NEW DRUGS

Long-lasting Triptan for Acute Migraine

The Food and Drug Administration (FDA) recently approved frovatriptan succinate (Frova, Elan Corporation, plc/UCB Pharma, Inc.) for the treatment of acute migraine attacks with or without aura in adults.

Frovatriptan succinate is the newest drug in the triptan class; it is unique because it has a half-life of 26 hours, which means its active ingredient remains in the blood for at least 20 hours longer than any other triptan. The drug treats migraine pain by constricting targeted blood vessels in the brain.

The efficacy and tolerability of frovatriptan succinate was demonstrated in five randomized, placebo-controlled clinical trials of 4,129 patients. Frovatriptan succinate reduced migraine pain compared to placebo. Less than half the patients taking frovatriptan succinate needed additional medication for their pain. It also offered relief from associated symptoms, such as nausea and sensitivity to light and sound.

Only 1% of the study patients withdrew because of adverse events; most were reported to be mild or moderate and transient. Adverse events reported included dizziness, fatigue, paresthesia, flushing, headache, dry mouth, hot or cold sensation, and chest pain.

The drug is available in 2.5-mg tablets that must be taken with fluids at the onset of a migraine. If relief is not achieved with the first dose, then a second dose may be taken two hours later.

New Prostate Cancer Drug-Delivery System

Leuprolide acetate for injectable suspension (Eligard 7.5 mg, Atrix Laboratories, Inc.), which is used to treat prostate cancer, is now available in the U.S. The company's Atrigel system has a precise mixture of biodegradable polymers in a liquid carrier. When the liquid carrier is mixed with the drug and injected into the body, it solidifies to form a solid implant. This implant releases leuprolide actetate over a one-month period as it is bioabsorbed. The Atrigel system obviates the need to use long or large-diameter needles and it delivers the drug in a way that results in a low level of testosterone.

This drug was FDA-approved in January of 2002. New drug applications have been filed for three- and four-month versions. Eligard 7.5 mg is contraindicated in women, pediatric patients, and patients with a sensitivity to GnRH, GnRH antagonists, or any of the drug's components. There might be an increase in serum concentrations of testosterone during the first week of treatment.

In the clinical study, the most common adverse events were hot flashes, sweating, malaise and fatigue, atrophy of the testes, dizziness, and gastroenteritis/colitis. At the injection site, there were reports of transient burning/stinging, and to a lesser degree, pain, erythema, and mild bruising. A majority of injection-site events were mild and brief.

DRUG NEWS

Possible Expansion for Otitis Media Drug

Otitis media is one of the most common bacterial infections in children. The Vaccines and Related Biological Products Advisory Committee to the FDA recently voted in favor of expanding the indication of Pneumococcal 7-valent Conjugate Vaccine (Diptheria CRM_{197} Protein). The drug is sold as Prevnar by Wyeth Vaccines.

The committee believed that there were adequate data to support the efficacy of the vaccine for the prevention of otitis media caused by *Streptococcus pneumonia,* because there are seven serotypes in the vaccine. This drug cannot prevent all middle ear infections, but it could lead to a reduction in the number of occurences.

Shorter Time to *H. pylori* Eradication

Data from a multicenter, double-blind, randomized trial, presented at the annual Digestive Disease Week meeting, showed that taking rabeprazole sodium (Aciphex, Eisai/Janssen) and antibiotics for seven days was just as effective at treating *Heliobacter pylori* (*H. pylori*) bacteria as omeprazole (Prilosec, AstraZeneca) and antibiotics for 10 days. *H. pylori* is believed to be the most common cause of peptic ulcers.

The study was conducted at 47 centers nationwide with 803 patients. Half of the patients had either an active peptic ulcer disease or a confirmed history of the condition. All patients underwent a series of diagnostic tests to confirm infection with *H. pylori*.

Patients were randomized into four treatment arms: three-day rabeprazole, amoxicillin, and clarithromycin (RAC); seven-day RAC, 10-day RAC; and 10-day omeprazole, amoxicillin, and clarithromycin (OAC). After seven days of therapy, 84% of the patients on RAC were free of *H. pylori*, and 86% of those on 10-day RAC therapy were *H. pylori*-free. Those on 10-day OAC were 82% *H. pylori*-free. The three-day RAC treatment arm did not meet the study's objective.

Rabeprazole sodium was approved for marketing by the FDA in 1999. Headache is the most common side effect. It is contraindicated in patients with a known sensitivity to rabeprazole, substituted benzimidazoles, or any component of the drug.

Sleep Problems in the Elderly

Older patients often report poor or disrupted sleep. In a study by researchers in Stockholm, more than one-third of 641 people aged 81 and older had sleep problems. The researchers found that the problems were most common among

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women and among people using a greater number of drugs. Depression, pain, and self-rated poor health were significantly linked to poor sleep. Another possible cause, discovered in the analysis, was the use of hypnotic sedatives. Researchers suggest that the complaints of the elderly should be carefully assessed to accurately diagnose and treat their sleep problems (Source: *J Gerontology* 57:M236-M240).

Rosiglitazone Not Hepatotoxic...

In clinical tests, involving more than 6,000 patients with type 2 diabetes who took rosiglitazone throughout North America and Europe, researchers found no hepatotoxic effects.

Researchers wondered whether rosiglitazone (Avandia, GlaxoSmithKline) would act similar to another thiazolidinedione, troglitazone (Rezulin, Warner-Lambert), which has been associated with idiosyncratic hepatic reactions leading to liver failure and death. They analyzed data from 13 double-blind clinical trials of rosiglitazone monotherapy and two ongoing, active-comparator clinical trials. No evidence of liver toxicity was observed either in monotherapy or in combination therapy for 5,006 patients.

The results aren't unexpected, the researchers say, because rosiglitazone and troglitazone are markedly different in their biochemical and metabolic features and hepatic effects. Rosiglitazone is a PPAR-γ agonist that is 100 times more effective than troglitazone. Both compounds have a thiazolinedione core, but they have different side chains. Unlike troglitazone, which has been shown to be directly toxic to cultured rat hepatocytes, rosiglitazone does not concentrate significantly in the liver, nor does it recirculate through the biliary system. The kidneys excrete 65% of the rosiglitazone. The researchers note that liver toxicity is unlikely to be a thiazolinedione or PPAR-γ agonist class effect (Source: *Diabetes Care* 25:815–821).

...But Diabetes Drugs Could Cause CHF

The possibility of fluid retention and congestive heart failure (CHF) have led to a label change for pioglitazone HCl (Actos, Eli Lily) and rosiglitazone maleate (Avandia, GlaxoSmithKline). Studies with both diabetes drugs turned up cases of CHF in patients taking either drug alone or with insulin.

In a 16-week U.S. trial involving 566 patients with type 2 diabetes, pioglitazone plus insulin was compared with insulin alone. Two of 191 patients receiving 15 mg of pioglitazone plus insulin and two of 188 receiving 30 mg of pioglitazone plus insulin developed CHF, whereas none of the patients who were taking insulin alone did. The four patients who developed CHF had previous histories of cardiovascular conditions including coronary heart disease, previous CABG procedures, and myocardial infarction.

In two 26-week U.S. trials involving 611 patients with type 2 diabetes, researchers found an increased incidence of cardiac failure and other cardiovascular adverse events in patients on rosiglitazone and insulin combination therapy compared with those only on insulin.

Although most of the patients who experienced heart failure were older, had a long-standing history of diabetes, and were on the higher (8-mg) dose of rosiglitazone, three of 10 patients who developed cardiac failure had no known prior evidence of CHF or pre-existing heart conditions.

The FDA notes that rosiglitazone is not indicated for use with insulin. Patients taking either rosiglitazone or pioglitazone should be monitored for signs and symptoms of heart failure. Patients who lose weight unusually rapidly, have edema, or have symptoms of heart failure, such as shortness of breath, should be encouraged to tell their physicians immediately. Rosiglitazone and pioglitazone have not been studied in patients with New York Heart Association Class III and IV cardiac status and are not recommended for those patients (Source: FDA).

A Model to Predict Diabetes?

The standard for detecting impaired glucose tolerance has been a two-hour oral glucose tolerance test. A simple clinical model, based on widely recognized risk factors, was comparable to the two-hour oral glucose tolerance test at identifying people at high risk for diabetes, say researchers from the University of Texas Health Science Center in San Antonio. They compared the two methods of detection in a study of 1,791 Mexican Americans and 1,112 non-Hispanic whites without diabetes at baseline.

The multivariable model, which uses readily available clinical data, was more accurate than the oral glucose tolerance testing alone. Adding the glucose variable to the model enhanced prediction, but it was only a slight improvement. The model is not only more convenient than the oral test, but it also allows for widespread adoption (i.e., for use in hand-held devices, programmable calculators, or computers). The limitations of the model include missing data for some people, the need to validate it in other populations, as well as the need for further validation in the populations already studied (Source: *Ann Intern Med* 136:575–581).

Balloon Device Controls Gynecologic Pain

Two studies presented at the American College of Obstetrics and Gynecology's annual meeting suggest that a balloon device called ON-Q would provide postoperative pain control. The balloon device dispenses a local anesthetic into the surgical site. In a study of 30 women who had undergone elective abdominal hysterectomy, 10% needed no additional pain medication beyond ON-Q, and 33% used

only nonsteroidal anti-inflammatory drugs. ON-Q delivered 0.5% ropivacaine, 0.5% bupivacaine, or 2% lidocaine to the surgical site at a rate of 2 ml per hour.

Another study, conducted at the University of Tennessee in Memphis, found that ON-Q reduced opioid use by 40% and delivered equivalent pain relief to patients who had cesarean sections (Source: ACOG annual meeting; Medscape).

Low-dose Aspirin Lowers Risk of Colon Polyps

A baby aspirin taken daily reduces the risk of recurring polyps in patients with advanced adenomas or colorectal cancer, researchers reported at the annual meeting of the American Association for Cancer Research. Their study of 1,121 patients had an unexpected finding: the lower dose (80 mg) had a greater preventive effect, reducing the risk of advanced adenoma by 40%. The 325-mg dose reduced the overall risk of adenoma recurrence by only 4% and the risk of recurrence of advanced adenomas and colorectal cancers by 19%.

It is premature to recommend a daily 80-mg aspirin regimen for all adults over 50 years of age, because this group is at an only mildly elevated risk. Study results are going to be analyzed to determine possible reasons for the different effects that resulted from different doses (Source: National Cancer Institute).

GERD Drug Limits Calcium Absorption

The popular drug omeprazole (Prilosec, AstraZeneca) might inhibit calcium absorption in women over 65 years of age, according to a study released at the annual meeting of the American Geriatrics Society in May.

Researchers at the University of Minneapolis and other institutions found that 16 of 18 women had lower calcium absorption after taking omeprazole for a week. Omeprazole is a proton pump inhibitor used to prevent acid reflux—but without acid, the body can't absorb calcium properly. The researchers note that further studies are needed to find out if higher calcium dosages, food intake, and other factors might affect the interaction (Source: www.americangeriatrics.org).

Insulin Aspart for Improved Glycemic Control

At the annual meeting of the American Diabetes Association (ADA), many studies presented data indicating that insulin aspart (rDNA origin) injection (Novolog, Eli Lily and Company) maintains adequate control of blood sugar levels for people with type 1 diabetes if the injection is administered right before or just after a meal. Human insulin has to be injected 30 minutes before a meal, which is problematic for many people with type 1 diabetes, because they need to calculate their insulin dose based on the amount of carbohydrates to be consumed in a meal.

The mealtime dosing study compared the use of insulin aspart before and after a meal. Results showed that postprandial glycemic control was adequate regardless of when the drug was administered, but glycemic response was 25% lower when insulin aspart was administered before a meal rather than after it.

Two other studies presented at the ADA showed that insulin aspart provided better glycemic control than regular human insulin (RHI). In one study, insulin aspart given just before a meal was compared with RHI given 30 minutes before the meal. Peak glucose levels were 25 minutes shorter, postprandial glucose surges were 20% lower (P=0.034), and peak insulin levels were reached 27 minutes earlier with insulin aspart than with RHI. The other study compared treatment with insulin aspart with or without bedtime insulin, RHI with or without NPH insulin, and human premixed insulin. Insulin aspart had greater reductions in HbA1c than the RHI group or the insulin premix group. Postprandial glucose levels decreased the most with insulin aspart.

Another study on insulin aspart focused on gestational diabetes. It included 15 women who were 18 to 28 weeks pregnant and unable to achieve adequate glycemic control through diet alone. The women underwent a series of tests on three different days in random order. In one test, no insulin was administered; in the other two tests, they received either insulin aspart or RHI. The study showed that insulin aspart was more effective than RHI in blunting the postprandial glucose peak 60 minutes after the meal and reducing the overall amount of glucose in the bloodstream (to which the fetus is exposed) following the meal.

Age, Not Gender, Bias Found in Heart Attack Study

According to a new study published in the June 19, 2002 issue of the *Journal of the American College of Cardiology*, the difference in treatment for heart attacks in men and women might be caused by age rather than by gender.

The Institute for Clinical Evaluative Sciences in Toronto, Ontario, Canada, studied data from 25,697 heart attack patients hospitalized in Ontario between April 1992 and December 1993. They examined the association of age and gender with treatment intensity and five-year survival. The researchers found that rates of angiography (an invasive imaging technique) fell 17.5% for women relative to men with every 10-year increase in age. Although care became progressively less aggressive for women as they aged, their long-term survival rates nevertheless improved compared to those of the men; the relative survival rate in women rose 14.2% for every 10-year increase in age. These results suggest an age bias rather than a gender bias in the treatment of heart attack patients (Source: *Journal of the American College of Cardiology*). ■