Inhaled Drug Limits Prolonged Migraine

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FROM THE ANNUAL MEETING OF THE AMERICAN HEADACHE SOCIETY

LOS ANGELES – An experimental inhaled form of dihydroergotamine appears to be effective in reducing migraine pain even if taken as late as 8 hours or more after the start of the headache, a post hoc analysis of a phase III clinical trial suggests.

Investigators analyzed data from the randomized, double-blind, placebo-controlled FREEDOM 301 study. Among 771 patients who treated a moderate to severe migraine and recorded both efficacy and the time from onset of headache to treatment, patients randomized to inhaled dihydroergotamine were significantly more likely than were those given placebo to report being pain free 2 hours after treatment if they took the drug within an hour of migraine onset, 1-4 hours after onset, or 4-8 hours after onset, Dr. Stewart J. Tepper and his associates reported.

VITALS

Major Finding: An investigational, inhaled form of dihydroergotamine was significantly more likely than was placebo to relieve pain within 2 hours in patients who took treatment more than 8 hours after headache onset (92% vs. 52%, respectively) and in patients who took treatment earlier.

Data Source: Post hoc analysis of data from a randomized, double-blind trial of 771 patients who treated a single moderate to severe migraine.

Disclosures: Dr. Tepper and each of his associates in the study has been a speaker or consultant for, or received funding from, MAP Pharmaceuticals Inc., which hopes to market the inhaled formulation of dihydroergotamine.

Rates of freedom from pain were not significantly higher with the drug compared with placebo in patients who took treatment more than 8 hours after the migraine started. Reports of pain relief, however, were significantly higher in the inhaled dihydroergotamine subgroups regardless of how long after headache onset they took treatment, he said at the meeting.

Triptans are known to provide the best relief when taken early in a migraine attack and to have reduced efficacy when treatment is delayed, said Dr. Tepper of the Cleveland Clinic. Inhaled dihydroergotamine may be an alternative for patients who delay starting migraine treatment, if the formulation wins approval, he added.

Freedom from pain at 2 hours post treatment was reported by 34% of 112 patients randomized to inhaled dihydroergotamine and 11% of 118 on placebo who took treatment within an hour of headache onset. In those who took treatment after an hour but within 4 hours of migraine onset, 18% of 152 patients on inhaled dihydroergotamine and 6% of 169 on placebo were pain free 2 hours later. Among patients who treated the migraine after 4 hours but within 8 hours of onset, 22 of 68 (32%) on inhaled dihydroergotamine and 8 of 53 (15%) on placebo were pain free 2 hours later.

For patients who started treatment more than 8 hours after migraine onset, 19 of 53 (36%) on inhaled dihydroergotamine and 9 of 46 (20%) on placebo were pain free 2 hours later. Although those rates were not significantly different, pain relief 2 hours after treatment was reported by 49 on inhaled dihydroergotamine (92%) and 24 on placebo (52%), a significant difference between groups.

"That's a very dramatic finding," Dr. Tepper said.

Pain relief rates in patients who started treatment within an hour of migraine onset were 60% with inhaled dihydroergotamine and 35% with placebo. Among those who started treatment after an hour but within 4 hours of migraine onset, 37% on inhaled dihydroergotamine and 21% on placebo reported pain relief 2 hours later. Pain relief also occurred in 53 patients on inhaled dihydroergotamine (78%) and 30 on placebo (57%) who took treatment after 4 hours but within 8 hours of migraine onset.

Data on adverse events in 404 patients in the inhaled dihydroergotamine group and 401 in the placebo group suggest that the drug is well tolerated, Dr. Tepper said. Typical triptan-related symptoms such as chest discomfort or chest pain occurred rarely and at similar rates in both groups. There were no drug-related serious adverse events and no clinically meaningful change in lung function in this single-dose study. The most common adverse events that occurred more often with inhaled dihydroergotamine than with placebo were bad taste (in 6% and 2%, respectively), nausea (4% and 2%), and cough or vomiting (both in 2% and 1%).

The main FREEDOM 301 trial included 792 patients in an intent-to-treat analysis, and showed significantly increased likelihood of pain relief 2 hours after treatment in all patients on inhaled dihydroergotamine (59%), compared with patients on placebo (35%). Pain relief rates were significantly different between groups within an hour of treatment and remained significantly different after 24 and 48 hours.

Dihydroergotamine has been used in both an oral form and as an infusion for migraine. The inhaled version may work more quickly by passing directly into the bloodstream through the lungs. ■

Cognitive Deficits in Migraineur With Aura, Circulatory Shunting

FROM THE ANNUAL MEETING OF THE AMERICAN HEADACHE SOCIETY

LOS ANGELES – Cognitive deficits can occur between episodes of migraine with aura in patients with a large right-to-left shunt in the heart, according to interim results from a small, prospective, double-blind, observational study.

In the Comorbidities Associated With Migraine and Patent Foramen Ovale (CAMP) study, 20 patients with large right-to-left shunts scored significantly lower on measures of auditory and verbal memory and learning than did 20 patients with no right-to-left shunt. There was a significant inverse relationship between test scores and the number of embolic tracks detected on transcranial Doppler sonography, Jill Jesurum, Ph.D., and her associates reported at the meeting.

VITALS

Major Finding: Patients who have migraine with aura and a heart with a large right-to-left shunt showed significant deficits in verbal learning and memory, compared with patients with no right-to-left shunting.

Data Source: Interim analysis of 40 patients in on ongoing prospective, double-blind, observational study.

Disclosures: The study was funded by the National Headache Foundation, Coherex Medical, NMT Medical, and the John L. Locke Jr. Charitable Trust. Dr. Jesurum has had financial associations with Coherex Medical, NMT Medical, Coaptus Medical, Terumo Cardiovascular Systems, and Boston Scientific Corp.

No significant differences between groups were seen in tests of visual memory, learning, and processing speed. Patients with large right-to-left shunts scored higher on one of seven tests of cognitive efficiency and attention, but overall there seemed to be no significant difference between groups in this category. The neuropsychological tests used in the study emphasized cognitive function in brain regions supplied by the posterior circulation.

These early trends suggest temporal or hippocampal involvement and vulnerability to microembolic hypoperfusion, said Dr. Jesurum, scientific director of the Heart and Vascular Institute at Swedish Medical Center, Seattle.

However, the source of the right-to-left shunts has not yet been confirmed by echocardiography as perhaps being due to a patent foramen ovale, she said.

Dr. Jesurum advised caution in interpreting these interim results on such a small number of patients.

She speculated that circulatory shunting of unfiltered microaggregates and vasoactive chemicals to the cerebral vasculature may occur with right-to-left shunting and produce recurrent transient ischemia, theoretically increasing the risk of cognitive dysfunction. ■

Visual Disturbances Following Foam Sclerotherapy Deemed Aura

FROM THE ANNUAL MEETING OF THE AMERICAN HEADACHE SOCIETY

LOS ANGELES – Visual disturbances reported by patients after foam sclerotherapy are migrainous aura and should not be confused with cerebrovascular events, a small, prospective, multicenter study suggests.

In the study, a headache specialist analyzed questionnaires that were completed by 20 consecutive patients who reported visual disturbances after undergoing foam sclerotherapy at 11 French outpatient phlebology clinics.

All patients underwent cerebral MRIs within 2 weeks that were interpreted by a radiologist and again by a neuroradiologist.

Dr. Anne Donnet of the Pôle Neurosciences Cliniques at Hôpital Timone, Marseille, France, and her associates concluded that six patients had aura with nonmigrainous headache, five had aura without headache, four patients had the characteristics of aura with migrainous headache, and five did not have a headache or aura classification identified.

Dr. Donnet and her colleagues reported their findings in a poster presentation.

The 20 patients, 16 of whom were women, had an average age of 47 years.

In every case, the foam for sclerotherapy was made with air. The visual disturbance occurred an average of 7 minutes after the end of the injection, and lasted less than 30 minutes in 11 of the 20 patients, the investigators reported.

In 11 patients with headache, the visual disturbance started before a headache in 10 and at the same time in 1. The headache lasted less than 4 hours in six patients, 4-12 hours in one patient, and more than 24 hours in three patients. The duration was not specified for one patient whose headache was slight. Nine patients did not get headaches.

Paresthesia was observed in five patients and dysphasic speech disturbance occurred in one. Other symptoms in 13 patients included nausea in 10, photophobia in 6, phonophobia in 5, and chest pressure in 3.

A total of 15 patients had a personal history of migraine – 13 with aura and 2 without.

In follow-up contacts 2-4 weeks after sclerotherapy, patients said the visual disturbances had been transient and reported no new symptoms. ■