Dementia in patients with the acquired immunodeficiency syndrome

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Central nervous system (CNS) manifestations are common in patients with the acquired immunodeficiency syndrome (AIDS). The most common CNS syndrome is a dementing illness referred to as the AIDS dementia complex, in which motor and cognitive changes may also be seen. Neurodiagnostic studies are fairly characteristic, though highly nonspecific. Dementia may precede overt manifestations of AIDS, and either an insidious or a fulminant course may be seen. Appropriate management of the patient with AIDS includes differentiating dementia from psychologic responses to the disease.

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The acquired immunodeficiency syndrome (AIDS) is due to infection by a retrovirus^{1,2} that is now termed the human immunodeficiency virus (HIV).³ Its clinical manifestations are protean. Symptomatic involvement of the central nervous system (CNS) occurs in at least 39% of all patients with AIDS; neoplasia and infection by viruses, fungi, and mycobacteria are common complications.⁴

The most frequent CNS manifestation of HIV infection is not a focal neurologic disease, but is instead a diffuse encephalitis. This disorder has been referred to as AIDS encephalopathy,⁵ subacute encephalitis,⁶ subacute AIDS

encephalitis,⁷ and the AIDS dementia complex (ADC).⁸ The reported incidence of ADC varies, affecting from 11%⁶ to 47%⁹ of AIDS patients seen. In August 1987, the Centers for Disease Control reported a revision of its case definition for AIDS,¹⁰ in which the presence of ADC in a person with laboratory evidence of HIV infection constitutes a diagnosis of AIDS.

Manifestations

The signs and symptoms of ADC have been described.^{6,8,11} Early manifestations involve cognitive, motor, and behavioral impairments. The most common early symptoms are cognitive and include forgetfulness, loss of concentration, and confusion. Motor symptoms may include loss of balance and leg weakness. Apathy and social withdrawal are behavioral changes frequently described, and a dysphoric mood is occasionally reported. Lethargy, malaise, and reduced sexual drive may also be present.

When first seen, a patient with ADC may have motor and verbal slowness as well as impaired cognition on mental status examination; normal findings on such examination, however, are not uncommon. Approximately half of the patients in whom ADC develops have abnormal findings on neurologic examination early in the course of ADC. Neurologic signs include ataxia, pyramidal tract signs, lower extremity weakness, and tremor.

In its later stages, ADC leaves the lives of patients utterly ravaged. The sine qua non of ADC is the eventual development of dementia, as defined by the *Diagnostic and Statisti-*

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cal Manual of Mental Diseases, third edition-revised (*DSM-III-R*)¹² criteria. The majority of these patients are bedridden and have severely limited intellectual and social capacities, although in some the ability to perform simple tasks is preserved. Psychomotor retardation is common. Patients sit awake with a wide-eyed stare—quiet, confused, and indifferent to their illness and surroundings.

An organic psychosis may occasionally be observed. Motor impairments are common in the later stages of ADC and may include ataxia, hypertonia, weakness (especially paraparesis), myoclonus, seizures (focal or generalized), and tremor. Many patients are incontinent. A peripheral neuropathy is far more likely to be found in an AIDS patient with ADC than in one without it.

Epstein and associates⁵ have reported a similar spectrum of changes in children with AIDS. Motor impairments, including ataxia, weakness, pyramidal tract signs, and seizures, predominated. They also observed apathy, and loss of intellectual and language abilities were also observed.

The presence of ADC is suggested by characteristic clinical features, yet it often may go undiagnosed.¹³ No single test is diagnostic. On computed tomographic (CT) scans, generalized cerebral atrophy is nearly always seen, often with ventricular dilation. Attenuated white matter may also be seen in a minority of patients, and magnetic resonance imaging may be more sensitive than CT in detecting this abnormality. On examination of the CSF, a mild to moderate elevation of the protein level is often seen, which may rise during the clinical course in a subset of patients. These findings are occasionally accompanied by a mild mononuclear pleocytosis and, much less often, hypoglycorrhachia. In virtually all cases, electroencephalograms show an abnormality, often a mild, diffuse, bilateral, nonfocal slowing.^{4,6,8,11,13}

Onset

Although the onset of dementia in ADC is most often insidious, a significant number of patients experience an acute onset or acceleration. Navia and associates⁸ reported that

once severely demented, the average ADC patient survives a mere 2 months. The total duration of dementia averages 4 months.⁸

Of the 112 patients with ADC seen by Navia and Price,¹³ one fourth had no manifestations of AIDS on initial examination; and full-blown AIDS did not subsequently develop in half of these asymptomatic patients, virtually all of whom were in groups at risk of AIDS and had documented HIV infection. When first seen, the majority of the 112 patients had the AIDS-related complex (ARC), although nearly 25% were clinically well. The mean duration of dementia averaged 8 months. This observed duration may be attributable to recognition of dementia earlier in the course of these patients' illness and supports the contention that ADC is often the manifestation of an insidious process.

Neuropathologic changes

Several studies have documented the neuropathologic changes of ADC. In 90% of brains from patients with AIDS or ARC, de la Monte and associates¹⁴ identified a subacute encephalomyelitis, characterized by astrocytosis of white matter, gliosis of gray matter, microglial nodules, and small foci of necrosis in both the gray and white matter. Demyelination and axonal changes were also seen. Of the 50% of brains in which these changes were moderate to severe, 37% were from patients in whom dementia had been recognized. Similar changes, including slight myelin pallor, were reported by Levy and coworkers.⁴ Diffuse demyelination and pallor of white matter were among the findings reported by Nielsen and coworkers⁹ in all the brains they examined. The neuropathologic changes in patients with AIDS, as found in several series, are reviewed by Rhodes.⁷

Navia and colleagues¹⁵ examined the brains from 46 demented AIDS patients who had neither focal CNS disease nor sustained metabolic encephalopathy. Abnormalities were found predominantly in the white matter and in subcortical structures, with relative sparing of the cortex. The most common finding was diffuse pallor in the white matter. The finding most specific to ADC was the presence of multinucleated cells; patients whose brains contained

these cells had a dementia of greater severity and duration.

Cummings and Benson¹⁶ have defined subcortical dementia on the basis of similarities in the dementia of several disorders, including Huntington's disease, progressive supranuclear palsy, and Parkinson's disease. Apathy, disorder of mood, impaired cognition, forgetfulness, motor deficits, and abnormalities of movement are common features. Navia and co-workers⁸ have pointed out that many of the clinical and pathologic features of ADC are consistent with its classification as a subcortical dementia.

The suspected cause of ADC is direct infection of the CNS by HIV owing to a tremendous amount of supporting evidence. A syndrome such as ADC has not been reported in other immunocompromised populations. Shaw and associates,¹⁷ using Southern blot analysis and in situ hybridization, were able to demonstrate the presence of HIV nucleic acid in five of 15 brains of patients with ADC. Ho and coworkers¹⁸ recovered HIV from the CNS of ten of 16 patients with ADC, but from none of 12 patients with no neurologic symptoms. Of the 11 brains from which HIV was recovered by de la Monte and colleagues,¹⁴ ten had the pathologic features of ADC. Using a monoclonal antibody, Pumarola-Sune and associates¹⁹ observed that viral distribution parallels neuropathologic abnormalities in ADC. Although identification of the HIV protein in the brain was 100% specific for a clinical course that had included ADC, less than half of the brains from patients who had ADC were reactive for the HIV protein in this study. The authors suggested that the occurrence of brains testing negative for HIV protein from ADC patients might be accounted for by a defective infection with a limited viral gene transcription, or by an antigen expression that resembles that of visna virus, a sheep retrovirus.

Psychologic deficits

Given the significant frequency with which dementia and its earlier symptoms may precede the more overt manifestations of AIDS and ARC,¹³ the assessment of psychologic deficits has become increasingly important. The psy-

chologic response to a diagnosis of AIDS involves medical, psychologic, and sociocultural factors.

Holland and Tross²⁰ have outlined common features in patients' responses. Aspects of the disease that may precipitate distress include physical stigmata, compromise of health, alteration of sexual behavior, frequent hospitalization, loss of employment, reduced independence, witnessing of a friend in the terminal stages of AIDS, forced identification as a member of a group at risk, and discrimination. The previous level of psychologic adjustment and social support are important in determining how the psychologic sequelae of AIDS will be expressed for a given patient.

The psychological symptoms, including the emotional reaction to AIDS and its complications, may be difficult to differentiate from ADC. Anxiety and depression are two examples.

To a large degree, the symptoms of distress experienced by a patient with AIDS are similar to those seen in patients with terminal cancer. Symptoms of anxiety, including worry, fear, and hypochondriacal concerns, occur. Symptoms of depression, such as sadness, helplessness, worthlessness, social withdrawal, apathy, and psychomotor retardation, are commonly encountered.

The most common *DSM-III-R* diagnoses observed by Dilley and colleagues²¹ in psychiatric consultation were adjustment disorder with depressed mood, major depression, or dysthymic disorder. Unfortunately, these findings may often go unrecognized. Perry and Tross,²² reviewing the charts of 52 patients with AIDS, found reference to neuropsychiatric symptoms appeared in 100% of the charts, with 83% of the patients reporting some form of depression. Nonetheless, psychiatric consultation was requested in only 19% of all cases. This finding is consistent with the observation¹³ that ADC often goes unrecognized.

It is therefore apparent that the presence of depressed mood, decreased memory, apathy, social withdrawal, and psychomotor retardation in a patient with AIDS may represent either a psychologic reaction to, or a neuropsychiatric manifestation of, the disease. Asympto-

matic HIV infection of the CNS can occur. Neuropathologic changes of ADC may be found without antecedent dementia^{14,15}; HIV infection of the CNS may occur without dementia¹⁸; and intra-blood-brain barrier synthesis of anti-HIV immunoglobulin G (IgG) may occur without neurologic symptoms.²³ Holland and Tross²⁰ assert that diagnosis of ADC should be suspected in all high-risk patients who manifest any change in mentation or neurologic functioning.

Management

Perry and Tross²² have outlined the following measures for dealing with the neuropsychiatric complications of AIDS, including ADC, during medical hospitalization.

- Mental status should be documented, as with the Mini-Mental State examination.²⁴
- Disorders of mood, thinking, or behavior should not be viewed presumptively as psychogenic until organic determinants have been ruled out.
- Pharmacologic intervention, including the use of neuroleptics in certain organic disorders, should be instituted as appropriate.
- Aftercare should be arranged as early as possible.

Faulstich²⁵ recommends neuropsychiatric testing as a differentiating tool, suggesting that monitoring of mental status and cognitive deficits should become an integral part of the overall management of patients with AIDS. Benzodiazepines, stress-management, antidepressant therapy, and problem-solving procedures may all be of benefit to selected patients.

Prognosis

The prognosis for ADC continues to be grim; however, with treatable syndromes in the differential diagnosis, an accurate diagnosis should be pursued aggressively. Furthermore, palliative therapy is available. The virustatic drug zivudine (azidothymidine; AZT) has been shown to achieve excellent penetration of the blood-brain barrier²⁶ and clinical effectiveness is now firmly established.

Comment

This article is intended as a broad-stroke over-

view for the primary care physician. Since this article was originally written, new important developments have been made in effective treatment strategies for those afflicted with this devastating disease, and extensive research continues in this important clinical area.

1. Barre-Sinoussi F, Chermann JC, Rey F, et al: Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* 1983;220:868-870.
2. Gallo RC, Salahuddin SZ, Popovic M, et al: Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science* 1984;224:550-502.
3. Coffin J, Haase A, Levy JA, et al: Human immunodeficiency viruses. *Science* 1986;232:697.
4. Levy RM, Bredesen DE, Rosenblum ML: Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): Experience at UCSF and review of the literature. *J Neurosurg* 1985;62:475-495.
5. Epstein LG, Sharer LR, Joshi VV, et al: Progressive encephalopathy in children with acquired immune deficiency syndrome. *Ann Neurol* 1985;17:488-496.
6. Snider WD, Simpson DM, Nielsen S, et al: Neurological complications of acquired immune deficiency syndrome: Analysis of 50 patients. *Ann Neurol* 1983;14:403-418.
7. Rhodes RH: Histopathology of the central nervous system in the acquired immunodeficiency syndrome. *Hum Pathol* 1987;18:636-643.
8. Navia BA, Jordan BD, Price RW: The AIDS dementia complex: I. Clinical features. *Ann Neurol* 1986;19:517-524.
9. Nielsen SL, Petito CK, Urmacher CD, et al: Subacute encephalitis in acquired immune deficiency syndrome: A postmortem study. *Am J Clin Pathol* 1984;82:678-682.
10. Centers for Disease Control: Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. *MMWR* 1987;36(1S):3S-15S.
11. Jordan BD, Navia BA, Petito CA, et al: Neurological syndromes complicating AIDS. *Front Radiat Ther Oncol* 1985;19:82-87.
12. American Psychiatric Association, Committee on Nomenclature and Statistics: *Diagnostic and Statistical Manual of Mental Disorders*, ed 3-revised. Washington, DC, American Psychiatric Association, 1987.
13. Navia BA, Price RW: The acquired immunodeficiency syndrome dementia complex as the presenting or sole manifestation of human immunodeficiency virus infection. *Arch Neurol* 1987;44:65-69.
14. de la Monte SM, Ho DD, Schooley RT, et al: Subacute encephalomyelitis of AIDS and its relation to HTLV-III infection. *Neurology* 1987;37:562-569.
15. Navia BA, Cho E, Petito CK, et al: The AIDS dementia complex: II. Neuropathology. *Ann Neurol* 1986;19:525-535.
16. Cummings JL, Benson DF: Subcortical dementia. *Arch Neurol* 1984;41:874-879.
17. Shaw GM, Harper ME, Hahn BH, et al: HTLV-III infection in brains of children and adults with AIDS encephalopathy. *Science* 1985;227:177-182.
18. Ho DD, Rota TR, Schooley RT, et al: Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neu-

rologic syndromes related to the acquired immunodeficiency syndrome. *N Engl J Med* 1985;313:1493-1497.

19. Pumarola-Sune T, Navia BA, Cordon-Cardo C, et al: HIV antigen in the brains of patients with the AIDS dementia complex. *Ann Neurol* 1987;21:490-506.

20. Holland JC, Tross S: The psychosocial and neuropsychiatric sequelae of the acquired immunodeficiency syndrome and related disorders. *Ann Intern Med* 1985;103:760-764.

21. Dilley JW, Ochitill HN, Perl M, et al: Findings in psychiatric consultations with patients with acquired immune deficiency syndrome. *Am J Psychiatry* 1985;142:82-86.

22. Perry SW, Tross S: Psychiatric problems of AIDS inpatients at the New York Hospital: Preliminary report. *Pub Health Rep* 1984;99:200-205.

23. Resnick L, diMarzo-Veronese F, Schupback J, et al: Intra-blood-brain-barrier synthesis of HTLV-III-specific IgG in patients with neurologic symptoms associated with AIDS or AIDS-related complex. *N Engl J Med* 1985;313:1498-1504.

24. Folstein MF, Folstein SE, McHugh PR: Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1976;12:189-198.

25. Faulstich ME: Acquired immune deficiency syndrome: an overview of central nervous system complications and neuropsychological sequelae. *Int J Neurosci* 1986;30:249-254.

26. Klecker RW, Collins JM, Yarchoan R, et al: Plasma and cerebrospinal fluid pharmacokinetics of 3'-azido-3'-deoxythymidine: A novel pyrimidine analog with potential application for the treatment of patients with AIDS and related diseases. *Clin Pharmacol Ther* 1987;41:407-412.

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CARDURA is well tolerated. In placebo-controlled studies, only three common side effects were reported more often than with placebo: dizziness, somnolence, and fatigue. These were generally mild and transient. Syncope has been reported, but rarely (<1%).

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References: 1. Dzau VJ: Evolution of the clinical management of hypertension: Emerging role of "specific" vasodilators as initial therapy. *Am J Med* 1987; 82 (suppl 1A): 36-43. 2. Data available on request from Roerg. 3. Scheen AJ, Castillo M, Salvatore T, et al: Lack of deleterious effects of the alpha₁-adrenoreceptor blocking agent doxazosin on insulin secretion and insulin sensitivity in healthy men. *Current Therapeutic Research* 1989; 46: 200-209. 4. Wilner KD, Ziegler MG: Effects of alpha₁ inhibition on renal blood flow and sympathetic nervous activity in systemic hypertension. *Am J Cardiol* 1987; 59: 82G-86G.

CARDURA® (doxazosin mesylate) Tablets Brief Summary of Prescribing Information

INDICATIONS AND USAGE

CARDURA (doxazosin mesylate) is indicated for the treatment of hypertension. CARDURA may be used alone or in combination with diuretics or beta-adrenergic blocking agents. There is limited experience with CARDURA in combination with angiotensin converting enzyme inhibitors or calcium channel blockers.

CONTRAINDICATIONS

CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g. prazosin, terazosin).

WARNINGS

Syncope and "First-dose" Effect:

Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with increases in dose every two weeks. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials involving over 1500 patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

PRECAUTIONS

General:

1. Orthostatic Hypotension:

While syncope is the most severe orthostatic effect of CARDURA, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo, can occur, especially at initiation of therapy or at the time of dose increases. These were common in clinical trials, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo controlled titration trials orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA.

2. Impaired liver function:

CARDURA should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY). There is no controlled clinical experience with CARDURA in patients with these conditions.

3. Leukopenia/Neutropenia:

Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean WBC (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. A search through a data base of 2400 patients revealed 4 in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm³ range over periods of 20 and 40 weeks. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA. No patients became symptomatic as a result of the low WBC or neutrophil counts.

Information for Patients:

Patients should be made aware of the possibility of syncope and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If

1 Begin all patients with CARDURA 1 mg once daily to minimize side effects. Evaluate supine and standing blood pressure. Prescribe CARDURA 2 mg once daily, if necessary.

2 Evaluate for blood pressure control. Prescribe 4 mg once daily, if necessary.

3 Evaluate for blood pressure control. Prescribe 8 mg once daily, if necessary. Maximum recommended dosage is 16 mg once daily.

dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with doxazosin, requiring caution in people who must drive or operate heavy machinery.

Drug Interactions:

Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that CARDURA has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta blocking agents, and nonsteroidal anti-inflammatory drugs.

Drug/Laboratory test interactions:

None known.

Cardiac Toxicity in Animals:

An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (150 times the maximum recommended human dose assuming a patient weight of 60 kg). There is no evidence that similar lesions occur in humans.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated concentrations (highest dose 40 mg/kg; about 150 times the maximum recommended human dose of 16 mg/60 kg) revealed no evidence of carcinogenicity in rats. There was also no evidence of carcinogenicity in a similarly conducted study (up to 18 months of dietary administration) in mice. The mouse study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 75 times the maximum recommended human dose. This effect was reversible within two weeks of drug withdrawal.

Pregnancy

Teratogenic Effects. Pregnancy Category B. Studies in rabbits and rats at daily oral doses of up to 40 and 20 mg/kg, respectively (150 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence of harm to the fetus. The rabbit study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

CARDURA has been administered to approximately 4000 patients, of whom 1679 were included in the clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled clinical trials directly comparing CARDURA to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue/malaise. Postural effects and edema appeared to be dose related.

The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. Table 1 summarizes those adverse experiences (possibly/probably related) reported for patients in these studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

TABLE 1: ADVERSE REACTIONS DURING PLACEBO CONTROLLED STUDIES

	DOXAZOSIN (N=339)	PLACEBO (N=336)
CARDIOVASCULAR		
Dizziness	19%	9%
Vertigo	2%	1%
Postural Hypotension	0.3%	0%
Edema	4%	3%
Palpitation	2%	3%
Arrhythmia	1%	0%
Hypotension	1%	0%
Tachycardia	0.3%	1%
Peripheral Ischemia	0.3%	0%
SKIN APPENDAGES		
Rash	1%	1%
Pruritus	1%	1%
MUSCULOSKELETAL		
Arthralgia/Arthritis	1%	0%
Muscle Weakness	1%	0%
Myalgia	1%	0%
CENTRAL & PERIPHERAL N.S.		
Headache	14%	16%
Paresthesia	1%	1%

	DOXAZOSIN (N=339)	PLACEBO (N=336)
	Kinetic Disorders	1% 0%
	Ataxia	1% 0%
	Hypertonia	1% 0%
	Muscle Cramps	1% 0%
AUTONOMIC	Mouth Dry	2% 2%
	Flushing	1% 0%
SPECIAL SENSES	Vision Abnormal	2% 1%
	Conjunctivitis/Eye Pain	1% 1%
	Tinnitus	1% 0.3%
PSYCHIATRIC	Somnolence	5% 1%
	Nervousness	2% 2%
	Depression	1% 1%
	Insomnia	1% 1%
	Sexual Dysfunction	2% 1%
GASTROINTESTINAL	Nausea	3% 4%
	Diarrhea	2% 3%
	Constipation	1% 1%
	Dyspepsia	1% 1%
	Flatulence	1% 1%
	Abdominal Pain	0% 2%
	Vomiting	0% 1%
RESPIRATORY	Rhinitis	3% 1%
	Dyspnea	1% 1%
	Epistaxis	1% 0%
URINARY	Polyuria	2% 0%
	Urinary Incontinence	1% 0%
	Micturition Frequency	0% 2%
GENERAL	Fatigue/Malaise	12% 6%
	Chest Pain	2% 2%
	Asthenia	1% 1%
	Face Edema	1% 0%
	Pain	2% 2%

Additional adverse reactions have been reported, but these are, in general, indistinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency between 0.5% and 1%: syncope, hypoaesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short-term clinical studies, including international studies. *Cardiovascular*: angina pectoris, myocardial infarction, cerebrovascular accident; *Autonomic Nervous System*: pallor; *Metabolic*: thirst, gout, hypokalemia; *Hematopoietic*: lymphadenopathy, purpura; *Reproductive System*: breast pain; *Skin Disorders*: alopecia, dry skin, eczema; *Central Nervous System*: paresis, tremor, twitching, confusion, migraine, impaired concentration; *Psychiatric*: paranoia, amnesia, emotional lability, abnormal thinking, depersonalization; *Special Senses*: parosmia, taste perversion, photophobia, abnormal lacrimation; *Gastrointestinal System*: increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System*: bronchospasm, sinusitis, coughing, pharyngitis; *Urinary System*: renal calculus; *General Body System*: hot flashes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or function tests. CARDURA has been associated with decreases in white blood cell counts (See Precautions).

OVERDOSAGE

The oral LD₅₀ of doxazosin is greater than 1000 mg/kg in mice and rats. The likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of CARDURA in hypertensive patients is 1 mg given once daily. Depending on the individual patient's standing blood pressure response (based on measurements taken at hours postdose and 24 hours postdose), dosage may then be increased to 2 mg thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve the desired reduction in blood pressure. Increases in dose beyond 4 mg increase the likelihood of extraneous effects including syncope, postural dizziness/postural, postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 2% compared to 3% for placebo.

HOW SUPPLIED

CARDURA (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin. CARDURA® TABLETS are available as 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) scored tablets. Bottles of 100: 1 mg (NDC 0049-2750-66), 2 mg (NDC 0049-2750-67), 4 mg (NDC 0049-2770-66), 8 mg (NDC 0049-2780-66). Recommended Storage: Store below 86°F (30°C).

CAUTION: Federal law prohibits dispensing without prescription.
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