Drug Monitor

New Drug for Menorrhagia

About three million women in the United States report experiencing menstrual bleeding so heavy it can disrupt daily life, even be incapacitating. Menorrhagia—defined as regular intervals of menstruation with excessive volume that may exceed 80 ml of blood loss per cycle—affects approximately 10% of women of reproductive age. In most cases, there is no underlying health condition. In November, the FDA approved the first nonhormonal, oral therapeutic agent indicated specifically for this condition: Lysteda (tranexamic acid), marketed by Xanodyne Pharmaceuticals, Inc. (Newport, KY).

Tranexamic acid was first approved in 1986 as Cyklokapron (Pfizer, New York, NY), an injection to reduce or prevent bleeding during tooth extraction in patients with hemophilia. It works by stabilizing a protein that helps blood clot. An abnormally high rate of clot breakdown in the uterus has been associated with menorrhagia. Lysteda works to reduce this activity.

Women who received Lysteda in clinical trials had a statistically significant reduction in menstrual blood loss compared with those taking placebo. The most common adverse reactions included headache; sinus and nasal symptoms; back, abdominal, muscle and joint pain; muscle cramps; anemia; and fatigue. Women taking hormonal contraceptives should take Lysteda only if there is a strong medical need because it can exacerbate the increased risk of blood clots, stroke, or heart attack associated with such contraceptives.

Sources: FDA press release. November 13, 2009.

Xanodyne Pharmaceuticals, Inc. press release. November 16, 2009.

Understanding the Risks of Neuropathic Pain After Chemotherapy

Neuropathic pain (NP), which occurs in nearly 40% of patients with cancer pain, can be particularly severe and difficult to control. It's been suggested that, for some patients, chemotherapy-induced peripheral neuropathy (CIPN) may precipitate development of NP, but this association has not been well studied. Researchers from the University of Texas M.D. Anderson Cancer Center, Houston, TX, therefore, set out to learn more about the link between CIPN and NP in patients previously treated for breast cancer with the chemotherapeutic agent paclitaxel.

They conducted a survey of breast cancer survivors who participated in clinical trials of paclitaxel between 1994 and 2001 at M.D. Anderson Cancer Center. Of the 430 patients who were alive and had current contact information on file as of July 2007, 240 consented to participate in the study. The presence of CIPN during treatment was defined as a sensory neuropathy grade of 2 or higher on the National Cancer Institute Common Toxicity Criteria. The questionnaire, which was mailed to participants, asked about NP diagnosis, comorbid conditions, current treatment for pain (including questions about number of provider visits and use of over-the-counter and prescription medications), and cancer recurrence. Participants' self-reports on the survey were not verified.

Of the 240 respondents, 64% had experienced CIPN during their clinical trial, and 27% of these had subsequently been diagnosed with NP. Patients with CIPN were shown to be three times more likely to report NP under both the univariate and multivariate logistic regression models. Age, hypertension, diabetes, rheumatoid arthritis, and osteoarthritis also were significantly associated with NP under the univariate model, but only diabetes and osteoarthritis remained significant predictors of NP after multivariate analysis.

Many of the participants had pain problems that required medical care. As many as 25% of the total sample reported being under the care of a health professional for pain and had a mean of two provider visits for pain in the past year. Twenty-seven percent of the group (50% of NP patients and 19% of non-NP patients) reported taking prescription medication for pain, and 46.5% (62.5% of NP patients and 45% of non-NP patients) reported taking over-the-counter medication.

The cumulative dose of paclitaxel was strongly associated with CIPN—and remained so after multivariate analysis. Because paclitaxel's antitumor activity promotes the formation of abnormal bundles of microtubules within the cytoplasm, a consequence of its use is impairment in neuronal development and function. At M.D. Anderson Cancer Center, the researchers say, patients taking weekly paclitaxel therapy are monitored every four to six weeks for symptoms of worsening CIPN. "If the intent of paclitaxel therapy is cure," they add, "the physician and patient should discuss the risks and befits of continuing the current dose of paclitaxel in the setting of worsening neuropathy."

Source: *J Pain.* 2009;10(11):1146–1150. doi:10.1016/j.jpain.2009.04.006.

Questioning the Long-Term Benefit of Aspirin in Patients with Diabetes

Contrary to current guidelines, aspirin may not be useful in reducing cardiovascular risks in people with diabetes. Researchers from Consorzio Mario Negri Sud, S. Maria Imbaro, Italy and University of Sydney and Cochrane Renal Group, both in Sydney, Australia conducted a meta-analysis of trials using Medline, the Cochrane central register of controlled trials, and reference lists of retrieved articles. Based on this analysis, they concluded that aspirin may be of less benefit in people with diabetes than in other high risk populations.

The meta-analysis included prospective, randomized, controlled, open or blinded trials involving participants with diabetes who were allocated to aspirin therapy or a control group (placebo or no treatment) for the primary prevention of cardiovascular disease. It also included data on diabetic subgroups from larger studies of the general population. Two authors independently reviewed the literature search results and identified 157 potentially eligible trials. Of these, six (with 10,117 participants) were eligible for inclusion; the trials were published between 1989 and 2008 and were carried out in the United States, Italy, Japan, and Scotland.

The researchers found no significant reduction in the risk of major cardiovascular events, myocardial infarction (MI), stroke, death from cardiovascular causes, or all-cause mortality with aspirin treatment compared with placebo or no treatment. Subgroup analysis did confirm that aspirin significantly reduced MI risk in men by 43%, but aspirin did not appear to have an effect in women. When analyzing stroke results, the risk of stroke was significantly reduced in trials in which a daily aspirin dose of 100 mg or less was used. The risk of stroke also was significantly lower with aspirin than with placebo or no treatment when the trial duration was more than five years. When looking at adverse effects, the researchers found no significant increase in the risk of any bleeding, gastrointestinal bleeding, gastrointestinal symptoms, or cancer with aspirin therapy compared with placebo or no treatment.

Taken together, the researchers say, "these data indicate either low efficacy of aspirin in people with diabetes or insufficient evidence." They suggest that factors specific to diabetes—such as hyperglycemia, hyperinsulinemia, increased oxidative stress, and advanced glycosylation—may play a role in atherothrombosis. If this is true, the researchers say, "people with diabetes may not simply be a subgroup of patients at high risk for cardiovascular events but a separate entity, with additional factors playing an important part in determining the efficacy of treatment." Therefore, they recommend case-by-case decision making, carefully evaluating the trade-offs between benefits and risks. The expected benefits might not outweigh the risk of major bleeding, particularly among patients with low cardiovascular risks (less than 20% over 10 years) or those aged 70 years or older who are at high risk of bleeding.

Theirs is the first and largest meta-analysis of aspirin trials in diabetic populations and represents a comprehensive review, based on a predefined study protocol and rigid inclusion criteria. The main weakness of their study, however, is the lack of high quality randomized trials. In addition, the researchers were concerned with the methodologic quality of the trials since many were relatively outdated and hardly applicable in current practice. The researchers also could not include some data from trials in which separate results for the diabetic subgroup were not available.

They note two ongoing trials—A Study of Cardiovascular Events in Diabetes (ASCEND) and the Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D)—that will enroll more than 15,000 participants and should help clarify the role of aspirin in the prevention of cardiovascular disease in people with diabetes. They also are hopeful that these trials will provide a better understanding of the pathophysiologic mechanisms involved in the response of platelets to aspirin and help identify those who are more likely to benefit from aspirin therapy. Until these results are known, the researchers conclude that they "cannot recommend using aspirin in the primary prevention of cardiovascular events in all patients with diabetes."

Source: *BMJ*. 2009;339:b4531. doi:10.1136/bmj.b4531.

Help for Postherpetic Neuralgia

About 10% to 15% of patients who have shingles experience postherpetic neuralgia (PHN)—chronic, often excruciating neuropathic pain that can persist for months or even years. Those affected by PHN may get some relief from a newly FDA-approved product: Qutenza (NeurogesX, San Francisco, CA), a capsaicin 8% patch. Qutenza is the first prescription drug containing pure, concentrated, synthetic capsaicin to be FDA approved for PHN.

Approval was based on results of two phase 3 clinical trials involving 818 patients with PHN. In these trials, patients received a single one-hour application of either the high concentration capsaicin 8% patch or a control

patch with a lower capsaicin concentration. At eight weeks, patients who received the high concentration patch had significantly greater reductions in pain scores from baseline compared with those who received the control patch. As a locally acting, nonopioid medication, Qutenza is unlikely to cause drowsiness or to interact with other drugs.

According to the manufacturer, one application of Qutenza can reduce PHN pain for up to 12 weeks. Up to four patches may be used during each one-hour session and can be cut to conform to the shape and size of the affected area. Since placement of the patch can be quite painful, necessitating use of a topical anesthetic, it must be applied by a health care professional. Patients who experience acute pain during or after the patch session may be treated with application of cold packs or analgesic medication. Qutenza treatment may be repeated every three or more months as needed for the return of pain.

In clinical trials, the most common adverse reactions to Qutenza were transient site redness, pain, itching, and papules. Serious adverse reactions included application site pain and blood pressure increases—which, on average, were less than 10 mm Hg. Since blood pressure changes occurred during or shortly after drug exposure and lasted for an average of two hours after patch removal, it is recommended that patients be monitored for at least one hour after the patch is applied. Among patients treated with Qutenza in clinical trials, approximately 1% discontinued treatment due to an adverse event.

Sources: FDA press release. November 17, 2009.

NeurogesX, Inc. press release. November 16, 2009.