**Methylnaltrexone Relieve Opioid-Induced Constipation**

**BY MARY ANN MOON**

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.

Since opioid-induced constipation is primarily mediated by peripheral opioid receptors, the researchers hypothesized that the blockade of these receptors “might relieve constipation without compromising the centrally mediated effects of opioid analgesia or precipitating withdrawal,” said Dr. Gretchel 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 is also 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 include amitriptyline, propranolol, 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 or/and prevention 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 advises.

She also recommended starting the patient on a prophylactic medication. Several transition regimes 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 Constrictive Drugs 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. Most patients improve 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 Obstetrics 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.

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