NEW DRUGS

COX-2 Inhibitor for Menstrual Pain
Valdecoxib tablets (Bextra, Pfizer), are now available for the treatment of osteoarthritis (OA), adult rheumatoid arthritis (RA), and menstrual cramping (primary dysmenorrhea). A 10-mg dose once daily can treat OA and RA for 24 hours. The recommended dose of valdecoxib for menstrual pain is 20 mg twice daily as needed. This COX-2-specific inhibitor was approved by the FDA late in 2001.

Valdecoxib was well-tolerated with a superior upper gastrointestinal safety profile. The incidence of observed gastrointestinal ulcers was lower for valdecoxib than for ibuprofen, diclofenac, and naproxen in two large three-month trials. The most common adverse events were headache, abdominal pain, dyspepsia, upper respiratory infection, nausea, and diarrhea.

Patients in their third trimester of pregnancy or those who have had an allergic reaction to aspirin or other NSAIDS should not be given valdecoxib. In patients with fluid retention or hypertension, those who have experienced heart failure, valdecoxib should be used with caution. Platelet function is not affected by valdecoxib, so it should not be used for cardiovascular prophylaxis.

Controlled-Release Paroxetine
A multilayered form of paroxetine (Paxil CR, GlaxoSmithKline), which controls dissolution and absorption of the drug in the body, is now available. This controlled-release version of paroxetine was created from Geomatrix technology licensed from SkyePharma PLC.

Controlled-release paroxetine was studied in two 12-week, flexible-dose, placebo-controlled studies of patients with major depressive disorder. Drug efficacy was measured by the Hamilton Rating Scale for Depression (HAM-D). There were statistically significant improvements as early as week two of treatment, and the controlled-release paroxetine was statistically significantly different from the placebo at week one on the Depressed Mood Item of the HAM-D.

In two 10-week, multicenter flexible-dose studies, the drug’s efficacy in treating patients with panic disorder, with or without agoraphobia, was established. After four weeks of therapy, almost half of these patients reported being panic-free, and 73% of the patients were panic-free at the end of the studies. Controlled-release paroxetine has the same side effects as paroxetine.

NEW INDICATION

Direct Thrombin Inhibitor for HIT
The FDA has approved a supplemental New Drug Application (sNDA) for the synthetic direct thrombin inhibitor Argatroban (GlaxoSmithKline). The FDA approval allows the use of Argatroban in patients with or at risk for heparin-induced thrombocytopenia (HIT) who are undergoing percutaneous coronary interventions (PCI). HIT is an immune-mediated response to heparin that can lead to serious thrombotic complications and death. Heparin is used in virtually all interventional coronary procedures.

The safety and efficacy of Argatroban were reviewed in three studies. Results from the trials showed that 98% of the 91 patients treated with Argatroban had adequate anticoagulation. Acute procedural success was achieved in 98% of the Argatroban patients compared to 94% in the control group. The major bleeding rates for Argatroban were 1.8% versus 3.1% for historical controls. The trials showed a reduction in the combined risk of new thrombosis, amputation, or death.

NEW STARTING DOSE FOR ATORVASTATIN
The cholesterol-lowering medication atorvastatin calcium (Lipitor, Pfizer) is now approved for stronger starting doses. The FDA had previously approved atorvastatin for a 10-mg starting dose. Now physicians will also be able to use 20 or 40 mg; the 40-mg dose is recommended for patients who require a reduction in low-density lipoprotein (LDL) cholesterol of more than 45%.

Long-term Interleukin-2 Therapy for HIV
At the 9th Conference on Retroviruses and Opportunistic Infections, the ANRS 079 study group reported that Interleukin-2 (IL-2) was given on a long-term basis to patients with HIV infection.

Patients who had never taken antiretroviral drugs containing a protease inhibitor, and who had CD4+ cell counts between 300 and 550 cells/mm³, were randomly divided into two groups. They were given either stavudine/lamivudine/indinavir (the highly active antiretroviral therapy [HAART]) alone or in combination with subcutaneous IL-2. They were monitored for durability of response over 74 weeks of therapy.

The median CD4+ cell counts rose 242 cells/mm³ in the 58 HAART patients but 835 cells/mm³ in the IL-2 group. Mean plasma levels of HIV-1 RNA declined in both groups. At the last follow-up, 78% of the HAART patients and 76% of the IL-2 patients had viral loads below 50 copies/mL. Both the increase in CD4+ cell counts and the decrease in HIV-1 RNA levels were maintained throughout the follow-up period.

Over the long term, patients tolerated the IL-2 therapy well. The researchers found no adverse virologic sequelae. Two more studies, SILCAAT and ESPRIT, will determine the clinical consequences of enhanced elevation of CD4+ cell counts in patients with HIV and whether the use of IL-2 is beneficial (for more information, see www.medscape.com/viewarticle/429257).

Investigating Pharmaceutical Pollution
The U.S. Environmental Protection Agency has given environmental engineers at
Johns Hopkins University a three-year, $525,000 grant to study the effects of pharmaceuticals and antiseptics in drinking water, sewage treatment plants, and coastal water. Johns Hopkins researchers have two new scientific tools to use on this project: a survey of the estimated environmental concentration of 200 drugs that are prescribed and sold most often, and a lab technique called gas chromatography–mass spectrometry. Early estimates of the probable environmental concentrations of those 200 pharmaceuticals indicate that antidepressants, anti-inflammatories, anti-cancer drugs, and antimicrobials are likely to be found at “toxicologically significant levels” in the environment. The gas chromatography–mass spectrometry technique can detect a gram of a pharmaceutical in more than one billion liters of water. This research is important because consumed prescription medicines are not rendered biologically harmless when they pass through the body; conventional sewage treatment systems do not always remove them. Unused drugs that are flushed down the toilet or thrown into the trash could end up in groundwater or surface water, where they have the potential to affect aquatic life and the quality of drinking water. The body’s serotonin levels, for example, are affected by popular antidepressants; and serotonin in the water causes many aquatic creatures to spawn. The natural breeding cycles of these creatures could therefore be affected by the release of serotonin into the wild. Small amounts of pharmaceuticals in drinking water could also harm pregnant women and their fetuses.

The project will study pharmaceutical removal in sewage treatment plants in Massachusetts and Maryland, and collect samples in the environmentally sensitive upper Chesapeake Bay, to check for the presence and concentration of drugs and antiseptics. By doing so, researchers hope to learn how efficiently nature’s self-cleaning processes are eliminating these man-made pollutants. For more information, see www.jhu.edu/news/home02/apr02/prescrip.html.

**Drug Combination for Chest Pain**

Results of the INTERACT (INTegrilin and Enoxaparin Randomized assessment of Acute Coronary syndromes Treatment) trial, presented at the 51st annual scientific sessions of the Academy of Cardiology, showed that patients who suffered from unstable angina or myocardial infarction had a statistically lower incidence of life-threatening outcomes when treated with the antiplatelet agent eptifibatide (Integrilin, Millenium Pharmaceuticals) and the anticoagulant enoxaparin (Lovenox, Aventis).

The INTERACT trial studied 746 patients from 54 hospitals across Canada. The eptifibatide/enoxaparin combination was associated with 44% less ischemia, which was measured by electrocardiographic changes. The combined incidence of death or heart attack within 30 days was 5% in this group versus 9% in the group that took eptifibatide and heparin (P=0.031). The eptifibatide/enoxaparin combination was also associated with a lower incidence of repeated ischemic events after drug discontinuation (12.7% vs. 25.9% for the eptifibatide/heparin group, P=0.0001) and a lower incidence of major bleeding outside of the setting of coronary bypass surgery (1.8% vs. 4.6% for the eptifibatide/heparin group at 96 hours, P=0.03).

**CRUSADE for Heart Therapy**

Researchers at Duke University Medical Center report that only one in four patients with acute coronary syndromes receives glycoprotein (GP) IIb/IIIa inhibitors, which prevent blood clots from forming. Keeping clots from forming reduces the risk of death and heart attacks. The information in their study was based on the fourth generation of the National Registry of Myocardial Infarction (NRMI4) databank. Of the 186,727 cases studied, 60,770 were eligible for the GP IIb/IIIa inhibitors. Data collected on the first 2,026 cases revealed that using evidence-based therapies such as aspirin and beta-blockers can reduce the risk of recurrent heart attacks and death. Although 80% of the patients received these therapies, only 36% of them received GP IIb/IIIa inhibitors. Patients in the database were older and sicker than the participants in the GP IIb/IIIa inhibitor trials.

The researchers plan a nationwide awareness effort called CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines), which plans to collect data on how more than 60,000 high-risk heart patients are treated at 600 hospitals across the U.S. The research study and CRUSADE were presented at the 51st Scientific Sessions of ACC. CRUSADE’s goal is to reduce treatment delays in the emergency rooms and to improve the use of beneficial therapies.

**New Treatment for Ankylosing Spondylitis**

Tumor necrosis factor alpha (TNF-α) has been found in the joints of patients with ankylosing spondylitis (AS), and it appears to play a significant role in the chronic inflammation associated with AS. A study published in the April 6 issue of *Lancet* discusses the use of infliximab in German patients with active AS. A total of 70 patients at eight clinics were randomized to receive either placebo or an infusion of infliximab 5 mg/kg at weeks 0, two, and six. After 12 weeks, 53% of the patients treated with infliximab had at least a 50% reduction in disease activity compared to 9% of those treated with placebo.

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There was also an improvement in everyday functionality and quality of life for the infliximab patients. Many patients (56%) taking infliximab decreased their use of non-steroidal anti-inflammatory drugs—usage was reduced by more than half compared to 19% of those treated with placebo.

Most patients tolerated infliximab treatment. However, there were three significant instances of side effects: one was tuberculosis, one was allergic granulomatosis of the lung, and the third was leucopenia. These side effects were treated, but tuberculosis screening is recommended before beginning infliximab treatment. This anti-TNF therapy is initially suggested only for centers with special rheumatological treatment experience.

**GENE THERAPY**

**Bone Marrow Therapy for “Baby in the Bubble” Syndrome**

British doctors have successfully used gene therapy for the first time to cure a Welsh toddler born without an immune system, according to the Great Ormond Street Hospital for Children in London. The hospital said last month that 18-month-old Rhys Evans had been cured of the fatal genetic condition X-linked Severe Combined Immunodeficiency Disease (X-SCID), commonly known as “baby in the bubble” syndrome. The disease meant that Rhys was born without an immune system and was highly susceptible to potentially fatal infections. He was forced to live in a totally sterile environment, isolated from other children, and spent much of his life in the hospital. Doctors removed some of Rhys’ bone marrow and genetically modified it to add a correct copy of the faulty gene that caused X-SCID. The marrow was then re-injected into his system.

The Evans case, which followed the opening of a gene therapy laboratory at the hospital last September, is one of the few clinically successful examples of gene therapy in the world. For more information, visit [http://genomics.biocompare.com/gnews.asp?id=4429](http://genomics.biocompare.com/gnews.asp?id=4429).

**SHORT TAKES**

**Transplantation Medicine**

Roche has signed an agreement with Isotechinka for the co-development of Isotechinka’s transplantation medicine ISATX247, a calcineurin inhibitor in phase II clinical development. ISATX247 will be developed as an immunosuppressive treatment for organ transplantation and autoimmune diseases. The drug, in early studies, appears to be more potent than, and also less toxic than, the existing immunosuppression agents in its class.

**GAD Study**

An eight-week study by researchers at Duke University showed that the experimental drug escitalopram (Lexapro, Forest Laboratories Inc.) reduced symptoms in patients with generalized anxiety disorder (GAD). Escitalopram reduced symptoms such as worry, dread, tiredness, and irritability. It took approximately four weeks for the drug’s benefits to appear. Patients were evaluated primarily using the Hamilton Anxiety Scale (HAMA), which scores people based on interviews with doctors. People in the study had a minimum HAMA score of 18, which represents a moderate level of GAD. The study, which included 240 patients, ranging from 18 to 80 years of age, was presented at the March meeting of the Anxiety Disorders of America (HealthScoutNews Reporter).