NEW DRUGS

Antihypertensive Agent
The Food and Drug Administration (FDA) has approved a new angiotensin II receptor blocker, olmesartan medoxomil (Benicar, Sankyo Pharm, Inc.). A study published in the September/October 2001 issue of the Journal of Clinical Hypertension involved two multicenter, randomized, double-blind, clinical trials that compared the starting doses of olmesartan medoxomil and losartan potassium (Cozaar, Merck) for the treatment of essential hypertension. The average reduction of cuff systolic and diastolic blood pressure with 20 mg of olmesartan medoxomil was significantly greater than with 50 mg of losartan potassium after eight weeks of therapy. Olmesartan medoxomil was also more effective in reducing average systolic and diastolic blood pressure, as measured by 24-hour ambulatory monitoring.

A second study, which included 316 patients, compared 20 mg of olmesartan medoxomil once daily with 100 mg of losartan potassium once daily. After 12 weeks of therapy, patients taking olmesartan medoxomil achieved a greater reduction of average systolic and diastolic blood pressure than those who took losartan potassium.

The only side effect that occurred at a higher incidence with olmesartan medoxomil than with placebo was dizziness. Olmesartan medoxomil has a favorable drug–drug interaction profile; no significant drug interactions were reported in studies in which it was co-administered with digoxin or warfarin. Olmesartan medoxomil is not metabolized by the cytochrome-P450 enzyme system, so it avoids interactions with drugs that inhibit, induce, or are metabolized by that system. This drug can be taken with or without food. Olmesartan medoxomil is not recommended for pregnant women.

NEW INDICATION

Zoloft for PMDD
The FDA recently approved sertraline HCl (Zoloft, Pfizer) for the treatment of premenstrual dysphoric disorder (PMDD). Studies supporting the new indication showed that sertraline HCl is significantly more effective than placebo in treating women who suffer from this condition. PMDD is characterized by severe emotional and physical symptoms that occur during the time between ovulation and menstruation.

In two randomized, double-blind, placebo-controlled trials involving 532 women diagnosed with PMDD, sertraline HCl was significantly more effective than placebo in improving PMDD symptoms, including emotional symptoms (e.g., feelings of depression, hopelessness, and being overwhelmed) and behavioral symptoms (e.g., being angry or irritable, and having conflicts with people). Improvement was noted whether sertraline HCl was dosed intermittently during the premenstrual phase of the menstrual cycle only, or dosed continuously throughout the cycle. Women who took sertraline HCl continuously throughout their menstrual cycles also experienced noticeable improvements in physical symptoms such as breast tenderness, bloating, and headache.

PMDD is distinguished from premenstrual syndrome (PMS) by the severity of symptoms and the degree of impact on a woman’s daily activities and relationships. In addition, the diagnostic criteria for PMDD require the presence of a distinct mood change during the symptomatic period, whereas PMS might not involve a mood change. As many as 3% to 5% of women in the U.S. experience premenstrual symptoms that are severe enough to meet the diagnostic criteria for PMDD.

The most common side effects of sertraline HCl include upset stomach, difficulty sleeping, diarrhea, abdominal pain, dry mouth, sexual side effects, drowsiness, tremor, indigestion, increased sweating, agitation, and decreased appetite. It is contraindicated until at least 14 days have passed since discontinuing a monoamine oxidase inhibitor (MAOI), and in patients with a hypersensitivity to any of the inactive ingredients in sertraline HCl.

DRUG NEWS

Contamination Precautions for Albuterol Sulfate
Contaminated bottles of albuterol sulfate have led the FDA to issue a public health advisory. Two recent hospital outbreaks of lower respiratory tract colonization and infection with B. cepacia were attributed to multidose bottles of albuterol sulfate solution for inhalation (0.5%). Infection with B. cepacia can have adverse outcomes such as pleural space infection, prolonged hospital stays, and even death. These outbreaks are not the first—others have been reported in the medical literature. Most cases occur in the ICU setting, often in patients receiving mechanical ventilation.

The contamination was likely caused by a failure to adhere to good aseptic technique, the FDA says, and from using a single bottle for more than one patient. The FDA urges clinicians (i.e., respiratory therapists and ICU staff) to be careful not to let the dropper tip touch any surface, including the nebulizer reservoir and associated ventilatory equipment, as directed by the product label (source: FDA).

Cholesterol Reduction for HoFH
A study to be published in the May 28th edition of Circulation describes the use of ezetimibe (Zetia, Merck/Schering-Plough Pharmaceuticals) in patients with homozygous familial hypercholesterolemia (HoFH). HoFH is a rare genetic disorder that results in extremely high cholesterol total levels. This multicenter, double-blind, placebo-controlled study represents the largest clinical study of patients with HoFH. All patients were initially taking a 40-mg dose of atorvastatin or simvastatin. They received one of three treatment regimens: doubling of their statin dose, the addition of ezetimibe to their statin or simvastatin. They received one of the following: doubling of their statin dose, or both doubling of the statin dose and the addition of ezetimibe. At the conclusion of the 12-week study, 33 patients, who were taking ezetimibe with either 40 or 80 mg of a statin, had their low-
density lipoproteins (LDL-C) reduced by an additional 20.7%, compared to 6.7% in patients who had statin therapy alone.

Long-Term Benefits for Crohn’s Disease
Patients with Crohn’s disease, a chronic inflammatory disorder of the intestines, are often treated with steroids, which can have severe side effects. A recently published study in the New England Journal of Medicine investigated long-term treatment with infliximab (Remicade, Centocor) in 335 patients with Crohn’s disease.

Patients were given an initial 5 mg/kg intravenous infusion of infliximab, then randomly assigned to repeat infusions of placebo, 5 mg/kg of infliximab, or 10 mg/kg of infliximab. Treatment was given at random intervals, after a month, and then every two months thereafter for a year. Patients who were given infliximab two every months were in remission after 30 weeks, compared to those given placebo, who responded to treatment for only 19 weeks. Those who were given infliximab were also more likely to discontinue the use of steroids.

Data from the same 54-week trial also found that at week 14, 69% of patients had sustained closure of at least 50% of their draining fistulas for one month after receiving three infusions of infliximab 5 mg/kg.

Weekly BMD Drug
The FDA has approved 35-mg dosage strength risedronate sodium tablets (Actonel, Procter & Gamble/Aventis) for once-a-week use. Approval was based on safety and efficacy data from a one-year, double-blind, multicenter study that included 1,456 postmenopausal women with osteoporosis. This study compared the effects of a 35-mg weekly dose and a 5-mg daily dose on bone mineral density (BMD). The significant increase in lumbar spine BMD and hip BMD at 12 months versus baseline was similar in both treatment groups; overall safety and tolerability profiles were similar. Patients with gastrointestinal disease (past or present) were not excluded from the study.

Low-Dose Transdermal Patch for Osteoporosis
Starting August 2002, Novogyne’s small, low-dose estrogen patch (Vivelle Dot) will be available for estrogen replacement therapy. This patch, which has been recently approved in the 0.025 mg/day dosage strength, delivers estradiol and is applied twice weekly. It is as small as a dime, thin, and nearly translucent. The original four doses of the patch (0.0375, 0.05, 0.075, and 0.1 mg) are currently available.

Protective Paint Covering
U.S. retail market clearance has been granted by the Environmental Protection Agency (EPA) for a non-toxic, natural, mineral-based, antimicrobial surface coating (Caliwel, Alistagen Corp.) for paint. The coating contains micro-encapsulated calcium hydroxide, which has inherently high alkalinity to kill microbes. Most airborne microbes are killed when they come into contact with treated surfaces, so people are exposed to fewer microbial spores.

The encapsulation of calcium hydroxide allows the coating to resist degrading for up to six years. Tests have shown that this product has been 99% effective against over 20 microbes that are responsible for diseases such as asthma, allergies, staphylococci, influenza, polio, hepatitis, cholera, and Legionnaires’ disease. The first formulation that will be available is a latex-based liquid coating, which is available in 10 colors and can be applied with a brush, roller, or sprayer.

MEETING PRESENTATIONS
Long-Term ADHD Studies
A series of studies on methylphenidate HCl (Concerta CII, McNeil) were presented at the 155th annual meeting of the American Psychiatric Association (APA). The studies covered the safety of the drug, its long term-effectiveness, its effects on height and weight, and preference of the drug over other attention deficit/hyperactivity disorder (ADHD) drugs.

A study examined the long-term safety and efficacy of methylphenidate HCl in 240 children who continued treatment in an open-label, non-randomized study into a second year. The patients were assigned to one of three dosing levels (18, 36, or 54 mg). Parents noted that they were “very satisfied” with methylphenidate HCl. It was well-tolerated by patients in the 21-month study.

Several studies demonstrated that methylphenidate HCl was effective in treating ADHD with minimal impact on tics. The drug is contraindicated in patients with pre-existing tics or Tourette’s Syndrome. In two separate controlled studies, children were enrolled in two seven-day, double-blind crossover trials and one 28-day, double-blind, parallel-group trial. Participants took either methylphenidate HCl, methylphenidate three times daily (TID), or a placebo. Most children experienced no tics, and the number of those who did was similar in all groups. Another study, which lasted one to two years, had parents record the severity of their children’s tics, if present. Only 40 out of 407 children had tics; children who had a history of tics reported a similar number of tic episodes in comparison to children who did not have a history of tics.

Two other studies evaluated parental preference for and satisfaction with ADHD medication under double-blind and open-label conditions. Additional research focused on persistence as an indicator of how long patients stayed on ADHD therapy. In one double-blind, double-dummy, randomized crossover study, once-daily methylphenidate HCl was compared to methylphenidate TID and a placebo. The medication or placebo was given three times daily so that the preference rating would not be influenced by the convenience of dosing. At the end of the study, 54.1% of the parents preferred methylphenidate HCl and 26% preferred methylphenidate TID. Improvements in...
SNRI for Long-Term Remission of Depression and GAD

New data presented at the APA meeting in May demonstrated the effectiveness of the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine HCl (Effexor XR, Wyeth) in maintaining long-term remission of depressive symptoms and reducing symptoms of generalized anxiety disorder (GAD).

Patients who responded to treatment with venlafaxine for depression and who remained relapse-free during a six-month period were randomly assigned to continue receiving the drug for 12 months or to be switched to placebo under double-blind conditions. After one year of therapy with the antidepressant, 67% of patients maintained remission of their symptoms ($P < 0.01$). Patients who achieve remission are less likely to relapse and are more successful at resuming activities in which they participated before they developed depressive symptoms.

An extended-release formulation of venlafaxine also produced a significant decrease in symptoms of generalized anxiety disorder (GAD) in a placebo-controlled, double-blind study among children and teens aged 6 to 17 years. Specifically, venlafaxine produced an average decrease of 18.6 points (compared to a 12.4 point decrease for placebo) ($P < 0.001$) from beginning scores that averaged 40.5, as rated on the standard scale, the Columbia KIDDIE Schedule of Affective Disorders and Schizophrenia Subsection.

Sixty-four percent of the venlafaxine group responded to the therapy, compared to 40% of those on placebo ($P < 0.004$), as measured by a rating of “very much improved” or “much improved” on the standard Clinical Global Impression-Improvement (CGI-I) scale. The most common treatment-related adverse events were asthenia, anorexia, weight loss, hyperkinesia, somnolence, and epistaxis.

Approximately 2.8% of U.S. adults and 5% of U.S. children suffer from GAD, excessive anxiety and worry that are difficult to control. GAD differs from normal feelings of nervousness because the symptoms are chronic and include alarming reactions that can occur for no apparent reason.

Antibiotic Against Heart Attack?

Animal and human studies have suggested that Chlamydia pneumoniae ($C. pneumoniae$) infection can contribute to the development of atherosclerosis. $C. pneumoniae$ has been found in up to 60% of atherosclerotic plaques.

Therefore, treatment with azithromycin might help attenuate the development of atherosclerosis in patients who have had $C. pneumoniae$ infection, according to the first major clinical study examining such a role for the antibiotic. Researchers from Duke University presented the results of the WIZARD (Weekly Intervention with Zithromax for Atherosclerosis and Related Disorders) study at the 51st Annual Scientific Session of the American College of Cardiology.

The worldwide study, conducted by Pfizer Inc., involved 7,700 patients who have had a myocardial infarction at least six weeks before the study and had evidence of $C. pneumoniae$ infection. They received either placebo or azithromycin 600 mg once daily for the first three days, then weekly for three months.

Preliminary results indicate a 7% reduction in the incidence of recurrent cardiovascular events, compared with placebo. The benefit showed up early but was not sustained over the length of the trial, the researchers said. Because the trial concluded only recently, the data have yet to be analyzed thoroughly. Results from a similar but longer study, the Azithromycin and Coronary Events Study (ACES), are expected next year (source: Pfizer; American College of Cardiology).

Statins Could Lower Alzheimer’s Risk

Statins—both natural and synthetic—might reduce the risk of Alzheimer’s disease (AD) by as much as 79%, according to a study reported at the American Academy of Neurology’s 54th Annual Meeting.

Researchers from Boston University School of Medicine studied 2,581 people from more than 800 families, at 15 medical centers. The MIRAGE (Multi-Institutional Research in Alzheimer’s Genetic Epidemiology) study builds on earlier observations that statins help protect against AD. However, those studies had methodological shortcomings, the researchers say, and, unlike MIRAGE, did not include African Americans, who may have different genetic susceptibilities to AD.
American, who have a higher risk of AD. In this study, the relationship between statins and AD held true for both Caucasians and African Americans. The earlier studies also did not assess the effect of the apolipoprotein E-e4, the gene variant associated with a higher risk of AD. The MIRAGE researchers found the same benefit for patients with or without the apoE-e4 gene. Cholesterol-lowering drugs other than statins were not associated with a lower AD risk.

For more recent developments relating to neurologic diseases, see Meeting Highlights from the American Academy of Neurology, page 295.

Late Rejection Reduction

According to the results of studies presented at the American Transplant Congress, the use of mycophenolate mofetil (CellCept, Roche) over a one-year-period reduced the incidence and risk of late rejection of kidney transplants compared to azathioprine, even in high-risk African-American (AA) patients.

A retrospective study of 47,853 transplant patients in the U.S. Renal Data System compared the incidence of late acute rejection in patients who remained on mycophenolate mofetil versus those who remained on azathioprine for a minimum of 12 months after transplantation. Data included patients who received solitary renal transplants between October 31, 1988 and December 31, 1998 and remained on mycophenolate mofetil or azathioprine. A majority in both groups were Caucasian, but a significant percentage were AA patients. Episodes of organ rejection were recorded at regular follow-up visits and reported to the registry by transplant centers.

The rate of rejection episodes beyond the first year was estimated by Kaplan-Meier survival analysis, which showed that a lower number of patients in the mycophenolate mofetil group developed acute rejection two and three years post-transplantation compared to those in the azathioprine group (3% vs. 9% at two years, 4% vs. 13% at three years). The results were consistent in AA patients as well.

Another study measured five-year survival in AA patients versus non-African Americans (non-AA). All patients were given an immunosuppression regimen that consisted of a calcineurin inhibitor, mycophenolate mofetil, and prednisone. During the first month after transplantation, AA patients received higher doses of mycophenolate mofetil than non-AA patients, but last doses were reduced to be comparable to those given to non-AA patients. Patient survival at three and five years was 91% and 88% in AA patients and 94% and 89% in non-AA patients, respectively. The rates of transplanted organ survival were 81% and 71% in AA patients and 88% and 81% in non-AA patients.

A prospective, multicenter, randomized, controlled study examined the effects of renal function when mycophenolate mofetil was added to an immunosuppressive regimen and followed by cyclosporine withdrawal in patients with biopsy-proven allograft (transplanted organ) dysfunction. The 143 patients in this study had been treated with a cyclosporine-based immunosuppressive regimen and were experiencing progressively deteriorating renal function.

Over a 34-week period, patients were randomized to either treatment with mycophenolate mofetil and cyclosporine withdrawal or continued treatment on cyclosporine. In 58% of patients taking mycophenolate mofetil, kidney function stabilized or improved, compared to 32% in patients taking cyclosporine. There was no incidence of acute rejection for patients taking mycophenolate mofetil compared to one patient taking cyclosporine. Among patients taking cyclosporine, there were four kidney losses; there were two among those taking mycophenolate mofetil. There were three deaths in the mycophenolate mofetil group. In the cyclosporine group, there were six opportunistic infections and one serious opportunistic infection compared to 16 and three in the mycophenolate mofetil group.

Results of a study conducted in nine Spanish hospitals showed that replacing azathioprine with mycophenolate mofetil and reducing the cyclosporine dose in the first year might help to protect renal function and delay the progression to end-stage kidney disease. This prospective, non-randomized, multicenter study included 83 heart transplant patients who had been treated with cyclosporine for more than 18 months. Researchers observed an improvement in serum creatinine levels at one and two years’ inclusion in the study. Ten patients were withdrawn from the study, four died during follow-up, and there were five acute rejection episodes greater than grade II, which were resolved with no complications.

Treating Infant RDS

Results of a study presented at the Pediatric Academic Societies Annual Meeting showed that poractant alfa (Curosurf, Dey, L.P.) was more effective than beractant (Survanta, Abbott Laboratories) in treating neonatal respiratory distress syndrome (RDS) in preterm infants. The study was a randomized, multicenter masked trial that compared 100 mg/kg poractant alfa, 200 mg/kg poractant alfa, and 100 mg/kg beractant in 239 preterm infants with established neonatal RDS.

The initial treatment of either dose of poractant alfa was associated with faster weaning of supplemental oxygen. Infants who were treated with an initial dose of 200 mg/kg poractant alfa and then given 100 mg/kg poractant alfa showed a modest benefit in the acute phase of RDS. Initial treatment with 200 mg/kg of poractant alfa was associated with a significantly decreased need for additional doses of surfactant (compared to beractant) and had the lowest neonatal mortality rate of all initial treatments.

Poractant alfa allows a smaller volume of dosing because it is a highly concentrated surfactant. One 200-mg/kg dose of poractant alfa was effective in 73% of the infants treated. Transient adverse effects seen with poractant alfa included bradycardia, endotracheal tube blockage, and oxygen desaturation.