Drug Monitor

Low Molecular Weight Heparin for Pulmonary Embolism

When compared to its unfractionated relative, low molecular weight heparin (LMWH) is more cost-effective, more convenient, and less likely to cause allergic reactions or thrombocytopenia. And since it's proven to be at least as safe and effective as unfractionated heparin in treating deep venous thrombosis (DVT), its use as a first-line therapy for this condition has become common. But when it comes to treating acute pulmonary embolism (PE), the role of LMWH is less clear.

Researchers from King's College Hospital, London, United Kingdom and University of Western Australia, Perth, Australia performed a meta-analysis of 12 randomized, controlled trials comparing unfractionated heparin and LMWH in 2,051 patients with nonmassive symptomatic PE or asymptomatic PE in the context of symptomatic DVT. Assessed outcomes included recurrent symptomatic venous thromboembolism (PE or DVT) at the end of treatment and at three-month follow-up, mortality from any cause, and major and minor bleeding events.

They found that the drugs were approximately equal. LMWH was associated with nonsignificantly fewer recurrent symptomatic events compared with unfractionated heparin, both at the end of treatment (1.4% versus 2.4%) and at three-month follow-up (3.3% versus 4.3%). The incidence of major bleeding was also nonsignificantly lower with LMWH (1.4%) than with unfractionated heparin (2.3%).

The researchers say the results aren't surprising given that DVT and PE increasingly are believed to be different faces of the same underlying disease process, which suggests that they should respond similarly to the same treatment. Although the relatively small number of patients and outcomes in this meta-analysis detracted from its statistical power, the researchers assert that their findings stood up to sensitivity analyses, tests for heterogeneity of outcomes, and comparison with individual trials and with other meta-analyses involving venous thromboembolism.

Source: *Ann Intern Med*. 2004; 140:175–183.

Severe Dermatologic Toxicity with Paclitaxel

Use of the antineoplastic agent paclitaxel is on the rise, and as clinical experience with the drug accumulates, previously unrecognized adverse effect patterns may emerge. Clinicians from the University of Illinois at Chicago caution that one type of reaction to look out for is delayed, severe, generalized dermatologic toxicity.

They report on the case of a 53-year-old man with stage III squamous cell cancer of the tongue who developed erythematous patches during his second cycle of induction chemotherapy with paclitaxel and carboplatin. On day 15 of this cycle, he presented for his last paclitaxel infusion with erythema at the infusion site (the left forearm) and reports of myalgia and dysphagia. When they found he was dehydrated, his providers admitted him and subsequently discovered diffuse erythema on the right forearm and both thighs. He was treated empirically with broad spectrum antibiotics and prednisone, but bacterial cultures were negative and prednisone was ineffective.

One week later, the left arm wound had become purpuric and formed a large blister (14 x 4 cm). The blister desquamated, leaving a necrotic stage IV ulcer. Similar blisters developed on the other arm and thighs but didn't desquamate. The ulcer was debrided and wound vacuum-assisted closure therapy was applied.

Although paclitaxel was withheld when the patient subsequently began his first cycle of chemoradiotherapy, the lesions on his right arm and thighs worsened temporarily with this new treatment, indicating a "recall effect" that's been described previously in medical literature. After a few days, however, these lesions—along with the wound on the left arm—began to heal. The patient received his next four cycles of chemoradiotherapy without incident.

The reporting clinicians say that dermatologic reactions to paclitaxel usually

are mild and related to extravasation of the drug during injection. Their patient, however, showed no signs of extravasation. Because of the patient's delayed, generalized symptoms, the clinicians believe he had an immunologically mediated hypersensitivity reaction—either to paclitaxel itself or to one of the formulation's solubilizing agents. This occurred despite premedication with dexamethasone before each dose to prevent such a reaction.

A new formulation of paclitaxel under investigation has demonstrated reduced potential for hypersensitivity in animal models. Until such formulations are available, however, the authors call for vigilance in reporting further cases of paclitaxel-associated severe dermatologic reactions so that these reactions can be understood and prevented.

Source: *Ann Pharmacother*. 2004;38:238–241.

Alfacalcidol Needs Calcium to Fight Falls

According to Swiss researchers from the Geriatric University Clinic, Basel and Universitätsklinik Balgrist, Zurich, alfacalcidol can bring a little stability back into the lives of older people at risk for falling. The catch? They say that this prodrug of the D-hormone calcitriol needs a minimum daily calcium intake of 512 mg to be effective.

The researchers conducted a 36-week, randomized, placebo-controlled trial in 378 community dwelling men and women aged 70 and older to determine whether alfacalcidol 1 µg/day would help prevent falls. The participants were mobile and independent. None were taking more than 500 mg/day of supplementary calcium or more than 200 mg/day of supplementary vitamin D.

Although fewer participants in the alfacalcidol group reported falling compared with those in the placebo group (odds ratio, 0.69), this difference was nonsignificant. When the researchers analyzed participants according to level of calcium intake, however, they found that those who were getting at least 512 mg of calcium daily were significantly less likely to fall if they took alfacalcidol (odds ratio, 0.45). For those who got less calcium, alfacalcidol treatment had no impact on falls. The drug's effects were the same for both men and women.

Regardless of calcium intake, alfacalcidol significantly reduced serum intact parathormone levels from baseline—whereas these levels rose in placebo patients. The researchers point out that serum intact parathormone levels have been associated inversely with both muscle strength and endurance and that parathormone may be an independent risk factor for reduced muscle strength and falls.

The most common adverse effects noted in both the alfacalcidol and placebo groups were itching and skin eruption. No serious adverse events were attributed to alfacalcidol. A few patients experienced transient hypercalcemia (one in the placebo group and five in the drug group), and two others (both taking alfacalcidol) had more prolonged but asymptomatic elevations in calcium levels.

Because most of their patients had normal baseline serum levels of vitamin D and D-hormone, the researchers don't attribute the reduction in falls to a correction in age-related clinical vitamin D deficiency. Instead, they suggest that the combination of alfacalcidol and at least 512 mg of calcium per day acts as a "pharmacologic treatment" to build up muscle power or neuromuscular coordination.

Source: *J Am Geriatr Soc*. 2004;52:230–236.

Gabapentin for Hot Flashes

When hormone replacement therapy isn't an option for your patient with hot flashes, you may want to consider the anticonvulsant gabapentin. A physician from the University of Buffalo School of Medicine, Buffalo, NY reports on a patient who was experiencing severe hot flashes 20 to 30 times a day after hysterectomy and bilateral salpingo-oophorectomy at age 32. The hot flashes were accompanied by profuse sweating and, occasionally, lightheadedness and palpitations. They also were disrupting her nighttime sleep.

Conjugated estrogen had no effect, despite a daily dose increased to 2.5 mg. Over the next 16 years, she tried a wide variety of estrogen preparations, all of which failed. Various selective serotonin reuptake inhibitors (SSRIs) also proved unsatisfactory for controlling her symptoms.

Based on anecdotal reports, her physician prescribed gabapentin 300 mg three times daily and discontinued her estradiol patch. Within three weeks, the incidence of hot flashes reduced dramatically—to only a few a day. When, a month later, they began to increase in frequency, the physician raised the gabapentin dosage to four times daily, with good effect. The patient's sleep also improved. She experienced no adverse effects.

The author notes that gabapentin, estrogen, and SSRIs all may work on different cellular sources of hot flashes. Gabapentin has been approved as a

treatment for neuropathic pain and as an anticonvulsant and has been shown to reduce chemotherapy-induced nausea—all of which, he points out, are linked to tachykinin-mediated activity.

Source: *J Pain Symptom Manage.* 2004;27:274–276.

How Long Can Galantamine Delay AD Progression?

While cholinesterase inhibitors have demonstrated efficacy in slowing the cognitive decline associated with Alzheimer's disease (AD) over three to six months, little has been confirmed about their potential as long-term therapy. For this reason, findings from an extended trial of the acetylcholinesterase inhibitor galantamine are welcome news: The researchers (from the University of Washington School of Medicine and the VA Puget Sound Health Care System, both in Seattle, WA and Johnson & Johnson Pharmaceuticals and Janssen Pharmaceutica Products, both in Titusville, NJ) say their results indicate the drug's cognitive benefits may be sustained for at least three years.

The researchers enrolled 194 patients (mean age, 76 years) with mild to moderate AD who had received 12 months of galantamine treatment during two earlier double-blind, placebo-controlled trials, and followed them as they continued to receive the drug on an open-label basis for an additional 24 months. They compared the rate of cognitive decline in these patients with that of a historical control group (who received placebo for 12 months in an earlier trial) and with that mathematically predicted to occur over three years in untreated patients. Both control groups were matched for baseline cognitive function. The 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog/11) was used to measure cognitive decline.

At 12 months of therapy, mean ADAS-cog/11 scores were at pretreatment baseline levels in the galantamine group, whereas they had increased a mean of 6.3 points in the historical control group. After three years, the 119 galantamine patients who completed the study had gained a mean of only 10.2 points on this scale, compared with the 20.5- to 22-point gain predicted for untreated patients. In fact, 80% of the galantamine patients had gained 20 points or fewer by study's end—and almost 20% were maintaining cognitive function at or above baseline levels. Overall, the researchers say, galantamine treatment delayed cognitive decline approximately 18 months compared to no treatment.

The drug was well tolerated. Most adverse events were transient, mild to moderate in intensity, and comparable to those of earlier trials. Nausea and vomiting, observed commonly in the previous short-term studies, were rare. The researchers note that the most frequent adverse events—psychiatric disorders such as agitation, insomnia, and depression—are characteristic of an elderly AD population followed for three years.

Source: *Arch Neurol.* 2004;61: 252–256.

FDA Approves Injectable Olanzapine

The standard treatment for acute agitation in schizophrenia or bipolar mania is an injectable antipsychotic. But until recently, only the older, "typical" antipsychotics were available for injection. On March 29, however, the FDA approved an injectable formulation of the atypical antipsychotic olanzapine—which is marketed as Zyprexa Intramuscular by Eli Lilly and Company (Indianapolis, IN).

This approval was based on findings from three randomized, double-blind, placebo-controlled trials, in which injectable olanzapine performed significantly better than placebo. This atypical antipsychotic also caused significantly fewer of such adverse effects as dystonia, tremor, muscle spasm, indigestion, blurred vision, and nausea and vomiting when compared with two typical antipsychotics (haloperidol and lorazepam) that are used commonly for acute agitation.

Previously, many clinicians treated acute agitation with an injectable typical antipsychotic and then switched the patient to an oral atypical agent when the condition had stabilized. With the approval of injectable olanzapine, patients now can take one atypical antipsychotic during both phases of treatment.

Clinicians should be aware, however, that the drug has some safety concerns. In addition to various non-life threatening adverse effects (such as weight gain, drowsiness, dizziness, back pain, amnesia, and muscle weakness), there have been rare instances of hypotension, bradycardia, and sinus pause. And recently, Eli Lilly and the FDA issued a "dear doctor" letter warning that olanzapine and other atypical antipsychotics may increase patients' risk of hyperglycemia and diabetes mellitus. ●

Sources: Eli Lilly News Release. March 30, 2004.

FDA MedWatch Safety Alert. March 1, 2004.