Drug Monitor

LMWH for Thromboprophylaxis After Knee Arthroscopy

Due to a scarcity of data from randomized, controlled trials, the use of low molecular weight heparin (LMWH) for thromboprophylaxis following knee arthroscopy was not endorsed by the latest American College of Chest Physicians Consensus Conference—and is not commonly practiced by hospitals. Recent findings from the Knee Arthroscopy Nadroparin Thromboprophylaxis (KANT) Study Group, however, suggest that LMWH can provide a significant benefit in this setting.

The study involved 1,761 patients scheduled to undergo knee arthroscopy at the Abano Terme Clinic, Abano Terme, Italy or the University Hospital of Padua, Padua, Italy. Patients were assigned randomly to wear full-length graduated compression stockings (GCS) for seven days (660 patients) or to receive a subcutaneous injection of the LMWH nadroparin once daily for either seven days (657 patients) or 14 days (444 patients). Efficacy was determined by the combined incidence of asymptomatic proximal deep venous thrombosis, symptomatic venous thrombosis, and all-cause mortality; safety was determined by the combined incidence of major and clinically relevant bleeding events. Ultrasonography was used to assess both legs at the end of prophylaxis—or sooner, if indicated.

The three-month cumulative incidence of the primary efficacy endpoint was 3.2% in the GCS group and 0.9% in both LMWH groups. (The 14-day LMWH group was stopped prematurely after the second interim analysis due to the apparent lack of additional benefit from the second week of therapy.)

No patients withdrew because of adverse events, and none of those receiving LMWH developed heparin-induced thrombocytopenia. There was a slightly higher incidence of clinically relevant nonmajor bleeding events in the seven-day LMWH group than in the GCS group. This difference, however, was accounted for by four hemarthroses of less than 300 mL of blood each.

The researchers believe their study to be the largest randomized trial of venous thromboprophylaxis after knee arthroscopy to date. Although their patients were at low risk for venous thromboembolism (they excluded patients who underwent prolonged procedures or had risk factors for thromboembolism), they say the absolute difference between GCS and LMWH in the incidence of the primary efficacy endpoint (2.3 percentage points) was statistically significant and clinically important.

Source: *Ann Intern Med.* 2008;149(2):73–82.

First Drug Approved to Treat Huntington Chorea

In August, tetrabenazine became the first FDA-approved treatment for chorea in patients with Huntington disease. The drug, which is being marketed as Xenazine by Prestiwick Pharmaceuticals (Washington, DC), reduces chorea by decreasing the amount of dopamine available to interact with certain brain synapses.

Efficacy was established in a randomized, placebo-controlled, multicenter trial. Along with improvement in chorea, however, patients taking tetrabenazine also showed slight worsening in mood, cognition, rigidity, and functional capacity. Additionally, the drug was associated with serious adverse effects, including depression and suicidal thoughts and actions—risks that are heightened in all patients with Huntington disease, the FDA says.

Given the potential dangers, the FDA is requiring providers to follow an established risk evaluation and mitigation strategy (REMS) to ensure that the benefits outweigh the risks for patients prescribed the drug. Included in the REMS are educational materials for prescribers, pharmacists, patients, and caregivers and a medication guide that must be distributed to patients and caregivers with each prescription.

Source: FDA news release. August 15, 2008.

Cardiorenal Benefits for Ramipril and Rosiglitazone in IGT and IGF?

We know that ramipril, an angiotensin converting enzyme inhibitor, and rosiglitazone, a thiazolidinedione antidiabetic agent, can protect high risk patients with diabetes from some adverse cardiovascular (CV) and renal outcomes associated with the disease. But can it do the same for those whose impaired glucose tolerance (IGT) or impaired fasting glucose (IGF) has not yet developed into diabetes? It doesn't seem likely, according to the results of the multicenter Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial.

The DREAM trial investigators randomly assigned 5,269 patients aged 30 and older with IGT or IGF—but

no known CV disease or renal insufficiency—to receive ramipril or placebo and rosiglitazone or placebo. Over a median follow-up of three years, patients were observed for a number of adverse CV and renal events, considered together (as a composite cardiorenal outcome) and separately.

Neither drug appeared to affect the composite cardiorenal outcome. Nor did ramipril alter either the CV or renal composite outcomes. Rosiglitazone, on the other hand, reduced the risk of renal disease by 20%—which was accompanied by a reduction in diabetes risk. At the same time, however, it increased the risk of heart failure.

The researchers note that the short follow-up and low incidence of CV events may have made it difficult to detect any CV benefits of the drugs. Even so, they found the lack of a definite cardiorenal benefit for rosiglitazone "surprising," given the "many favorable effects of rosiglitazone on surrogate markers of CV [disease]." Although the actual incidence of heart failure in rosiglitazone-treated patients in this study (0.5%) was lower than that observed in previous studies of higher risk patients (1.5%, 1.7%, and 5.7%), the researchers say their findings provide "new evidence" that low risk patients "are not protected" from this adverse effect.

Source: *Diabetes Care*. 2008;31(5):1007–1014.