

AHA Spearheads STEMI Response Initiative

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A community-based push to create standardized response systems could decrease mortality and streamline acute care for patients suffering an ST-elevation myocardial infarction.

The American Heart Association's ambitious "Mission: Lifeline" program will go far beyond past efforts at improving treatment times through public outreach and

education, Dr. Alice Jacobs said during a press conference. "Regrettably, prior public awareness campaigns and community-based interventions have not yet been effective in reducing the time from symptom onset to first medical contact, or in increasing the number of patients who use emergency medical services [EMS] to get to hospitals where they can receive the appropriate care."

"Despite the proven benefits of quickly restoring blood flow to the heart muscle

during a heart attack, 30% of STEMI patients do not receive any reperfusion therapy," neither fibrinolytics nor primary percutaneous coronary intervention (PCI), said Dr. Jacobs, director of the cardiac catheterization lab at Boston Medical Center. "And only 50% of those who get fibrinolytics and 40% of those who undergo PCI do so within the recommended time frames."

The group's recommendations are published in the journal *Circulation* (DOI:10.

1161/CIRCULATIONAHA.107.184043).

The ideal system would combine several key elements, she said:

► **Public education.** "People need to understand the signs and symptoms of a heart attack, and the importance of activating the EMS system as quickly as possible," Dr. Jacobs said.

► **Improving EMS diagnosis of STEMI.** "If EMS systems have the personnel, training, and appropriate resources, they can acquire, interpret, and transmit 12-lead electrocardiograms that can show the patient is having a STEMI heart attack," she said.

► **Quick, efficient transfer to hospitals equipped with cardiac catheterization teams.** Under the proposed system, patients transported to a non-PCI-capable hospital would remain on the stretcher with EMS personnel in attendance until the decision is made about whether to transport to a PCI-capable receiving hospital.

► **Hospital incentives and certification.** "We will be working with payers and policy makers to ensure that mechanisms are in place for appropriate reimbursement," Dr. Jacobs said. A STEMI Center Certification program will establish treatment and accountability protocols for both referring and receiving hospitals.

The AHA will play a pivotal role in bringing these parties together, said Dr. Raymond Gibbons, president of the AHA, beginning with an assessment of EMS effectiveness for STEMI patients. The AHA will use this information to construct a basic response system that can be tailored to different regions.

Funding these systems, Dr. Gibbons said, will be largely left to localities. AHA will provide support in seeking the money necessary for implementation—industry grants, for example—but the group won't be contributing financially to any individual project.

A few AHA-led pilot programs are already underway, Dr. Gibbons noted. A 2004 grant from The Annenberg Foundation made it possible for Los Angeles to create a response system that relies on 12-lead ECG readings by EMS providers. The AHA Greater Southeast Affiliate has convened a state-level STEMI task force and helped introduce a legislative bill to develop emergency angioplasty centers for STEMI patients. And in Texas, a task force met in January to discuss ways to more effectively manage STEMI patients.

Although establishing such a response system is an enormous challenge, the payoff is just as big, said Dr. Tim Henry, interventional cardiologist and director of research at the Minneapolis Heart Institute. Four years ago, the facility instituted a two-pronged standardized care system for STEMI patients based on their distance from a regional PCI-capable facility.

"Our approach involves different protocols for patients who live within either 60 miles [zone 1] or 60-210 miles [zone 2] from these hospitals. Our median time from the STEMI referral hospitals to balloon inflation at the receiving hospital is now 96 minutes for those in zone 1 and 118 minutes in zone 2."

VAPRISOL® (conivaptan hydrochloride injection)

BRIEF SUMMARY OF PRESCRIBING INFORMATION
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INDICATIONS AND USAGE

VAPRISOL is indicated for the treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients.

Important Limitation:

VAPRISOL is not indicated for the treatment of congestive heart failure. VAPRISOL should only be used for the treatment of hyponatremia in patients with underlying heart failure when the expected clinical benefit of raising serum sodium outweighs the increased risk of adverse events for heart failure patients. (See PRECAUTIONS AND ADVERSE REACTIONS)

CONTRAINDICATIONS

VAPRISOL is contraindicated in patients with hypovolemic hyponatremia.

The coadministration of VAPRISOL with potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir, is contraindicated. (See PRECAUTIONS: Drug Interactions for details and other important considerations)

PRECAUTIONS

Congestive Heart Failure: The number of heart failure patients with hypervolemic hyponatremia who have been treated with intravenous VAPRISOL is too small to establish safety in patients with underlying congestive heart failure. (See ADVERSE REACTIONS)

Overly Rapid Correction of Serum Sodium: An overly rapid increase in serum sodium concentration (>12 mEq/L/24 hours) may result in serious sequelae. In controlled clinical trials of VAPRISOL, about 9% of patients who received VAPRISOL in doses of 20-40 mg/day IV met laboratory criteria for overly rapid correction of serum sodium, but none of these patients had permanent neurologic sequelae. Although not observed in the clinical studies with VAPRISOL, osmotic demyelination syndrome has been reported following rapid correction of low serum sodium concentrations. Serum sodium concentration and neurologic status should be monitored appropriately during VAPRISOL administration, and VAPRISOL administration should be discontinued if the patient develops an undesirably rapid rate of rise of serum sodium. If the serum sodium concentration continues to rise, VAPRISOL should not be resumed. If hyponatremia persists or recurs (after initial discontinuation of VAPRISOL for an undesirably rapid rate of rise of serum sodium concentration), and the patient has had no evidence of neurologic sequelae of rapid rise in serum sodium, VAPRISOL may be resumed at a reduced dose.

Hepatic Impairment: The use of VAPRISOL in patients with hepatic impairment (including ascites, cirrhosis, or portal hypertension) has not been systematically evaluated.

Increased systemic exposures after oral administration of conivaptan have been seen in patients with stable cirrhosis and moderate hepatic impairment. Intravenous VAPRISOL resulted in higher conivaptan exposure than did oral conivaptan, in study subjects without hepatic function impairment. Caution should be used when administering VAPRISOL to patients with hepatic impairment.

Renal Impairment: The effect of renal impairment on the elimination of conivaptan after intravenous administration has not been evaluated. However, following oral administration of conivaptan, the AUC for conivaptan was up to 80% higher after a single oral dose and 35% higher with repeated oral dosing in patients with renal impairment (CL_{CR} < 60 mL/min/1.73 m²) as compared to those with normal renal function. Intravenous VAPRISOL resulted in higher conivaptan exposure than did oral conivaptan, in study subjects without renal function impairment. Caution should be used when administering VAPRISOL to patients with renal impairment.

Injection Site Reactions: Conivaptan may cause significant injection site reactions, even with proper dilution and infusion rates. (See ADVERSE REACTIONS) Conivaptan must only be administered when properly prepared and diluted (see Preparation) via large veins, and the infusion site should be rotated every 24 hours. (See DOSAGE AND ADMINISTRATION)

Drug Interactions

(See CLINICAL PHARMACOLOGY: Drug-Drug Interactions)

CYP3A4: Conivaptan is a substrate of CYP3A4. Coadministration of VAPRISOL with CYP3A4 inhibitors could lead to an increase in conivaptan concentrations. The consequences of increased conivaptan concentrations are unknown. Concomitant use of VAPRISOL with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir is contraindicated. Conivaptan is a potent inhibitor of CYP3A4. VAPRISOL may increase plasma concentrations of coadministered drugs that are primarily metabolized by CYP3A4. In clinical trials of oral conivaptan hydrochloride, two cases of rhabdomyolysis occurred in patients who were also receiving a CYP3A4-metabolized HMG-CoA reductase inhibitor. Concomitant use of VAPRISOL with drugs that are primarily metabolized by CYP3A4 should be closely monitored or the combination should be avoided. If a clinical decision is made to discontinue concomitant medications at recommended doses, allow an appropriate amount of time following the end of VAPRISOL administration before resuming these medications.

Digoxin: Coadministration of digoxin, a P-glycoprotein substrate, with oral conivaptan resulted in a reduction in clearance and increases in digoxin C_{max} and AUC values. Therefore, if digoxin is administered with VAPRISOL, the clinician should be alert to the possibility of increases in digoxin levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Standard lifetime (104 week) carcinogenicity bioassays were conducted in mice and rats. Mice were given oral doses of 3, 10 or 30 mg/kg/day in males and 1, 3 or 10 mg/kg/day in females by gavage. Rats were given oral doses of 0.3, 1, 3 or 10 mg/kg/day in males and 1, 3, 10 or 30 mg/kg/day in females by gavage. No increased incidence of tumors was observed at doses up to 30 mg/kg/day in mice (6 times human systemic exposure of an IV bolus of 20 mg on Day 1 followed by IV infusion 40 mg/day for 3 days based on AUC comparison) or rats (2 times human systemic exposure of an IV bolus of 20 mg on Day 1 followed by IV infusion 40 mg/day for 3 days based on AUC comparison).

Conivaptan was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, in human peripheral blood lymphocytes, or *in vivo* rat micronucleus assay.

In fertility studies after 4 weeks treatment by intravenous bolus at 0.5, 1.25 or 2.5 mg/kg/day, male fertility was unaffected. However, in females given IV bolus conivaptan 15 days before mating through gestation day 7 there was prolonged diestrus, decreased fertility and increased pre- and post-implantation loss at 2.5 mg/kg/day (systemic exposures less than the therapeutic dose).

Pregnancy

Pregnancy Category C

Conivaptan has been shown to have adverse effects on the fetus when given to animals during pregnancy at systemic exposures less than those achieved at a therapeutic dose based on AUC comparisons. There are no adequate and well-controlled studies in pregnant women. VAPRISOL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The patient should be apprised of the potential hazard to the fetus. Conivaptan crosses the placenta and is found in fetal tissue in rats. Fetal tissue levels were <10% of maternal plasma concentrations while placental levels were 2.2-fold higher than maternal plasma concentrations indicating that conivaptan can be transferred to the fetus. Conivaptan that is taken up by fetal tissue is slowly cleared, suggesting that fetal accumulation is possible. Milk levels were up to 3 times higher than maternal plasma levels following an intravenous dose of 1 mg/kg (systemic exposures less than therapeutic based on AUC comparisons).

In female rats given an intravenous bolus dose of 0.5, 1.25 or 2.5 mg/kg/day conivaptan hydrochloride before mating and continuing through gestation day 7, prolonged diestrus, decreased fertility and increased pre- and post-natal implantation loss occurred at 2.5 mg/kg/day (systemic exposures less than the therapeutic dose).

In pregnant rats given intravenous doses of 0.5, 1.25 or 2.5 mg/kg/day from gestation day 7 through 17 (organogenesis), no significant maternal or fetal effects were observed at systemic exposures less than therapeutic exposure based on AUC comparisons.

Pregnant rats were administered intravenous conivaptan hydrochloride at a dose of 2.5 mg/kg/day (systemic exposures less than therapeutic based on AUC) from gestation day 7 through lactation day 20 (weaning), and the pups showed decreased neonatal viability, weaning indices, delayed growth and physical development (including sexual maturation), and delayed reflex development. No discernible changes were seen in pups from dams administered conivaptan hydrochloride at 0.5 or 1.25 mg/kg/day from this same period. No maternal adverse effects were seen with conivaptan hydrochloride administration (0.5, 1.25, or 2.5 mg/kg/day from gestation day 7 through lactation day 20; systemic exposures less than therapeutic dose based on AUC comparisons). In pregnant rabbits given intravenous doses of 3, 6 or 12 mg/kg/day from gestation day 6 through 18 (organogenesis) there were no fetal findings; however, maternal toxicity was observed in all groups (systemic exposures less than the therapeutic dose).

In bolus intravenous postnatal rat studies, decreased neonatal viability, decreased weaning indices, delayed growth/physical development and delayed sexual maturation of offspring were observed at 2.5 mg/kg/day (systemic exposures less than the therapeutic dose).

Labor and Delivery

The effect of conivaptan on labor and delivery in humans has not been studied. Conivaptan hydrochloride delayed delivery in rats dosed orally at 10 mg/kg/day by oral gavage (systemic exposures equivalent to the therapeutic dose based on AUC comparisons.) Administration of conivaptan hydrochloride at 2.5 mg/kg/day intravenously increased peripartum pup mortality (systemic exposures were less than the therapeutic dose based on AUC comparisons). These effects may be associated with conivaptan activity on oxytocin receptors in the rat. The relevance to humans is unclear.

Lactating Women

It is not known whether conivaptan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VAPRISOL is administered to a lactating woman. Conivaptan is excreted in milk and detected in neonates when given by intravenous administration to lactating rats. Milk levels of conivaptan in rats reached maximal levels at 1 hour post dose following intravenous administrations and were up to 3 times greater than maternal plasma levels. Administration of conivaptan hydrochloride at 2.5 mg/kg/day intravenously increased peripartum pup mortality; systemic exposures were less than the therapeutic dose based on AUC comparisons.

Pediatric Use

The safety and effectiveness of VAPRISOL in pediatric patients have not been studied.

Geriatric Use

In clinical studies of intravenous VAPRISOL administered as a 20 mg IV loading dose followed by 20 mg/day or 40 mg/day IV for 2 to 4 days, 89% (20 mg/day regimen) and 60% (40 mg/day regimen) of participants were greater than or equal to 65 years of age and 60% (20 mg/day regimen) and 40% (40 mg/day regimen) were greater than or equal to 75 years of age. In general, the adverse event profile in elderly patients was similar to that seen in the general study population.

ADVERSE REACTIONS

The most common adverse reactions reported with VAPRISOL administration were infusion site reactions. In studies in patients and healthy volunteers, infusion site reactions occurred in 73% and 63% of subjects treated with VAPRISOL 20 mg/day and 40 mg/day, respectively, compared to 4% in the placebo group. Infusion site reactions were the most common type of adverse event leading to discontinuation of VAPRISOL. Discontinuations from treatment due to infusion site reactions were more common among VAPRISOL-treated patients (3%) than among placebo-treated patients (0%). Some serious infusion site reactions did occur. (See DOSAGE AND ADMINISTRATION in full Prescribing Information)

The adverse reactions presented in Table 1 are derived from 72 healthy volunteers and 243 patients with euvolemic or hypervolemic hyponatremia who received VAPRISOL 20 mg IV as a loading dose followed by 40 mg/day IV for 2 to 4 days, from 37 patients with euvolemic or hypervolemic hyponatremia who received VAPRISOL 20 mg IV as a loading dose followed by 20 mg/day IV for 2 to 4 days in an open-label study, and from 40 healthy volunteers and 29 patients with euvolemic or hypervolemic hyponatremia who received placebo. The adverse reactions occurred in at least 5% of patients treated with VAPRISOL and at a higher incidence for VAPRISOL-treated patients than for placebo-treated patients.

Table 1
IV VAPRISOL: Adverse Reactions Occurring in ≥5% of Patients or Healthy Volunteers and VAPRISOL Incidence > Placebo Incidence Hyponatremia and Healthy Volunteer Studies

| Term | Placebo N=69 n (%) | 20 mg N=37 n (%) | 40 mg N=315 n (%) |
|--|--------------------------|------------------------|-------------------------|
| Blood and lymphatic system disorders | | | |
| Anemia NOS | 2 (3%) | 2 (5%) | 18 (6%) |
| Cardiac disorders | | | |
| Atrial fibrillation | 0 (0%) | 2 (5%) | 7 (2%) |
| Gastrointestinal disorders | | | |
| Constipation | 2 (3%) | 3 (8%) | 20 (6%) |
| Diarrhea NOS | 0 (0%) | 0 (0%) | 23 (7%) |
| Nausea | 3 (4%) | 1 (3%) | 17 (5%) |
| Vomiting NOS | 0 (0%) | 2 (5%) | 23 (7%) |
| General disorders and administration site conditions | | | |
| Edema peripheral | 1 (1%) | 1 (3%) | 24 (8%) |
| Infusion site erythema | 0 (0%) | 0 (0%) | 18 (6%) |
| Infusion site pain | 1 (1%) | 0 (0%) | 16 (5%) |
| Infusion site phlebitis | 1 (1%) | 19 (51%) | 102 (32%) |
| Infusion site reaction | 0 (0%) | 8 (22%) | 61 (19%) |
| Pyrexia | 0 (0%) | 4 (11%) | 15 (5%) |
| Thirst | 1 (1%) | 1 (3%) | 19 (6%) |
| Infections and infestations | | | |
| Pneumonia NOS | 0 (0%) | 2 (5%) | 7 (2%) |
| Urinary tract infection NOS | 2 (3%) | 2 (5%) | 14 (4%) |
| Injury, poisoning and procedural complications | | | |
| Post procedural diarrhea | 0 (0%) | 2 (5%) | 0 (0%) |
| Investigations | | | |
| Electrocardiogram ST segment depression | 0 (0%) | 2 (5%) | 0 (0%) |
| Metabolism and nutrition disorders | | | |
| Hypokalemia | 2 (3%) | 8 (22%) | 30 (10%) |
| Hypomagnesemia | 0 (0%) | 2 (5%) | 6 (2%) |
| Hyponatremia | 1 (1%) | 3 (8%) | 20 (6%) |
| Nervous system disorders | | | |
| Headache | 2 (3%) | 3 (8%) | 32 (10%) |
| Psychiatric disorders | | | |
| Confusional state | 2 (3%) | 0 (0%) | 16 (5%) |
| Insomnia | 0 (0%) | 2 (5%) | 12 (4%) |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pharyngolaryngeal pain | 3 (4%) | 2 (5%) | 3 (1%) |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | 0 (0%) | 2 (5%) | 2 (1%) |
| Vascular disorders | | | |
| Hypertension NOS | 0 (0%) | 3 (8%) | 20 (6%) |
| Hypotension NOS | 2 (3%) | 3 (8%) | 16 (5%) |
| Orthostatic hypotension | 0 (0%) | 5 (14%) | 18 (6%) |

Adapted from MedDRA version 6.0

Although a dose of 80 mg/day of intravenous VAPRISOL was also studied, it was associated with a higher incidence of infusion site reactions and a higher rate of discontinuation due to adverse events than was the 40 mg/day intravenous VAPRISOL dose. The maximum daily dose of VAPRISOL (after the loading dose) is 40 mg/day.

Congestive Heart Failure

In clinical trials where intravenous VAPRISOL was administered to 79 hypervolemic hyponatremic patients with underlying heart failure and intravenous placebo administered to 10 patients, adverse cardiac failure events, atrial dysrhythmias, and sepsis occurred more frequently among patients treated with VAPRISOL (32%, 5% and 8% respectively) than among patients treated with placebo (20%, 0% and 0% respectively). The number of heart failure patients with hypervolemic hyponatremia who have been treated with intravenous VAPRISOL is too small to establish safety in this specific population. VAPRISOL should only be used in patients with underlying heart failure when the expected clinical benefit of raising serum sodium outweighs the risk of adverse events.

In ten Phase 2/pilot heart failure studies, VAPRISOL did not show statistically significant improvement for heart failure outcomes, including such measures as length of hospital stay, changes in categorized physical findings of heart failure, change in ejection fraction, change in exercise tolerance, change in functional status, or change in heart failure symptoms, as compared to placebo. In these studies, the changes in the physical findings and heart failure symptoms were no worse in the VAPRISOL-treated group (N=818) compared to the placebo group (N=290).

DRUG ABUSE AND DEPENDENCE

VAPRISOL does not have known potential for psychogenic drug abuse and/or dependence.

OVERDOSAGE

Although no data on overdosage in humans are available, VAPRISOL has been administered as a 20 mg loading dose on Day 1 followed by continuous infusion of 80 mg/day for 4 days in hyponatremia patients and up to 120 mg/day for 2 days in CHF patients. No new toxicities were identified at these higher doses, but adverse events related to the pharmacologic activity of VAPRISOL, e.g. hypotension and thirst, occurred more frequently at these higher doses.

In case of overdose, based on expected exaggerated pharmacological activity, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is recommended.

Rx only

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References: 1. Vaprisol Prescribing Information. Astellas Pharma US, Inc. 2. Data on file. Astellas Pharma US, Inc.