ALTERNATIVE MEDICINE
AN EVIDENCE-BASED APPROACH

Coenzyme Q10 for Migraine Prophylaxis

History and Rationale for Use

Coenzyme Q10 is a naturally occurring hydrophobic substance that is involved in electron transfer across the mitochondrial membrane from the NADH dehydrogenase complex and the succinate-Q reductase complex to cytochrome *c* (Cephalalgia 2002;22:137-41). As such, coenzyme Q10 is essential for cellular energy metabolism.

The coenzyme was first isolated in 1957 from bovine heart mitochondria by Frederick L. Crane, Ph.D., of the University of Wisconsin Enzyme Institute in Madison. A year later, its chemical structure was identified by researchers at Merck Laboratories. In 1978, British scientist Peter D. Mitchell, Ph.D., won the Nobel Prize in chemistry for his work demonstrating the role of coenzyme Q10 in mitochondrial energy transfer.

During the ensuing decades, researchers have investigated potential therapeutic applications for coenzyme Q10 in congestive heart failure, cancer, and neurologic disorders. It has also been studied extensively for use in mitochondrial cytopathies such as Kearns-Sayre syndrome.

The rationale for its use in migraine derives from findings on magnetic resonance spectroscopy and DNA analysis suggesting that mitochondrial dysfunction and inadequate energy production in the brain may be involved in the pathogenesis of migraine.

► The dietary supplement coenzyme Q10 is being studied for use in migraine prophylaxis, based on the hypothesis that mitochondrial dysfunction may be involved in the pathogenesis of the disorder.

► A small double-blind trial found significant benefits in reducing the number and frequency of headaches.

Clinical Studies

In an open-label study, 26 women and 6 men with International Headache Society–defined episodic migraine with or without aura were treated with 150 mg of coenzyme Q10 each day for 3 months. Patients began keeping a headache diary 1 month before starting treatment and continued throughout, recording duration of headache, severity, and associated symptoms such as nausea.

The study's primary outcome measure was the percentage of patients who achieved a greater than 50% reduction in the number of days with migraine. A total of 61.3% of patients met that outcome measure by 3 months, and 93.5% had at least a 25% reduction (Cephalalgia 2002;22:137-41).

During the month prior to initiation of treatment, the average number of days with headache was 7.34; this decreased to 2.95 days during the last 2 months of treatment, which is a statistically significant difference.

Attack frequency decreased significantly, from 4.85 during the month prior to treatment to 2.81 during the final 60 days of the study.

Headache intensity did not decrease, and there was no difference in response between patients with and without aura. No adverse events were seen in the study.

Coenzyme Q10 also was evaluated in a double-blind trial that included 42 patients with or without aura. All patients received placebo for 1 month; if they experienced a migraine during that time, they then were randomized to receive placebo or a liquid formulation of coenzyme Q10, 100 mg three times per day, for 3 months. This dose was chosen because it was used previously in a study of patients with Parkinson's disease (Neurology 1998;50:793-5). The primary outcome measure was change from baseline in attack frequency after the 3 months of treatment.

The number of attacks per month was 4.4 at baseline in both the treatment and placebo groups. This number decreased by 0.09 in the placebo group and by 1.19 in the active treatment group, a difference that is statistically significant. There also was a significant continuous decrease in attack frequency between months 1 and 4 in the treatment group (Neurology 2005;64:713-5).

Severity, duration, and acute medication use did not differ between the groups. One patient in the treatment group experienced a cutaneous allergic reaction, but no other adverse events were seen.

The investigators noted that there typically is a lag before significant improvement is seen with coenzyme Q10. "It is conceivable that a clinical effect due to improved mitochondrial function might build up more slowly than one mediated by receptor blockade (for example, β-blockers)," they said.

They also said that the placebo response they found, 14%, was low and reflected the exclusion of four patients who had no headaches during the month-long placebo phase of the study and who might have been placebo responders.

The study was sponsored by MSE Pharmaceuticals, Bad Homburg, Germany, the manufacturer of the liquid formulation of coenzyme Q10 used.

Real-World Experience

Dr. Alan M. Rapoport, founder and director of the New England Center for Headache, Stamford, Conn., has tried coenzyme Q10 in about 100 migraine patients.

"After the double-blind study was published, I began using it in many of my patients to see if it decreased or prevented migraines. But I tend to not be very scientific with over-the-counter medications, using two or three of them together and possibly in combination with a preventive medication," he said in an interview.

This, of course, makes it difficult to know precisely what is working if the patient does improve.

"I'm just glad they're better," he said. "My feeling is that it does work in some patients to reduce the frequency of headaches, and it doesn't seem to have any side effects," said Dr. Rapoport, who is also a clinical professor of neurology at Columbia University, New York.

His experience has suggested that coenzyme Q10 seems to be most useful in younger patients—those in their teens, 20s, and 30s—and in those who do not have daily, very severe headaches.

He would like to see a larger trial, also double blind and placebo controlled, but for now, he said, he is "cautiously optimistic."

—Nancy Walsh

Opiate Dependence May Or May Not Be Addiction

BY TIMOTHY F. KIRN
Sacramento Bureau

SCOTTSDALE, ARIZ. — Addiction specialists do see chronic pain patients who are so dependent on opiates that they require detoxification, but the question of whether such patients are "addicted" is difficult to determine clinically, two presenters said at a workshop at the annual meeting of the American Academy of Addiction Psychiatry.

One of the presenters said he prefers to detoxify these patients slowly and gently, using codeine. The other said he prefers a rapid method using naltrexone.

Many doctors have attempted to distinguish dependence from addiction, but the most clinically useful determination might be made by asking two questions, said Dr. Carl R. Sullivan of West Virginia University, Morgantown.

Does the patient misuse the medication or take it strictly based on the prescribed regimen? Is the patient honest about using the medication?

"I think that is a nice, easy way to look at it. If you see misuse and deceit, you are usually looking at addiction," said Dr. Sullivan, who treats many chronic pain patients.

Dr. Sullivan also said he thinks chronic pain patients who truly become addicts are rare, and most who do have had substance abuse issues in the past.

"That seems not to happen very much," he said. "Usually, if you are seeing addiction, and you think it is iatrogenic addiction, just look into the history a little bit."

Still, both Dr. Sullivan and the workshop's other presenter, Dr. A. K. Roy, said they have little use for opiates in chronic pain. Other treatments such as tricyclics and physical rehabilitation are better.

Opiates can be somewhat effective at first, but after some patients have taken them for years, things begin to backfire, causing hyperalgesia and impeding functionality, said Dr. Roy, an addiction specialist who practices in Metairie, La.

"I have a concept that opiate use is temporary, though I don't know exactly what the definition of temporary is," he said. "The liability for harm increases with the length of use."

Dr. Sullivan said he has heard very articulate discussions on the rationale for switching opiate treatments periodically to avoid dependence and diminished efficacy. "To me, most of the time it just looks like … you are just switching a green M&M for a red one. There's just not that much difference.

"I'm not an opiate guy; I think there are so many better ways to deal with chronic pain." he added.

More collaboration among pain medication and addiction treatment specialists might reduce the problems that some patients get into, but " some places I go they do everything but shoot guns at each other," he said.

Of the approaches used for withdrawing a dependent patient from an opiate, Dr. Sullivan said he prefers to use a time-tested regimen using codeine that has mostly fallen into disuse. "I know it is an old-fashioned drug," he said. "But it is very cheap and very effective, and it is a nice, short-acting agent."

The advantage of the short-acting agent is that one can more precisely tailor the administration of the drug to symptoms. It also avoids a problem he has seen when longer-acting agents such as buprenorphine or methadone are used. That is, the drug effects can take several days to wear off, so patients who were thought to be fully detoxified start having symptoms days after the drug is stopped.

For the first 24 hours, the patient is given 30 mg of codeine every half hour, as needed, to stave off withdrawal symptoms. They also are given supportive medications, including a benzodiazepine and nonopiates for pain, if needed.

At the end of 24 hours, the total amount of codeine given is counted as the baseline dosage. That amount is then divided for dosing every 3-4 hours. The codeine is gradually scaled back over 10-14 days, Dr. Sullivan said.

Dr. Roy said he often prefers a rapid detox using naltrexone. It lets the patient have symptoms (with supportive benzodiazepine treatment), and results in a complete detoxification in 3-4 days.

It is not the very rapid detoxification that is done with anesthesia, but it is almost as rapid. Instead, it is a newer approach that has been pioneered at Loma Linda University and the Mayo Clinic with good reported results. When the patients are finished, they are no longer dependent and have no cravings, said Dr. Roy.

"This is not something I would do outside of a locked unit," he said.

After detoxification, patients who are thought to have an addiction problem should then be referred to Alcoholics Anonymous, Narcotics Anonymous, or some other form of psychosocial support, Dr. Sullivan said.

The backbone of a new pain treatment program should be exercise and physical rehabilitation, because the fundamental goal needs to be improving functionality, Dr. Roy stressed. ■