Cautious Dosing Urged for Intrathecal Pain Drug

BY BETSY BATES
Los Angeles Bureau

PALM SPRINGS, CALIF. — Ziconotide is a welcome addition to alternatives for relieving pain via intrathecal infusion, but many questions remain about its dosing, side effects, and potential best use, pain specialists said at the annual meeting of the American Academy of Pain Medicine.

"There are a lot of nuances with this drug," said Samuel J. Hassenbusch III, M.D., professor of neurosurgery at the University of Texas, Houston.

"It's got to be on the market maybe 5 years before we can really say what its role is," he said.

The Food and Drug Administration approved the nonopioid, N-type calcium channel blocker in December for treating chronic, intractable pain via an implanted intrathecal pump, making it the only analgesic other than morphine approved for intrathecal use. (Baclofen, marketed as Lioresal, is approved for intrathecal use in the treatment of cerebral spasticity.)

In practice, ziconotide (Prialt) will probably be used alone or in combination with other drugs to treat intractable malignant and nonmalignant pain.

A synthetic equivalent of a peptide used by the *Conus magus* marine snail to numb its prey, ziconotide is said to be 1,000-fold more potent than morphine in blocking phase 2 pain responses.

A combined analysis of three controlled trials presented at the meeting found the mean Visual Analogue Scale of Pain Intensity (VASPI) scores of 402 patients with nonmalignant pain improved 23%, compared with an 8% improvement in patients receiving placebo from the initial dose to the end of titration. The difference between the groups was significant.

In 51 patients with malignant pain, VASPI scores improved by 37% with ziconotide treatment, compared with 9% for placebo.

Within the study conducted by Ronald Collins, M.D., in private practice in Hampton Cove, Ala., significant VASPI score improvement was found in patients with myelopathic pain (19% vs. 0.1%), neuropathic pain (29% vs. 9%), radiculopathic pain (44% vs. 4%), spinal pain (21% vs. 7%), and failed back surgery syndrome (22% vs. 7%).

A trend toward significance was seen for patients with bone pain, according to the study findings, which were presented in poster form.

Dizziness, nausea, headache, and confusion are commonly reported side effects of ziconotide. Serious adverse events have been reported, including neurologic problems (such as confusion and somnolence) and urinary retention. The incidence and severity of side effects are believed to be modifiable with careful dosing and titration.

Indeed, the ideal dosing of the powerful drug—specifically, the initial intrathecal dose and titration schedule—drew significant attention at the meeting.

Many early study patients received an initial dose of 0.4 mcg/hour, with upward dose adjustments at 12-hour intervals. However, a safety evaluation conducted after 48 patients had been enrolled in a phase III trial prompted investigators led by Peter S. Staats, M.D., to decrease the initial dose to 0.1 mcg/hr and schedule increases in titration at 24-hour intervals (JAMA 2004;291:63-70).

The FDA-approved package insert recommends initiation at a dose of no more than 0.1 mcg/hour (2.4 mcg/day), with dose increases at intervals of no more than 2-3 times per week.

Some specialists at the meeting cautioned that the dose in the package insert may still be too high and the titration schedule too fast.

"You really do have to go low and very slow," said Dr. Staats, chief of the division of pain medicine at Johns Hopkins University in Baltimore.

Aggressive dosing can trigger what Dr. Staats called a "fly by" effect; that is, the precipitation of side effects before pain relief sets in.

"The package insert says to change the dose every few days; I wouldn't even go there," said Dr. Staats, who consults for Elan Pharmaceuticals Inc., the maker of ziconotide, and receives research support from Medtronic Inc., maker of a pump used to infuse ziconotide.

An initial dose of 0.5 mcg/day with dose adjustments every other week was recommended by Elliot Krames, M.D., a private practitioner in San Francisco. Dr. Krames disclosed that he receives research support and is on an advisory/review panel for Elan. ■

Acute Neuropathic Pain Requires Treatment With Corticosteroids

BY SHERRY BOSCHERT
San Francisco Bureau

SAN DIEGO — Neuropathic pain can be acute instead of chronic, and treatments for the two differ, Scott M. Fishman, M.D., said at a psychopharmacology congress sponsored by the Neuroscience Education Institute.

"There seems to be a prevalent belief that neuropathic pain is only a disorder of chronic illness," said Dr. Fishman, chief of the pain medicine division and professor of anesthesiology and pain medicine at the University of California, Davis.

Few physicians appear to know that the proper treatment for acute neuropathic pain is corticosteroids, not the anticonvulsants, antiarrhythmics, or antidepressants used conventionally for chronic neuropathic pain, he added.

For a patient who comes out of the operating room with a positional neuropathy or patients with acute-onset neuropathy due to trauma or a cut nerve, treat with corticosteroids. "That acute neuropathic pain actually is a neuritis," and steroids will cure the pain in most cases.

Dexamethasone dosing for acute neuropathic pain ranges from 4-8 mg orally b.i.d. or t.i.d. to 10-20 mg by IV every 6 hours. Methylprednisolone dosing for acute neuropathic pain usually ranges from 16-32 mg orally b.i.d. or t.i.d. to 40-80 mg by IV every 6 hours, he said.

These regimens also have been used to treat metastatic bone pain or cancerous soft tissue infiltration. Cancer patients frequently develop neuropathic pain due to a tumor's compressing or infiltrating nerves or resulting from paraneoplastic syndromes. The neuropathic pain may be a side effect from surgery, chemotherapy, or radiotherapy. Immunocompromise from cancer also can cause neuropathic pain, as can malignancy-related infection, bleeding, or fracture.

"I've seen oncologists becoming much better at treating pain," Dr. Fishman said, adding that he's less likely today to see patients with cancer whose neuropathic pain was undertreated by oncologists, compared with a few years ago. ■

Neuropathic Pain Points Test

Think you know about neuropathic pain? Test yourself with this quiz provided by Dr. Fishman.

1. Neuropathic pain is distinguished from somatic pain by the fact that:
   a. It's never acute.
   b. It always represents a dysfunction within the nervous system.
   c. It always has a component of "burning."
   d. It's not responsive to opioids.
2. Pain associated with nonpainful stimuli is termed:
   a. Hyperalgesia.
   b. Causalgia.
   c. Hyperpathia.
   d. Allodynia.
3. Most conventionally used medications for neuropathic pain are:
   a. Anticonvulsants.
   b. Antidepressants.
   c. Benzodiazepines.
   d Antiarrhythmics.
   e. All of the above.
4. First-line treatment for acute-onset neuropathic pain (within the first week of onset) is usually:
   a. Lidocaine.
   b. Neurontin.
   c. Ibuprofen.
   d. Corticosteroids.
   e. Amitriptyline.

Answers: 1. b; 2. d; 3. e; 4. d.

Tender Point Criteria for Fibromyalgia Called Flawed

BY KERRI WACHTER
Senior Writer

DESTIN, FLA. — The tender point criteria commonly used to diagnose fibromyalgia are not useful and in fact may even explain why the disease appears to disproportionately affect women, Daniel Clauw, M.D., said at a rheumatology meeting sponsored by Virginia Commonwealth University.

According to the American College of Rheumatology's 1990 classification criteria, patients must have both widespread pain and tenderness in 11 of 18 tender points in order to be diagnosed with fibromyalgia.

Yet "tender points merely represent areas of the body where everyone is more tender," explained Dr. Clauw, the executive director of the Chronic Pain and Fatigue Research Center at the University of Michigan in Ann Arbor.

Fibromyalgia patients and healthy individuals were found to have different thresholds of pain in those tender points. These two groups also had different thresholds of pain in areas not thought to be tender—the forehead and fingernails, for example—as at the recognized tender points. In addition, the cutoff of 11 out of 18 tender points is arbitrary. "We know that tenderness varies a great deal from day to day and week to week, especially in women," he said.

In clinical practice, many physicians are realizing the arbitrary nature of the diagnostic criteria.

The diminished role of tender points represents a shift in the way that they view the disorder. In the past, the disorder was considered a discrete illness with pain and focal areas of tenderness. In more recent years, fibromyalgia has been appreciated as part of a larger continuum, with many somatic symptoms and diffuse tenderness all over the body——not just at tender points.

Tender points are "not even a good way to measure tenderness," as study findings suggest that the number of tender points correlates better with a patient's general stress than with pain, Dr. Clauw pointed out.

Women are 10 times more likely to have achy and tender points, so the higher incidence of fibromyalgia among them may be attributable to a selection bias created by the tender point criteria, he continued.

Men who have chronic widespread pain but not many tender points in many cases are given diagnoses other than fibromyalgia, "when in fact they probably have the exact same problem as women, who have a lot of tender points and meet other criteria for fibromyalgia." ■