

Dr. Haro and colleagues implemented a quality initiative after a chart review of data from July 2002 to September 2003 showed that the hospital's DTBT was 200 minutes, he said at a meeting sponsored by the American Heart Association.

The initiative involved new processes to streamline communication between providers in the emergency department (ED), the catheterization lab, and the quality department.

"It was very hard to figure out where to find the data, since there are five or six areas to look for information, such as the ED chart and the cath lab report," said Dr. Haro, quality chair of emergency medi-

cine. A group from quality, communications, cardiology, nursing, and the ED met biweekly for 3 months before implementing the changes. The project's goals were to achieve a door-to-ECG time of 5 minutes, a door-to-activation time of 15 minutes, a door-to-departure-to-cath-lab time of 45 minutes, and a door-to-PCI time of 90 minutes. After closer scrutiny of the original data, the investigators adjusted the initial DTBT to 104 minutes.

The first change was to replace several ED clocks to server-based ones that display official U.S. time, since some of the original discrepancies in the data had to do with how times were recorded in the

charts. "Now that every minute counts, it must be accurate," said Dr. Haro.

Time stamps on a patient's small triage sheet track the initial door time, rather than the registration time, which was used as a point of reference in the past.

"When a patient has chest pain, we place them in a bed immediately and start the evaluation and initial management. Before, we had artificial times, since charts were sometimes generated after a patient had aspirin, oxygen, or an electrocardiogram, meaning 10-15 minutes were spent before their door time was recorded," said Dr. Haro. Door-to-ECG times dropped from 14.4 minutes to 9.1 minutes.

Several other changes were made. Registration personnel use wireless laptops at patients' bedsides to help capture real-time data, which is immediately displayed on a monitor in the ED. This allows providers to assess whether their performance goals are being accomplished for that given patient.

The ED physician now activates the cardiac catheterization team without a cardiac consultation. Previously, time was wasted through numerous phone calls made among the ED, the CCU and cath team to try and organize a PCI. Now, the entire team is activated by a single group page within 15 minutes of the patient's arrival. The pagers display text to state the problem, the patient's location, and when the patient will be on the table. "It runs similar to a trauma system," said Dr. Haro. Cath team members make one call in to a communications center to acknowledge the page, whereas CCU personnel just show up to join the team.

To improve door-to-departure times, 2-hour priority parking was given to cath lab members, who previously parked at a distance from the hospital; a dedicated phone line was established between the ED and the cath lab; and elevator keys were given to cath team members to bypass stopping at floors, which used to slow them down.

The American College of Cardiology recommends a 60-120 minute DTBT, while the Joint Commission on the Accreditation of Healthcare Organizations recently changed recommended times from 90 to 120 minutes. ■

## Better GI Bleeding Prophylaxis Needed After Stenting

CHICAGO — Cardiologists might not be adequately protecting their coronary artery-stenting patients against the risk of upper GI bleeding due to antiplatelet therapy, according to a poster presented at the annual Digestive Disease Week.

The study, led by Steven Chang, M.D., was a chart review of 636 randomly selected patients who received stents at three institutions, including Chicago's Northwestern Memorial Hospital. Most patients received aspirin before (72%) and/or after (97%) stent placement, which increased their risk of peptic ulcer-related bleeding, according to Dr. Chang and his colleagues.

After stenting, however, only 24% were prescribed a proton pump inhibitor (PPI), reported Dr. Chang, who is a consultant to Santarus, a manufacturer of omeprazole.

Three of the stent recipients had a documented history of upper-GI bleeding, 23 had a history of peptic ulcer disease, and 30 were receiving NSAID therapy that was not stopped before stenting. "Few coronary stent patients who are started on aspirin and other antiplatelet agents receive appropriate GI prophylaxis," Dr. Chang wrote.

But it might not be cost effective to prescribe a PPI to all patients before stent placement, he added. "We recommend that cardiologists give PPIs to patients at risk [of upper GI bleeding] before stenting."

—Kathleen Loudon

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Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of up to 300 mg/kg/day (83 times the maximum daily human dose of 32 mg on a body surface area basis).

#### Pregnancy

*Pregnancy Categories C* (first trimester) and *D* (second and third trimesters)—See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

#### Nursing Mothers

It is not known whether candesartan is excreted in human milk, but candesartan has been shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

#### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

#### Geriatric Use

##### Hypertension

Of the total number of subjects in clinical studies of ATACAND, 21% (683/3260) were 65 and over, while 3% (87/3260) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In a placebo-controlled trial of about 200 elderly hypertensive patients (ages 65 to 87 years), administration of candesartan cilexetil was well tolerated and lowered blood pressure by about 12/6 mm Hg more than placebo.

##### Heart Failure

Of the 7599 patients with heart failure in the CHARM program, 4343 (57%) were age 65 years or older and 1736 (23%) were 75 years or older. In patients  $\geq 75$  years of age, the incidence of drug discontinuations due to adverse events was higher for those treated with ATACAND or placebo compared with patients  $< 75$  years of age. In these patients, the most common adverse events leading to drug discontinuation at an incidence of at least 3%, and more frequent with ATACAND than placebo, were abnormal renal function (7.9% vs. 4.0%), hypotension (5.2% vs. 3.2%) and hyperkalemia (4.2% vs. 0.9%). In addition to monitoring of serum creatinine, potassium, and blood pressure during dose escalation and periodically thereafter, greater sensitivity of some older individuals with heart failure must be considered.

### ADVERSE REACTIONS

#### Hypertension

ATACAND has been evaluated for safety in more than 3600 patients/subjects, including more than 3200 patients treated for hypertension. About 600 of these patients were studied for at least 6 months and about 200 for at least 1 year. In general, treatment with ATACAND was well tolerated. The overall incidence of adverse events reported with ATACAND was similar to placebo.

The rate of withdrawals due to adverse events in all trials in patients (7510 total) was 3.3% (ie, 108 of 3260) of patients treated with candesartan cilexetil as monotherapy and 3.5% (ie, 39 of 1106) of patients treated with placebo. In placebo-controlled trials, discontinuation of therapy due to clinical adverse events occurred in 2.4% (ie, 57 of 2350) of patients treated with ATACAND and 3.4% (ie, 35 of 1027) of patients treated with placebo.

The most common reasons for discontinuation of therapy with ATACAND were headache (0.6%) and dizziness (0.3%).

The adverse events that occurred in placebo-controlled clinical trials in at least 1% of patients treated with ATACAND and at a higher incidence in candesartan cilexetil (n=2350) than placebo (n=1027) patients included back pain (3% vs. 2%), dizziness (4% vs. 3%), upper respiratory tract infection (6% vs. 4%), pharyngitis (2% vs. 1%), and rhinitis (2% vs. 1%).

The following adverse events occurred in placebo-controlled clinical trials at a more than 1% rate but at about the same or greater incidence in patients receiving placebo compared to candesartan cilexetil: fatigue, peripheral

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edema, chest pain, headache, bronchitis, coughing, sinusitis, nausea, abdominal pain, diarrhea, vomiting, arthralgia, albuminuria.

Other potentially important adverse events that have been reported, whether or not attributed to treatment, with an incidence of 0.5% or greater from the 3260 patients worldwide treated in clinical trials with ATACAND are listed below. It cannot be determined whether these events were causally related to ATACAND. **Body as a Whole:** asthenia, fever; **Central and Peripheral Nervous System:** paresthesia, vertigo; **Gastrointestinal System Disorder:** dyspepsia, gastroenteritis; **Heart Rate and Rhythm Disorders:** tachycardia, palpitation; **Metabolic and Nutritional Disorders:** creatine phosphokinase increased, hyperglycemia, hypertriglyceridemia, hyperuricemia; **Musculoskeletal System Disorders:** myalgia; **Platelet/Bleeding-Clotting Disorders:** epistaxis; **Psychiatric Disorders:** anxiety, depression, somnolence; **Respiratory System Disorders:** dyspnea; **Skin and Appendages Disorders:** rash, sweating increased; **Urinary System Disorders:** hematuria.

Other reported events seen less frequently included angina pectoris, myocardial infarction, and angioedema.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

#### Heart Failure

The adverse event profile of ATACAND in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the CHARM program, comparing ATACAND in total daily doses up to 32 mg once daily (n=3803) with placebo (n=3796), 21.0% of patients discontinued ATACAND for adverse events vs. 16.1% of placebo patients.

#### Post-Marketing Experience:

The following have been very rarely reported in post-marketing experience:

**Digestive:** Abnormal hepatic function and hepatitis.

**Hematologic:** Neutropenia, leukopenia, and agranulocytosis.

**Metabolic and Nutritional Disorders:** hyperkalemia, hyponatremia.

**Renal:** renal impairment, renal failure.

**Skin and Appendages Disorders:** Pruritis and urticaria.

Rare reports of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

#### Laboratory Test Findings

##### Hypertension

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with the administration of ATACAND.

**Creatinine, Blood Urea Nitrogen**—Minor increases in blood urea nitrogen (BUN) and serum creatinine were observed infrequently.

**Hyperuricemia**—Hyperuricemia was rarely found (19 or 0.6% of 3260 patients treated with candesartan cilexetil and 5 or 0.5% of 1106 patients treated with placebo).

**Hemoglobin and Hematocrit**—Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.2 grams/dL and 0.5 volume percent, respectively) were observed in patients treated with ATACAND alone but were rarely of clinical importance. Anemia, leukopenia, and thrombocytopenia were associated with withdrawal of one patient each from clinical trials.

**Potassium**—A small increase (mean increase of 0.1 mEq/L) was observed in patients treated with ATACAND alone but was rarely of clinical importance. One patient from a congestive heart failure trial was withdrawn for hyperkalemia (serum potassium = 7.5 mEq/L). This patient was also receiving spironolactone.

**Liver Function Tests**—Elevations of liver enzymes and/or serum bilirubin were observed infrequently. Five patients assigned to candesartan cilexetil in clinical trials were withdrawn because of abnormal liver chemistries. All had elevated transaminases. Two had mildly elevated total bilirubin, but one of these patients was diagnosed with Hepatitis A.

##### Heart Failure

In the CHARM program, small increases in serum creatinine (mean increase 0.2 mg/dL in candesartan-treated

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patients and 0.1 mg/dL in placebo-treated patients) and serum potassium (mean increase 0.15 mEq/L in candesartan-treated patients and 0.02 mEq/L in placebo-treated patients), and small decreases in hemoglobin (mean decrease 0.5 gm/dL in candesartan-treated patients and 0.3 gm/dL in placebo-treated patients) and hematocrit (mean decrease 1.6% in candesartan-treated patients and 0.9% in placebo-treated patients) were observed.

#### OVERDOSAGE

No lethality was observed in acute toxicity studies in mice, rats, and dogs given single oral doses of up to 2000 mg/kg of candesartan cilexetil. In mice given single oral doses of the primary metabolite, candesartan, the minimum lethal dose was greater than 1000 mg/kg but less than 2000 mg/kg.

The most likely manifestation of overdosage with ATACAND would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Candesartan cannot be removed by hemodialysis.

**Treatment:** To obtain up-to-date information about the treatment of overdose, consult your Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdose, consider the possibilities of multiple-drug overdoses, drug-drug interactions, and altered pharmacokinetics in your patient.

### DOSAGE AND ADMINISTRATION

#### Hypertension

Dosage must be individualized. Blood pressure response is dose related over the range of 2 to 32 mg. The usual recommended starting dose of ATACAND is 16 mg once daily when it is used as monotherapy in patients who are not volume depleted. ATACAND can be administered once or twice daily with total daily doses ranging from 8 mg to 32 mg. Larger doses do not appear to have a greater effect, and there is relatively little experience with such doses. Most of the antihypertensive effect is present within 2 weeks, and maximal blood pressure reduction is generally obtained within 4 to 6 weeks of treatment with ATACAND.

No initial dosage adjustment is necessary for elderly patients, for patients with mildly impaired renal function, or for patients with mildly impaired hepatic function (see CLINICAL PHARMACOLOGY, Special Populations). In patients with moderate hepatic impairment, consideration should be given to initiation of ATACAND at a lower dose (See CLINICAL PHARMACOLOGY, Special Populations). For patients with possible depletion of intravascular volume (eg, patients treated with diuretics, particularly those with impaired renal function), ATACAND should be initiated under close medical supervision and consideration should be given to administration of a lower dose (see WARNINGS, Hypotension in Volume- and Salt-Depleted Patients).

ATACAND may be administered with or without food.


If blood pressure is not controlled by ATACAND alone, a diuretic may be added. ATACAND may be administered with other antihypertensive agents.

#### Heart Failure

The recommended initial dose for treating heart failure is 4 mg once daily. The target dose is 32 mg once daily, which is achieved by doubling the dose at approximately 2-week intervals, as tolerated by the patient.

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