Even Low-Risk Patients May Have Plaque on CTA

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BOSTON — Direct screening for atherosclerosis using CT coronary angiography may provide a more accurate cardiovascular risk picture than do routine clinical predictors. However, the value of the imaging method in asymptomatic patients must be demonstrated in clinical trials before it can be used to modify therapy.

In a study that was designed to determine the prevalence of coronary atherosclerosis in patients with varying clinical predictors and to identify the limitations of traditional cardiac risk factors for predicting individual atherosclerotic burden, computed tomographic angiography (CTA) revealed evidence of calcific and noncalcific coronary atherosclerosis in a cohort of consecutive patients with low to intermediate Framingham risk scores (FRS).

This finding, together with the absence of atherosclerotic plaques in some patients with high FRS, suggests that the use of routine clinical predictors may be insufficient for identifying patients who might benefit from aggressive risk factor modification, Dr. Benjamin Chow reported at the annual meeting of the American Society of Nuclear Cardiology.

Of 1,247 consecutive patients who underwent CTA at the University of Ottawa (Ont.) Heart Institute between February 2006 and March 2008, Dr. Chow and his coinvestigators identified 554 patients (mean age, 55 years) who did not have a history of myocardial infarction, revascularization, or diabetes mellitus, and who were not on current statin therapy.

Approximately half of the patients were men, and the mean body mass index was 28.5 kg/m^2.

The mean pretest probability for obstructive coronary artery disease was 24.4%, he said.

Using a 17-segment model of the coronary arteries to assess for the presence of calcific or noncalcific plaque, the investigators calculated a total plaque score by summing the number of coronary segments with visible atherosclerotic plaque. They calculated the FRS using age, sex, total cholesterol level, HDL cholesterol level, smoking history, and blood pressure.

Of the patients in the very-low- and low-risk groups, more than half had visible evidence of atherosclerotic plaque on CT angiography.

Based on the FRS, 408 of the patients were considered to have a very low (5% or less) or low (10% or less) 10-year risk for cardiac events, whereas 93 patients had an intermediate risk (11%-19%) and 53 were considered high risk (20% or greater), Dr. Chow said. Of the patients in the very-low- and low-risk groups, more than half had visible evidence of atherosclerotic plaque on CTA, he said.

Additionally, about 9% of patients in the high-risk category had no evidence of calcific or noncalcific plaques.

"Although the mean atherosclerotic plaque burden did increase with the 10-year Framingham risk, the correlation between [the FRS] and plaque was fair," Dr. Chow reported.

The findings suggest that, although the FRS is moderately predictive of plaque burden in this patient population, "it may underestimate total plaque burden," he said.

The value of identifying subclinical coronary atherosclerosis through CTA has yet to be established in clinical trials, said Dr. Chow of the University of Ottawa Heart Institute.

"Although many would argue that more aggressive risk-factor modification is warranted for patients with evidence of coronary atherosclerosis, prospective studies are needed to determine whether modifying therapy [based on imaging evidence] is appropriate," he said.

Currently, the main suggested indication for CTA is for symptomatic patients or those with equivocal stress tests, Dr. Chow noted.

CT angiography "is not currently indicated to screen for coronary atherosclerosis because the benefit of doing so has yet to be [proved]," he said.

Dr. Chow reported no conflicts of interest with respect to his presentation. ■

AMRIX® Rx Only
(Cyclobenzaprine Hydrochloride Extended-Release Capsules)

Brief Summary of Prescribing Information. The following is a brief summary only. Please see full Prescribing Information for complete product information.

DESCRIPTION
AMRIX® (Cyclobenzaprine Hydrochloride Extended-Release Capsules) is a skeletal muscle relaxant which relieves muscle spasm of local origin without interfering with muscle function. The active ingredient in AMRIX extended-release capsules is cyclobenzaprine hydrochloride, USP.
AMRIX extended-release capsules for oral administration are supplied in 15 and 30 mg strengths.

INDICATIONS AND USAGE
AMRIX is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, and limitation of motion.
AMRIX should be used only for short periods (up to two or three weeks) because adequate evidence of effectiveness for more prolonged use is not available and because muscle spasm associated with acute, painful musculoskeletal conditions is generally of short duration and specific therapy for longer periods is seldom warranted.
AMRIX has not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease or in children with cerebral palsy.

CONTRAINDICATIONS
- Hypersensitivity to any component of this product.
- Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation.
- Hyperpyretic crisis seizures and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor drugs.
- During the acute recovery phase of myocardial infarction, and in patients with arrhythmias, heart block conduction disturbances, or congestive heart failure.
- Hyperthyroidism.

WARNINGS
AMRIX is closely related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. In short term studies for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm, some of the more serious central nervous system reactions noted with the tricyclic antidepressants have occurred (see **WARNINGS**, below, and **ADVERSE REACTIONS** section of full Prescribing Information).
Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke. AMRIX may enhance the effects of alcohol, barbiturates, and other CNS depressants.
As a result of a two-fold higher cyclobenzaprine plasma levels in subjects with mild hepatic impairment, as compared to healthy subjects, following administration of immediate-release cyclobenzaprine and because there is limited dosing flexibility with AMRIX, use of AMRIX is not recommended in subjects with mild, moderate or severe hepatic impairment.
As a result of a 40% increase in cyclobenzaprine plasma levels and a 56% increase in plasma half-life following administration of AMRIX in elderly subjects as compared to young adults, use of AMRIX is not recommended in elderly.

PRECAUTIONS
General
Because of its atropine-like action, AMRIX should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, and in patients taking anticholinergic medication.

Information for Patients
AMRIX, especially when used with alcohol or other CNS depressants, may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Drug Interactions
AMRIX may have life-threatening interactions with MAO inhibitors. (See **CONTRAINDICATIONS**.)
AMRIX may enhance the effects of alcohol, barbiturates, and other CNS depressants. Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds. Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol (ULTRAM® [tramadol HCl tablets, Ortho-McNeil Pharmaceutical] or ULTRACET® [tramadol HCl and acetaminophen tablets, Ortho-McNeil Pharmaceutical]).

Carcinogenesis, Mutagenesis, Impairment of Fertility
In rats treated with cyclobenzaprine for up to 67 weeks at doses of approximately 5 to 40 times the maximum recommended human dose, pale, sometimes enlarged, livers were noted and there was a dose-related hepatocyte vacuolation with lipidosis. Cyclobenzaprine did not affect the onset, incidence, or distribution of neoplasia in an 81-week study in the mouse or in a 105-week study in the rat. At oral doses of up to 10 times the human dose, cyclobenzaprine did not adversely affect the reproductive performance or fertility of male or female rats.
A battery of mutagenicity tests using bacterial and mammalian systems for point mutations and cytogenic effects have provided no evidence for a mutagenic potential for cyclobenzaprine.

Pregnancy
Pregnancy Category B: Reproduction studies have been performed in rats, mice, and rabbits at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cyclobenzaprine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because cyclobenzaprine is closely related to the tricyclic antidepressants, some of which are known to be excreted in human milk, caution should be exercised when AMRIX is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of AMRIX has not been studied in pediatric patients.

Use in the Elderly
The plasma concentration and half-life of cyclobenzaprine are substantially increased in the elderly when compared to the general patient population (see **CLINICAL PHARMACOLOGY**, ***Pharmacokinetics***, **Special Populations**, *Elderly* in full Prescribing Information). Accordingly, AMRIX should not be used in the elderly.

ADVERSE REACTIONS
The most common adverse reactions in the two 14-day clinical efficacy trials are presented in Table 1.

Table 1: Incidence of the Most Common Adverse Reactions Occurring in ≥3% of Subjects in Any Treatment Group in the Two Phase 3, Double-Blind AMRIX Trials

	AMRIX 15 mg N = 127	AMRIX 30 mg N = 126	Placebo N = 128
Dry mouth	6%	14%	2%
Dizziness	3%	6%	2%
Fatigue	3%	3%	2%
Constipation	1%	3%	0%
Somnolence	1%	2%	0%
Nausea	3%	3%	1%
Dyspepsia	0%	4%	1%

In a postmarketing surveillance program (7607 patients treated with cyclobenzaprine 10 mg TID), the adverse reactions reported most frequently were drowsiness, dry mouth, and dizziness.
Among the less frequent adverse reactions, there was no appreciable difference in incidence in controlled clinical studies or in the surveillance program. Adverse reactions which were reported in 1% to 3% of the patients were: fatigue/tiredness, asthenia, nausea, constipation, dyspepsia, unpleasant taste, blurred vision, headache, nervousness, and confusion. The following adverse reactions have been reported in post-marketing experience or with an incidence of less than 1% of patients in clinical trials with the 10 mg TID tablet:
Body as a Whole: Syncope; malaise.
Cardiovascular: Tachycardia; arrhythmia; vasodilatation; palpitation; hypotension.
Digestive: Vomiting; anorexia; diarrhea; gastrointestinal pain; gastritis; thirst; flatulence; edema of the tongue; abnormal liver function and rare reports of hepatitis, jaundice, and cholestasis.
Hypersensitivity: Anaphylaxis; angioedema; pruritus; facial edema; urticaria; rash.
Musculoskeletal: Local weakness.
Nervous System and Psychiatric: Seizures, ataxia; vertigo; dysarthria; tremors; hypertonia; convulsions; muscle twitching; disorientation; insomnia; depressed mood; abnormal sensations; anxiety; agitation; psychosis, abnormal thinking and dreaming; hallucinations; excitement; paresthesia; diplopia.
Skin: Sweating.
Special Senses: Ageusia; tinnitus.
Urogenital: Urinary frequency and/or retention.

DRUG ABUSE AND DEPENDENCE
Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when AMRIX (Cyclobenzaprine Hydrochloride Extended-Release Capsules) is administered, even though they have not been reported to occur with this drug. Abrupt cessation of treatment after prolonged administration rarely may produce nausea, headache, and malaise. These are not indicative of addiction.

OVERDOSAGE
Although rare, deaths may occur from overdosage with AMRIX. Multiple drug ingestion (including alcohol) is common in deliberate cyclobenzaprine overdose. **As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment.** Signs and symptoms of toxicity may develop rapidly after cyclobenzaprine overdose; therefore, hospital monitoring is required as soon as possible.
All patients suspected of an overdose with AMRIX should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage and emesis is contraindicated.
The principles of management of child and adult overdosage are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

DOSAGE AND ADMINISTRATION
The recommended adult dose for most patients is one (1) AMRIX 15 mg capsule taken once daily.
Some patients may require up to 30 mg/day, given as one (1) AMRIX 30 mg capsule taken once daily or as two (2) AMRIX 15 mg capsules taken once daily.
It is recommended that doses be taken at approximately the same time each day.
Use of AMRIX for periods longer than two or three weeks is not recommended (see **INDICATIONS AND USAGE**).
Dosage Considerations for Special Patient Populations: AMRIX should not be used in the elderly or in patients with impaired hepatic function (see **WARNINGS**).

HOW SUPPLIED
AMRIX extended-release capsules are available in 15 and 30 mg strengths, packaged in bottles of 60 capsules.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. IN CASE OF ACCIDENTAL OVERDOSE, SEEK PROFESSIONAL ASSISTANCE OR CONTACT A POISON CONTROL CENTER IMMEDIATELY.

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