratologic effects observed. Two studies were conducted. In the first study, pregnant rabbits were dosed with 8/2, 80/20, and 160/40 mg/kg/day of atenolol/chlorthalidone. 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, doses of atenolol/chlorthalidone were 4/1, 8/2, and 20/5 mg/kg/day. No teratogenic or embryotoxic effects were demonstrated. It is concluded that the no-effect level for embryonic resorptions is 20/5 mg/kg/day of atenolol/chlorthalidone (approximately ten times the maximum recommended human dose*). 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 antihypertensive 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 antihypertensive dose.* There are no adequate and well-controlled studies in pregnant women.

*Based on the maximum dose of 100 mg/day in a 50 kg patient weight.

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 in the following table were derived 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.

	Volunteered (US Studies)		Total-Volunteered and Elicited (Foreign + US Studies)	
	Atenolol % (n = 164)	Placebo % (n = 206)	Atenolol % (n = 399)	Placebo % (n = 407)
CARDIOVASCULAR				
Bradycardia	3	0	3	0
Cold Extremities	0	0.5	12	5
Postural Hypotension	2	1	4	5
Leg Pain	0	0.5	3	1
CENTRAL NERVOUS SYSTEM/ NEUROMUSCULAR				
Dizziness	4	1	13	6
Vertigo	2	0.5	2	0.2
Light-Headedness	1	0	3	0.7
Tiredness	0.6	0.5	26	13
Fatigue	3	1	6	5
Lethargy	1	0	3	0.7
Drowsiness	0.6	0	2	0.5
Depression	0.6	0.5	12	9
Dreaming	0	0	3	1
GASTROINTESTINAL				
Diarrhea	2	0	3	2
Nausea	4	1	3	1
RESPIRATORY (see Warnings)				
Wheeziness	0	0	3	3
Dyspnea	0.6	1	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. Discontinuance 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, parasthesias, xanthopsia; Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; Hypersensitivity: purpura, photosensitivity, rash, urticaria, necrotizing angiitis (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 catatonia; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; 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 psoriasiform 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.

DOSAGE 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.

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multiple sclerosis, leukodystrophies, hydrocephalus, previous head trauma, brain irradiation, vasculitides, sickle cell disease, and Binswanger's disease (subcortical arteriosclerotic encephalopathy).[23–25]

Most authors,[21,23–30] in keeping with the near 100% prevalence of LA in vascular dementias, believe from pathological correlations that these areas represent demyelination, hyalinosis, fibrosis, and injury secondary to hypoperfusion (vascular insufficiency). Indeed, recently Brun et al[22] have documented that incomplete, evolving microinfarctions were noted in 60% of brains from patients with Alzheimer's disease and correlated with the areas of LA caused by CAA. Awad et al[26] have performed pathologic correlations to areas of LA seen on MRI and once again verified areas of demyelination, arteriolar thickening, and hypoperfusion injury. Several reports[20,28,29] have verified the nearly 100% prevalence of LA in CAA-affected brains. Once again pathologic studies implicate vascular insufficiency as the cause of these radiographic lesions.

Given this evolving database, investigators[21–25,29,30] have begun to wonder about the functional role of the white matter lesions of putative hypoperfusion in the development of dementia. As Scheinberg[21] and Brun and Englund[22] have so eloquently stated, perhaps we have overlooked a vascular component (? CAA) to the dementia of Alzheimer's disease. Do these deep, white matter lesions in some way modulate the expression of clinical dementia?

Clearly, despite enormous progress in neuropathology, neuropharmacology, and cerebral imaging, we are still a long way from understanding dementing illness. The etiology and pathogenesis of CAA still remain speculative at best. Links between cerebral amyloid angiopathy, dementia, and brain aging will continue to shed light on the development of dementia and raise anew the question of the role of cerebral hypoperfusion in Alzheimer's disease.

FOLLOW-UP

DR KONEN: Fortunately, Ms M. has not suffered any further intracranial bleeding during this past year of follow-up. Nevertheless, she remains cognitively disabled and unable to return to gainful employment.

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