Propoxyphene Nixed for Mild to Moderate Pain

BY ELIZABETH MECHCATIE

GAITHERSBURG, MD. — If the Food and Drug Administration agrees with an advisory panel's narrow recommendation to take Darvon and other products that contain propoxyphene off the market, the void may not make much difference to rheumatologists, who appear to be among the lowest prescribers of these products.

At a joint meeting of the FDA's Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee last month, the panelists voted 14-12 that the risk-benefit profile on these products did not support their continued marketing for the treatment of patients with mild to moderate pain. The majority of panelists agreed that there was "marginal" or "modest" evidence at best indicating that propoxyphene, an opioid analgesic, was effective as monotherapy, or that propoxyphene plus acetaminophen was more effective than acetaminophen alone. Several panel members said they did not believe there was any evidence of efficacy for propoxyphene, either alone or in combination with acetaminophen.

The FDA held the meeting to review the safety of these products, first approved in 1957, in response to a Citizen's Petition filed by Public Citizen's Health Research Group in February 2006, calling for a phased withdrawal of all propoxyphene-containing products from the market.

Darvon and Darvocet (propoxyphene plus acetaminophen) are the branded versions of propoxyphene, which is a schedule IV drug. There are multiple generic formulations available. In the petition, the group maintained that the risks of these products outweigh their benefits, citing insufficient evidence that propoxyphene alone effectively alleviates pain and offers little, if any, added benefit when combined with acetaminophen. The petition states that propoxyphene and its main metabolite are cardiotoxic, and that it has a narrow therapeutic index and was associated with 2,110 reports of accidental deaths in the United States from 1981 through 1999.

Based on data from U.S. outpatient retail pharmacies presented by the FDA, rheumatologists wrote about 525,000 prescriptions for propoxyphene-acetaminophen in 2007 (2.4% of the total).

Propoxyphene "just simply is not a very good drug," and has become less popular over the past few years, said Dr. Roy Altman, professor of rheumatology and immunology at the University of California, Los Angeles.

In an interview, Dr. Altman said that he has not used propoxyphene in more than a decade, "mostly because it's such a weak analgesic." Moreover, because of the side effects associated with propoxyphene, a more potent analgesic effect would be needed to justify its use, he added. In fact, when he was at the University of Miami several years ago, these products were contraindicated in elderly patients because of the multiple central nervous system side effects—such as depression, depersonalization, drowsiness, and unsteadiness—in this population, so the outcome of the FDA panel meeting does not surprise him, nor would it surprise others in the geriatric community, he said, adding that the main reason these products remain in use now is because of the critical need for more analgesic options.

At the FDA meeting, Dr. Sidney Wolfe, director of Public Citizen's Health Research Group, presented data from DAWN (Drug Abuse Warning Network), which received reports of 446 propoxyphene-related deaths from U.S. emergency departments in 2006, and 503 such reports in 2007. (DAWN, which collects data on drugs associated with emergency department visits or deaths, covers only a fraction of the U.S. population; during this time, the number of jurisdictions reporting to DAWN increased.)

Among the other data he presented were reports made to the medical examiner in Florida in 2007 (not included in the DAWN data), in which 314 deaths were related to propoxyphene; in 25% of the cases, the medical examiner concluded that the drug was the cause of death.

Continued on following page

Continued from previous page

The panelists agreed there was no evidence that at therapeutic levels, propoxyphene has been associated with an increased risk for cardiotoxicity, largely because of an insufficient amount of data. However, the panel agreed that if propoxyphene remained on the market, the cardiotoxicity potential should be studied further—in studies that evaluate QT and EKG changes as well as in observational studies, including in elderly populations. The panel also recommended that the label should be changed to discourage chronic use, which has not been studied. The panel cited concerns over the lack of data on safety and efficacy in chronic use and use in the elderly.

Panelists were split on whether the lack of conclusive evidence on efficacy—most of which was from single-dose studies conducted in the 1970s—or on safety justified keeping these products available in the U.S. Sean Hennessy, Pharm.D., of the University of Pennsylvania, Philadelphia, said he voted no because in the "absence of benefit, no risk is acceptable."

At the meeting, the FDA presented efficacy data from seven acute-pain, single-dose trials that compared propoxyphene alone with acetaminophen alone, with propoxyphene plus acetaminophen, and with placebo, as well as a review of the medical literature through December 2008. Based on a review of these data, the agency concluded that propoxyphene had a weak analgesic effect in some of the acute-pain trials, and that the contribution of propoxyphene to the analgesic effects of acetaminophen was "variable across acute pain trials," said Dr. Jin Chen, a medical officer in the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products. There were no data on chronic pain submitted to the FDA, and there is insufficient information in the literature to make any conclusions about its analgesic effects with chronic use, he said.

Other data presented by FDA reviewers indicated that there are possible drug-drug interactions with CYP3A4 inhibitors, and that the pharmacokinetics of the drug are altered with hepatic and renal impairment and in the elderly. Animal data indicate that propoxyphene may affect cardiac conduction and toxicity, possibly through its effects on sodium and potassium channels. There also have been case reports of cardiac effects in humans, such as prolonged PR interval and QRS widening associated with drug concentrations that exceed the clinical therapeutic level.

But it is unclear whether the cardiac effects seen in nonclinical studies would be a risk in people who are taking therapeutic doses of propoxyphene-containing drugs, according to the FDA reviewers.

Of the 65 unduplicated adverse event reports associated with propoxyphene-containing products that were submitted to the FDA's Adverse Event Reporting System between 2006 and 2007, 17% (11 cases) were cardiac-related events—including 4 cases of bradycardia, 2 cases of cardiorespiratory arrest, and 2 cases of tachycardia—but 82% of the cardiac cases were confounded by other factors that made it difficult to attribute the report to the drug, according to the FDA. The other cases included accidental multiple drug overdoses in 14% (nine cases) and 18% that were psychiatry related, such as hallucinations or changes in mental status; 40% of the reports overall were in the elderly, and 18% overall were fatal accidental overdoses.

Panelist Dr. William Hiatt, professor of medicine at the University of Colorado, Denver, said that based on these efficacy data, it appears that acetaminophen and propoxyphene alone are more effective than placebo, but that the combination did not clearly exceed pain relief with either component alone in studies of a single dose in people with acute postoperative or postpartum pain.

He also cited preclinical evidence of possible cardiotoxicity, particularly its effect on sodium channels, and recommended that if the products remained on the market, clinical studies should be conducted to evaluate QT changes associated with the drug, and whether the drug increases the background risk of cardiac events in an elderly population.

The FDA usually follows the recommendations of its advisory panels, which are not binding. ■

FDA to Subject Some Opioids to Risk Control

BY ELIZABETH MECHCATIE

A risk-management plan will be required to address the ongoing problems of misuse, abuse, inappropriate prescribing, and accidental overdoses of certain opioid medications, the Food and Drug Administration announced.

The agency said that letters had been sent to 16 manufacturers of 24 opioid products stating that a Risk Evaluation and Mitigation Strategy (REMS)—which is intended to address serious risks, including fatalities associated with the improper use of these drugs—will be required for their products. The FDA has addressed this problem in the past, with efforts that have included adding warnings to the product labels, direct communications to prescribers, and working with other federal agencies.

"Despite these efforts, the rates of misuse and abuse and of accidental overdosages of opiates have risen over the past decade," Dr. John Jenkins, director of the Office of New Drugs in the FDA's Center for Drug Evaluation and Research, said during a briefing. In 2007, 21 million prescriptions for these 24 products were dispensed to 3.7 million individual patients and were associated with "hundreds" of reports of deaths, he said.

Under legislation passed in 2007, the FDA can require a company to provide a REMS if the agency determines that such a plan is needed to ensure that the benefits of a drug outweigh its risks. The REMS may include a medication guide, provided to patients with each prescription filled; a patient package insert; and education of prescribers.

The opioid drugs on the FDA's list include fentanyl (Duragesic extended-release transdermal system), methadone (Dolophine tablets), oxycodone (OxyContin extended-release tablets), oxymorphone (Opana extended-release tablets), and several extended-release oral morphine products. These products are responsible for the greatest proportion of serious adverse events and deaths, according to Dr. Jenkins.

He emphasized that patients and physicians should follow the directions on the label. Although these products are intended only for people who experience moderate to severe pain, are opioid tolerant, and require around-the-clock pain relief, the FDA receives reports of adverse events in opioid-intolerant people who are inappropriately prescribed one of these products for conditions like a sprained ankle, he noted.

In an interview, Dr. Roy Altman, professor of rheumatology at the University of California, Los Angeles, noted that the majority of physicians tend not to use narcotics for chronic noncancer pain when indicated, because of legal ramifications, potential addiction risks, and other issues.

The agency will be holding several meetings to discuss the REMS plan for these products, and to obtain input from interested parties, including physicians, industry representatives, members of the pain- and addiction-treatment communities, and patient advocacy groups, beginning with a meeting on March 3 for manufacturers. ■

The full list of the drugs, along with the FDA's statement, is available at www.fda.gov/cder/drug/infopage/opioids/default.htm. Serious or unexpected adverse events can be reported to MedWatch at www.fda.gov/MedWatch/report.htm.

Tai Chi Reduced WOMAC Pain Scores in Knee Osteoarthritis

BY SHERRY BOSCHERT

SAN FRANCISCO — The gentle martial art tai chi significantly lessened pain and improved physical function in a randomized, controlled trial in 40 patients with knee osteoarthritis.

Participants were randomly selected to attend hour-long classes twice a week for 12 weeks to learn and practice 10 modified forms of tai chi or to receive wellness education and engage in stretching in a control group. Patient characteristics were similar between groups, with baseline pain scores of 209 in the tai chi group and 220 in the control group on the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index, which was the main outcome measure.

After 12 weeks, scores decreased by 157 points in the tai chi group and 39 points in the control group, a significant difference ($P = .004$), Dr. Chenchen Wang reported at the annual meeting of the American College of Rheumatology.

Although the WOMAC pain scores remained significantly different between groups at 24 weeks, they did not at 48 weeks, as some patients stopped tai chi once the 12-week intervention had ended. Those who continued, however, showed significant improvements in pain and secondary measures of function, compared with controls, said Dr. Wang of Tufts University, Boston.

The tai chi group also showed significant improvements, compared with the control group, in the WOMAC physical function score; the patient and physician global assessment scores (on visual analog scales); a timed chair-stand test; an assessment of knee proprioception; and in depression scores on the Center for Epidemiologic Studies–Depression scale.

Sessions in the current trial included a warm-up, review of technique, and practice of the meditative movements, some of which were modified for the osteoarthritic cohort by incorporating chairs or other accommodations.

Patients were obese, with a baseline body mass index of 30 kg/m^2 in both groups. The mean age was 63 years in the tai chi group and 68 years in the control group. Both groups were predominantly white and female. Patients had had knee osteoarthritis for a mean of 10 years.

All patients completed the 12-week trial, with 85% attendance in the tai chi sessions and 89% in the control sessions.

The Arthritis Foundation promotes a tai chi practice based on the Sun style that differs in some respects from the Yang style used in the study, she noted. ■

Tai chi uses an integrated mind-body approach to enhance muscle function, balance, and flexibility.