Cost Separates Old Migraine Drugs From New

BY KERRI WACHTER
Senior Writer

WASHINGTON — Newer drugs aren't any better for migraine prophylaxis than are older treatments and might be worse choices for many patients when cost is a factor.

"There's no proof of increased efficacy with the newer drugs," said Dr. Gretchen E. Tietjen, chair of the department of neurology at the University of Toledo (Ohio).

Topiramate (Topamax), a newer drug, has been compared with several other drugs in head-to-head, double-blind studies, including divalproex sodium, nadolol, propranolol, and amitriptyline, she said at the annual meeting of the American College of Physicians. "In these head-to-head studies, there was similar efficacy."

Propranolol probably is the best-studied agent for migraine prevention and is Food and Drug Administration–approved for that indication. "There are—so far—no other drugs that have been shown to have better efficacy," Dr. Tietjen said. However, because many of her patients have depression or asthma, two relative contraindications to using the drug, she prescribes it infrequently.

Open-label studies have suggested that, in patients who did not respond to propranolol alone or topiramate alone, the combination might be more effective, but more research is needed.

It's also important to consider potential side effects, Dr. Tietjen said. While topiramate doses of up to 100 mg are well tolerated, it has several uncommon but potentially serious side effects, including paresthesias of the extremities, loss of appetite, depression, and confusion.

Cost also is a consideration. In her own informal survey of a local pharmacy, the monthly cost of the typical dosage of amitriptyline was $10, propranolol was $53, divalproex sodium was $128, and topiramate was $235.

"So there's really a difference [in cost], especially when you don't see much difference in efficacy," Dr. Tietjen said.

In a 2000 evidence-based review by the U.S. Headache Consortium—made up of several specialty societies—group I drugs were considered to have medium to high efficacy with good strength of evidence and mild to moderate side effects.

These included amitriptyline, propanolol, timolol, and divalproex sodium. All but amitriptyline are FDA approved for migraine.

Group II medications either had lower efficacy or limited strength of evidence. This group included several β-blockers (nadolol, metoprolol, atenolol), calcium-channel blockers (verapamil, nifedipine), an anticonvulsant (gabapentin), nonsteroidal anti-inflammatory drugs (naproxen sodium), magnesium, and vitamin B. (Topiramate had not been approved when this review was published.)

Med Overuse or Analgesic Rebound Headache

The International Headache Society's most recent criteria for medication overuse headache include a headache present for more than 15 days/month, regular use for at least 3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache, and a headache that has developed or markedly worsened during medication use (Cephalalgia 2004;24[suppl 1]:9-160).

Educating patients about the potential for developing medication overuse headaches and monitoring their medications are probably the most useful tools in treating these chronic headaches, Dr. Tietjen said.

Discontinuation of the use of abortive medications is the key to treatment. "For somebody you suspect of medication overuse headache … you want to stop the medication they're using. Whether you do it gradually or abruptly depends on the medication and depends on the patient," she said.

She also recommended starting the patient on a prophylactic medication. Several transition regimens have been suggested, though these have not been well studied. Dr. Tietjen often uses dihydroergotamine 0.5-1 mg every 8 hours for 2-3 days. This is a particularly good option for hospital inpatients who are stopping opioids and butalbital, she said.

Oral Contraceptives for Hormonal Migraines

Hormonal headaches include pure menstrual headaches and those related to the menstrual cycle. Pure menstrual migraines occur in a consistent relationship with menstruation and do not occur at other times of the month. It's estimated that about 15% of women with migraine have the pure menstrual variety. Menstruation-related migraines occur not only in a consistent relationship with menstruation but also at other times of the month. An estimated 60% of women migraineurs have this type.

"Studies have really strongly suggested that menstrual migraines are generally more severe, more intractable to therapy, [and] usually have more associated symptoms, like nausea and sensitivity to light and sound," Dr. Tietjen said.

In studies that have looked at low-dose (30-35 mcg ethinyl estradiol) oral contraceptives for the treatment of menstrual headaches, half to two-thirds of women reported no change, a quarter to a third reported migraine worsening, and only about 10% reported improvement.

Triptans appear to be effective for both menstrual and nonmenstrual headaches. Analgesics, such as naproxen sodium, also appear to be effective.

Several studies have looked at triptans for short-term prevention of predictable menstrual headaches. Naratriptan 1 mg or frovatriptan 2.5 mg administered twice daily for 6 days/month have been shown to be effective and well tolerated.

Both the World Health Organization and the American College of Obstetricians and Gynecologists have published consensus guidelines addressing migraine. Both recommend that women with migraine who are older than 35 years generally should not use oral contraceptives nor should women of any age with migraine with aura.

In general, Dr. Tietjen does not use oral contraceptives to treat menstrual migraines. If a migraine patient wants to use oral contraceptives, she recommends a low-dose monophasic regimen.

Dr. Tietjen reported that she has received research support from GlaxoSmithKline Inc. and NMT Medical Inc. ■

Methylnaltrexone Relieves Opioid-Induced Constipation

BY MARY ANN MOON
Contributing Writer

A single dose of methylnaltrexone relieved opioid-induced constipation three times more often than did placebo in a phase III clinical trial of 133 terminally ill patients, investigators have reported.

The treatment did not interfere with analgesia or cause opioid withdrawal, according to Dr. Jay Thomas of San Diego Hospice and the Institute for Palliative Medicine, San Diego, and his associates.

Most responders were able to defecate within 1 hour of the injection of methylnaltrexone.

DR. THOMAS

Since opioid-induced constipation is primarily mediated by peripheral opioid receptors, the researchers hypothesized that selective blockade of these receptors "might relieve constipation without compromising the centrally mediated effects of opioid analgesia or precipitating withdrawal." Methylnaltrexone, produced by *N*-methylation of the opioid antagonist naltrexone, has a limited ability to cross the blood-brain barrier and thus acts primarily in the periphery.

Dr. Thomas and his associates compared subcutaneous injections of methylnaltrexone with placebo in a double-blind trial at 27 U.S. and Canadian nursing homes, hospices, and palliative care centers.

The 133 patients (median age 71 years) were taking a median opioid dose of 100 mg of oral morphine equivalent and had constipation that failed to respond to a median of two classes of laxative therapy (N. Engl. J. Med. 2008;358:2332-43).

Patients were randomly assigned to receive injections of methylnaltrexone (62 subjects) or placebo (71 subjects) on alternate days for 2 weeks. The study was supported by Progenics Pharmaceuticals Inc.

Within 4 hours of receiving the first dose, 48% of subjects in the methylnaltrexone group defecated, compared with 15% in the placebo group. Over the course of the trial, the proportion of patients who defecated three or more times per week was significantly higher with methylnaltrexone (68%) than with placebo (45%).

In addition, the median time to defecation after the first dose was 6.3 hours with methylnaltrexone, compared with more than 48 hours in the placebo group. Most responders were able to defecate within 1 hour of the injection, and half were able to do so within 30 minutes—a significantly more predictable onset of action than is typically seen with standard laxative treatments, the investigators noted.

Moreover, "more patients in the methylnaltrexone group than in the placebo group had reductions in the difficulty of laxation and distress associated with constipation," Dr. Thomas and his associates said.

In a subjective assessment, the majority of patients given methylnaltrexone reported that their bowel status had improved with therapy, while the majority of those given placebo reported that their bowel status was unchanged.

At the conclusion of the double-blind phase of the trial, 89 patients opted to receive methylnaltrexone for up to 3 months in an open-label extension of the study. The drug's efficacy persisted throughout this phase of the study, the investigators said.

Mild or moderate abdominal pain and flatulence were the most common adverse events reported. The rates of both adverse events and treatment discontinuation were similarly low in both groups.

Approximately half of patients did not respond to the first dose of methylnaltrexone. It is possible that in at least some of these cases, constipation may have been a result of causes other than opioid use. These include "immobility, decreased oral intake, a low-fiber diet, metabolic and endocrine imbalances, neurologic disorders, concomitant drug side effects, inadequate toileting arrangements, sedation, depression, and advanced age," Dr. Thomas and his associates noted.

Progenics Pharmaceuticals is collaborating with Wyeth Pharmaceuticals in submitting to the Food and Drug Administration subcutaneous methylnaltrexone for treating opioid-induced constipation in patients receiving palliative care. Dr. Thomas disclosed that he has received consulting and lecture fees, and served on advisory boards for Wyeth Pharmaceuticals. ■

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