

# Inhaled Migraine Drug Brings Quick Pain Relief

*In addition to relief of pain, significantly more of the patients who took the drug were free of pain.*

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PHILADELPHIA — An inhaled form of dihydroergotamine provided significant relief of migraine pain, with sustained pain reduction and few adverse events, according to a phase III, placebo-controlled trial.

The drug conferred 4 hours of pain relief on 65% of those who took it; 48 hours later, 39% still reported pain relief, Dr. Stephen D. Silberstein reported at the International Headache Congress.

Dihydroergotamine has been used in oral form and as an infusion for migraine. The inhaled version passes directly into the bloodstream through the

lungs, working much more quickly, said Dr. Silberstein, director of the Jefferson Headache Center at Thomas Jefferson University in Philadelphia. It also bypasses the problem of nauseous patients vomiting an undigested tablet.

The FREEDOM 301 study randomized 903 patients with severe, recurrent migraine to either a placebo inhaler or to the inhaled dihydroergotamine; 792 were included in the intent-to-treat analysis. Patients were a mean of 40 years old; their Headache Impact Test-6 score was 66, indicating severe disability. Most of the patients (91%) were women.

The study consisted of a 28-day washout period, followed by 8 weeks of

randomized treatment. Two 8-week, open-label, follow-up trials are underway.

The primary end point was pain relief at 2 hours. A pain curve separation began 30 minutes after dosing, but the groups were not significantly different.



**Of those who took the drug, 65% reported 4 hours of pain relief; 48 hours later, 39% still reported pain relief.**

DR. SILBERSTEIN

At 1 hour, differences became significant and 48% of the active group and 28% of the placebo group reported relief. At 2 hours, pain relief was present in 59% of the active group and 35% of

the placebo group. Significantly more patients treated with the study drug than with placebo sustained relief at 24 hours (44% vs. 20%), and at 48 hours (36% vs. 17%).

Freedom from pain was an important secondary end point. Again, significantly more of those taking the drug were free of pain at 2 hours (28% vs. 10%), 4 hours (39% vs. 17%), 24 hours (23% vs. 7%), and 48 hours (18% vs. 6%).

Adverse events were mild, occurring in 31% of the study drug group and 25% of the placebo group, with the drug's taste being most commonly reported.

The study was sponsored by MAP Pharmaceuticals Inc., which hopes to market the inhaled formulation as Levadex. Dr. Silberstein disclosed he has received grants and honoraria from the company and he has also been an advisory board member or consultant. ■

## Target Complications Associated With Migraine

PHILADELPHIA — Migraine with or without aura is associated with a significant increase in the risk of cardiovascular disease, including stroke and heart attack.

Numerous studies have hinted at the association between migraine with aura and cardiovascular events, Dr. Marcelo E. Bigal reported at the International Headache Congress.

But the population-based study he performed with his colleague, Dr. Richard Lipton, was the first to examine the association in a large national sample in which migraine, with and without aura, had been officially diagnosed according to accepted standards.

Dr. Bigal of Merck Research Laboratories, Whitehouse Station, N.J., and his co-author, Dr. Lipton of Albert Einstein College of Medicine, New York, extracted their data from the American Migraine Prevalence and Progression Study.

The study by Dr. Bigal and Dr. Lipton was the largest of migraine sufferers ever conducted.

It analyzed symptoms and treatment patterns in a representative sample of 162,576 Americans aged 12 years and older.

The cardiovascular substudy included data on 6,102 adults with migraine and 5,243 controls.

Overall, the investigators found that migraineurs were significantly more likely than controls to have diabetes (13% vs. 9%, respectively), hypertension (33% vs. 26%), and hypercholesterolemia (33% vs. 26%).

In addition, Dr. Bigal and Dr. Lipton found that Framingham risk scores also were significantly higher for overall migraine and for those with migraine with and without aura (mean 11) than

they were for controls (mean 9).

Myocardial infarction had occurred in 2% of controls and 4% of migraineurs, which yielded an unadjusted odds ratio of 2.2.

Stroke occurred in 1.2% of the controls and 2% of the migraineurs—a significant 60% increased odds.

Rates of stroke were higher in those who had migraine with aura (4%) than without aura (1%), Dr. Bigal and Dr. Lipton found.

The significantly increased risks remained after adjusting for gender, age, disability, triptan use, diabetes, smoking, hypertension, and high cholesterol.

Overall, migraineurs were twice as likely as controls to have experienced a heart attack and 50% more likely to have experienced a stroke, the investigators found.

Migraineurs with aura were three times more likely than controls to have experienced either of those outcomes.

Migraineurs without aura were twice as likely as controls to have had a heart attack. However, Dr. Bigal and Dr. Lipton found that migraineurs without aura had no increased risk of stroke.

“Both migraine with and without aura are associated with cardiovascular disease and providers should be aware of these association to properly identify individuals at particularly high risk, as well as to plan treatment that targets not only migraine, but the complications potentially associated with it,” Dr. Bigal said.

Dr. Bigal is a full-time employee of Merck Research Laboratories.

Dr. Lipton has received research grants and honoraria from Merck and is a member of its advisory board. ■

## Migraine With Aura Increases Risk of Cardiovascular Death

PHILADELPHIA — Men and women who experience migraine with aura were significantly more likely to die from cardiovascular disease and than were those without headache.

Women with nonmigraine headache were also significantly more likely to die from cardiovascular disease than were women without headache, but the hazard ratio was smaller, Dr. Larus S. Gudmundsson wrote in a poster presented at the annual meeting of the International Headache Society.

Dr. Gudmundsson of the University of Iceland, Reykjavik, and his colleagues used data extracted from the Reykjavik Studyckd, a population-based cohort of adults followed from middle age, representing 474,360 person-years of observation. The cohort comprised 18,882 subjects who were a mean of 53 years old at baseline. Baseline interviews took place between 1967 and 1991.

The investigators divided the cohort into four categories: those without a headache once or more per month; those with nonmigraine headache; those with migraine without aura; and those with migraine and aura. Auroras were defined as visual, sensory or both.

Patients with nonaura headache symptoms, including nausea, unilateral location, and photophobia, were placed in the “with migraine without aura” category.

After entering the study, subjects were followed for up to 40 years (mean follow-up 26 years). Statistics on those who died during that time were obtained

from the Icelandic government and hospital records.

The Cox regression analysis controlled for age, body mass index, smoking, blood pressure, hypertension medication, oral contraceptive use, diabetes, and lipid levels.

In an assessment of all-cause mortality, both men and women with migraine and aura were at a significantly increased risk of death, compared with subjects without headache (20%).

For men, the risk rose when only cardiovascular death was considered (hazard ratio 1.38). For women with migraine and aura, the risk of cardiovascular death dipped slightly (HR 1.18).

Migraine without aura did not increase the risk of cardiovascular death, compared with those without headache.

However, women with nonmigrainous headaches were at a slightly—though still statistically significant—elevated risk of cardiovascular mortality, compared with women without headache (HR 1.14).

The risk did not change significantly for men with nonmigrainous headache, Dr. Gudmundsson and his colleagues found.

The authors pointed out that the increased risk of death, while significant, was not as great as the risks conferred by other common factors.

“The risk is relatively low when compared with conventional risk factors such as hypertension, high cholesterol, and smoking,” they said. ■

**After entering the study, the subjects were followed for up to 40 years. Statistics on those who died were obtained from the Icelandic government and hospital records.**