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INSIDE

Pharmacology Update

The Latest Information on New Drugs and New Indications

Jane henney, md, the clinton administration's candidate to replace David Kessler, MD, as the Commissioner of the **FDA**, was finally confirmed by the Senate on October 20. Her confirmation had been in doubt recently as her views on RU-486 and the tobacco industry had raised the hackles of the Republican leadership. But, bipartisan support along with lobbying from Donna Shalala, secretary of Health and Human Services, helped to resolve any opposition. Henney most recently held the position of vice president for Health Sciences at the University of New Mexico. Prior to that, she held leadership roles at both the FDA and NIH. The position has been vacant since Kessler left to assume the role of Dean of the Yale University School of Medicine.

The **flu** has arrived early in some parts of the country and the flu vaccine arrived late, but full supplies should be available by mid-November. **Wyeth-Ayerst** was in the process of changing its manufacturing process when the CDC announced the antigens for this year's vaccine, thus, falling behind the normal production schedule. But, other manufacturers, especially **Pasteur Merrieux Connaught**, are rushing to fill the void. There should be plenty of vaccines available by the end of the month. There actually may be some advantages to vaccinating later rather than earlier, with the effects of the vaccine waning after six months and the flu season generally starting in December and running well into the late spring.

The Diabetes Complications and Control Trial (DCCT) demonstrated the benefits of tight blood sugar control in type 1 diabetes, and to a great extent, changed the standard of care for this disease. Now, the results of the largest study ever done on type 2 diabetes has been published. The **United Kingdom Prospective Diabetes Study (UKPDS)** followed more than 4000 type 2 diabetics for 20 years. The study was designed as a prospective, randomized trial, with patients randomized to intensive blood sugar control using sulfonylureas and insulin, or conventional care. A separate wing of the study looked at metformin use in overweight diabetics. The results of the study have been published recently (*BMJ* 1998;317:703-713; *Lancet* 1998;352:837-853; *BMJ* 1998:317:13-20). The results of this important study will be interpreted for years to come. The primary findings were that intensive control decreased the incidence of microvascular complications such as retinopathy and nephropathy, but did not seem to affect the rate of stroke or cardiovascular disease. Overall mortality was also unaffected by intensive control. (*The Physician's Therapeutics & Drug Alert supplement contains a reference to help with the prescribing of drugs for type 2 diabetes.*)

Children with **croup** do better with a dose of corticosteroids according to a study published in August (*N Engl J Med* 1998;339:498-503). One hundred

forty-four children with croup were randomized to receive recepinephrine along with intramuscular dexamethasone, nebulized budesonide, or placebo. Both treatment groups did far better, with the dexamethasone group having the most favorable outcomes, including significantly less need for hospitalization (23% vs 71% for placebo).

Paroxetine (Paxil) has been found to be effective in treating social phobia, this country's third most common psychiatric disorder, following depression and alcoholism. One hundred eighty-seven patients were randomized to paroxetine in doses of up to 50 mg daily or placebo (*JAMA* 1998;280:708-713). More than half of the treated patients reported improvement after 11 weeks, while only one quarter of the placebo group was improved. SSRI side effects, including sexual symptoms and headache, were common in the treatment group.

The mechanism by which **hormone replacement therapy (HRT)** lowers cardiovascular risk may be multifactorial. Along with improving lipid profiles, HRT may also lower ambulatory blood pressure. A recent study from the Netherlands (*Am J Hypertens* 1998;11:1147-1152) showed that blood pressure was lowered an average of 5.5/4.2 mmHg in women taking cyclical HRT for more than one year. The study was performed on healthy women with no history of hypertension or cardiovascular disease.

If your patients are unsuccessful at quitting smoking, remain encouraging and supportive. A recent Gallup survey reveals that the average smoker attempts quitting four times before they finally kick the habit.

The **Physician's Desk Reference** is branching out. **Medical Economics**, the company that publishes PDR, has announced that they will soon release a PDR for Herbal Medicines. The reference will contain information on more than 600 herbal remedies. Much of the information will be based on European data, especially data from Germany.

Alendronate (Fosamax) may cause more GI symptoms than previously suspected. In a recent study based on telephone interviews with women who had filled prescriptions for the alendronate, nearly one-third of women taking the drug experienced gastrointestinal problems, and more than 28% of women discontinued the drug because of side effects. The study (*J Man Care Pharm* 1998;4:488-492) was based out of **Kaiser Permanente** in Northern California and was partially funded by Novartis. The study also revealed that many women were not adequately instructed on the use of the drug or did not comply with instructions for taking it, especially instructions about the timing of eating and taking other medications.

The **FDA** has put two drugs on the fast track approval process. **Discovery Labs** synthetic lung surfactant **SP-B peptide (Surfaxin)** is in phase III trials for treatment of acute respiratory distress syndrome (ARDS). The drug replaces lost surfactant in ARDS and is administered via an endotrachial tube directly into the lungs. Advanced **Corneal Systems hyaluronidase (Vitrase)**, which was also given fast tract status, is an enzyme used to treat vitrous hemorrhages. The hyaluronidase breaks up hyaluronic acid in the vitrous, allowing faster clearing of trapped blood and it's eventual reabsorption. ■

Citalopram: New SSRI for Treatment of Depression

By William T. Elliott, MD, and James Chan, PharmD, PhD

A new selective serotonin reuptake inhibitor (SSRI), citalopram, was approved by the FDA in July for the treatment of depression. The drug is to be marketed under the trade name Celexa by Forest Laboratories and Parke-Davis. It is the fifth SSRI to be approved for use in this country, joining fluoxetine, paroxetine, sertraline, and fluvoxamine. Its action appears to be limited to the potentiation of serotonergic activity in the central nervous system, with minimal effect on norepinephrine and dopamine transmitter reuptake.[1] It has no or minimal affinity for serotonin, histamine, muscarinic, adrenergic, dopamine, gamma aminobutyric acid, or benzodiazepine receptors.[1] Citalopram is well-absorbed and has a long elimination half-life (35 hours) that permits once daily dosing. The drug also appears to have a low potential for drug interactions involving the cytochrome P450 system.

Indications

Citalopram is indicated for the treatment of depression.

Dosing

Citalopram is available as 20 mg and 40 mg tablets. The initial dose is 20 mg once daily. It may be administered in the morning or evening and may be taken without regard to meals. The dose may be increased to 40 mg once daily. Increases should occur in increments of 20 mg at intervals of no less than one week. Certain patients may require a dose of 60 mg/d; however, doses above 40 mg are not ordinarily recommended.[1] A dose of 20 mg

once daily is the recommended dose for most elderly patients and those with hepatic impairment. Titrate to 40 mg only for nonresponding patients.[1]

Potential Advantages

Based on limited data, citalopram appears to be a weak inhibitor of cyctochrome P450 isoenzymes 1A2, 2D6, and 2C19 and does not appear to inhibit 3A4.[1,2] Fluvoxamine has been reported to inhibit 1A2; fluoxetine, norfluoxetine, sertraline, and paroxetine, 2D6; fluoxetine, sertraline, and fluvoxamine, 2C; and fluvoxamine, nefazodone, fluoxetine, and sertraline, 3A4.[1,2]

Potential drug interactions involving 2D6 include antipsychotics, antiarrhythmics, and secondary amine tricyclic antidepressants. Those involving 2C include phenytoin and diazepam; 3A4 interactions include carbamazepine and aprazolam, and 1A2 interactions include theophylline and haloperido.[l,12]

In studies involving normal volunteers, citalopram (40 mg/d) did not impair intellectual function or psychomotor performance. It does not appear to potentiate the cognitive and motor effects of alcohol, although coadministration is not recommended.[1]

Potential Disadvantages

Side effects reported (compared to placebo) with citalopram include dry mouth (20% vs 14%), nausea (21% vs 14%), somnolence (18% vs 10%), and ejaculation disorder (6% vs 1%). In vitro data indicate that citalopram is metabolized via cytochrome P450 3A4 and 2C19. Potential inhibitors of these isoenzymes may reduce the metabolism of citalopram.[1] Citalopram may increase the plasma level of metoprolol. While coadministration had no significant effects on blood pressure or heart rate, the cardioselectivity of metoprolol may be decreased.[1]

Comments

Citalopram has been available, and has been used extensively, in Europe for many years (e.g., United Kingdom since 1989). It has a good track record in Europe, where it has generally been found to be effective and well tolerated. The majority of published data on the drug are from European studies. Comparative studies with other SSRIs, namely fluoxetine and sertraline, suggest that citalopram is at least as effective and has similar side effects.[3,4] In an eight-week study involving 357 patients with unipolar depression, citalopram 20 mg was reported to be similar to 20 mg fluoxetine in improving various depression scores (MADRS, HAM-D, and CGI). Back pain occurred more frequently in the citalopram-treated patients (3.3% vs 0%). The onset of effect may be earlier with citalopram, with a higher percent of patients showing improvement at the two-week assessment period. No significant difference was observed after two weeks.[4] Patients not receiving benzodiazepines may respond better to citalopram than those receiving benzodiazepines.[9] In a 24-week study (n = 400), sertraline was compared to citalopram (mean dose of 82 mg and 32 mg, respectively) in patients with major depression. No statistical differences were seen in efficacy, incidence of side effects, or medication compliance.[3] Comparative trials with tricyclic antidepressants indicated similar efficacy but a lower frequency of adverse events.[5,6]

Studies have indicated that citalopram is efficacious and well-tolerated by elderly patients with depression with or without dementia disorder.[7,8]

Clinical Implications

Depression is a common mental disorder seen in clinical practice. It is frequently underdiagnosed and inadequately treated. The point prevalence of this disorder is 2.3-3.2% for men and 4.5-9.3% for women, with a lifetime incidence of 7-12% in men and 20-25% in women. Only one-third to one-half of patients with major depression are diagnosed by primary care and other practitioners.[10] With pharmacotherapy, there appears to be high variability in patient response. In general, there is a high rate of discontinuation and switching of antidepressants and variability in medication adherence.[11] Citalopram provides clinicians with another effective SSRI that may have the advantage of reduced potential for drug-drug interactions for those patients who are on multiple medications.

The wholesale price of citalopram is about $2.00 per tablet for either the 20 mg or 40 mg strength. Cost is competitive to or slightly less than other SSRIs. ■

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Ribavirin Capsules and Interferon alfa-2b

By William T. Elliott, MD and James Chan, PharmD, PhD

Hepatitis c is one of this country's greatest public health concerns. Some 4 million Americans are chronically infected with the virus, of which 20-50% will go on to develop chronic liver inflammation and cirrhosis. As many as 30% of those will develop liver failure or liver cancer as a result of the disease. The disease is so prevalent that hepatitis C infection has become the leading reason for liver transplantation in the United States.[1]

Interferon (alfa-2 and alfacon-1) has been the mainstay of therapy for hepatitis C, but the results have been variable, and the treatment is often poorly tolerated. Now, the FDA has approved a new treatment, a combination product involving interferon alfa-2b and the antiviral drug ribavirin.

Interferon alfa-2b is a large, water soluble protein produced by recombinant DNA technology using a strain of *E. coli* bacteria. Interferon is believed to have immunomodulating activity. The drug must be given parenterally and is generally given subcutaneously. Ribavirin is an oral nucleoside analog antiviral agent with in vitro activity against respiratory syncytial virus, influenzae virus, and herpes simplex virus. The combination is being marketed by Schering-Plough under the name Rebetron. It is approved by the FDA only for patients who have relapsed on conventional interferon treatment.

Indications

Rebetron is indicated for the treatment of chronic hepatitis C in patients with compensated liver disease who have relapsed following alpha interferon therapy.

Dosage

For patients who are less than 75 kg: 3 million IU of interferon injected subcutaneouly three times weekly for 24 weeks. Ribavirin is administered orally as 400 mg (2 × 200 mg) in the morning and 600 mg (3 × 200 mg) in the evening. The drug may be taken without regards to meals.

For patients greater than 75 kg: 3 million IU of interferon injected subcutaneouly three times weekly for 24 weeks. Ribavirin is administered orally as 600 mg 3 × 200 mg) in the morning and 600 mg (3 × 200 mg) in the evening.

The recommended regimen is six months (24 weeks). Safety and efficacy have not been established beyond 24 weeks of treatment.[2]

Rebetron is supplied as six single dose vials (3 million IU each) or as 18 million IU multidose vials with 84, 70, or 42 capsules of ribavirin. Each unit is a 14-day supply.

Potential Advantages

Interferon and ribavirin have been reported to produce a decrease in hepatitis C viral RNA and normalization of alanine aminotransferase compared to retreatment with intereron alfa-2b in patients who relapse after interferon therapy.[1,2] In phase III studies, retreatment with interferon and ribavirin was compared with interferon and placebo. Sustained virological response (no detectable virus 24 weeks after end of treatment) was 43-48% vs. 4-5%, respectively, and histological response of 49-51% vs. 31-36%, respectively.[2] Histological response was defined as improvement in liver, Knodell histology activity index (HAI) of 2 points or greater. The combination has also been shown to be more effective than interferon alone in interferon-naïve patients in sustaining virological response.[3] While the response rates (no detectable HCV RNA by PCR) after therapy were identical, the responses 48 weeks later were 46% for the combination and 21% for monotherapy ($P = 0.02$).[3] Normalization of ALT was 44% for the combination and 24% for monotherapy 24 weeks post-treatment ($P = 0.057$).

Potential Disadvantages

Anemia was observed in 10% of interferon/ribavirin patients in clinical trials. This adverse event usually occurred within 1-2 weeks of initiation of therapy. In a recently published trial, the mean hemoglobin concentration decreased from 14.7 to 12.1 g/dL in the interferon/ribavirin group, compared to a decrease of 14.5-13.8 g/dL in the interferon/placebo group ($P < 0.001$).[3] Ribavirin has significant teratogenic and/or embryocidal potential and is contraindicated in women who are or may become pregnant.[2] Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis, and pneumonia, including fatality, have been reported during interferon/ribavirin therapy.[2] Nausea is more common with the combination than interferon alone (34% vs 12%; $P = 0.02$).[3] Severe psychiatric reactions including depression and suicidal behavior have been reported with alpha interferon monotherapy and interferon/ribavirin.[2]

Comments

Hepatitis C virus is an RNA virus of the Flaviviridae family. It does not exist as a homogenous species but, rather, as a closely related heterogenous population of viral genomes or quasispecies. This genetic heterogeneity may explain variations in clinical course, lack of response, and difficulty in vaccine development.[6] There are several genotypes and subtypes of the virus, with type 1 being the dominant genotype.[7] Current therapy of chronic hepatitis C are alfa interferon and alfacon-1 interferon. Efficacy of treatment is defined as reduction in hepatitis viremia, normalization of serum ALT, and mean changes in liver histology score. Sustained response is generally assessed 24-48 weeks after the end of a 24-week course of therapy.

Typical response rates are 27-35% for virological response and 37-42% in biochemical response at the end of treatment. Sustained responses are 11-12% and 20%, respectively, 24 weeks after treatment.[8] There appears to be a higher response rate in patients infected with genotype 2 and 3 compared to genotype 1.8 In addition, patients with lower serum HCV RNA (< 1,000,000 copies/mL) and absence of cirrhosis may be predictive of response to therapy.[6] Selection of quasispecies may occur during interferon therapy.[10] For nonresponders, treatment with a newer alfacon-1 interferon at a higher dose (15 mcg TIW compared to 9 mcg TIW) and longer duration (48 weeks) provides marginal benefit (13% sustained response). Retreatment of relapse patients at a higher dose produced a sustained response of 28% after a 24-week treatment and 58% after a 48-week treatment.[8]

Interferon/ribavirin appears to offer some promise in relapse patients, as well as interferon-naïve patients. A sustained response rate of 47% has been reported in relapse patients and 36% in treatment-naïve patients.[2,3] While data are limited, it appears that patients who fail to achieve a sustained effect with interferon may have favorable response to the combination, but success in non-responders is limited.[4,9]

Clinical Implications

It is estimated that nearly 4 million Americans are infected with hepatitis C. Given the high prevalence of infected individuals, it is urgent that effective intervention (i.e., education, vaccine, and antiviral drugs) be developed to prevent future infections and delay the progression of liver disease after infections.

Currently, the options are limited. Treatment is recommended for patients with chronic hepatitis who are at the greatest risk for developing cirrhosis. Characteristics of these patients include consistently elevated ALT, HCV viremia, and evidence of portal or bridging fibrosis and moderate degrees of inflammation and necrosis.[6]

Treatment success with interferon monotherapy has been limited. Prior to the approval of interferon/ribavirin, the NIH had recommended initial therapies of 12-month duration to improve the rate of sustained response.[6] The combination of ribavirin and interferon provides an important option. It is currently approved by the FDA for patients who relapsed on interferon but is soon expected to gain approval for treatment-naïve patients. Resistance to interferon is still problematic and the combination does not appear to be the solution. More active anti-HCV agents are needed, and combination therapy similar to those used for HIV therapy may improve efficacy.

Interferon/ribavirin is expensive. Wholesale cost for a 24-week therapy is $6120-$6720. This is about three times the cost for interferon alone. ■

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Cefdinir: Another Orally Administered Cephalosporin

Source: *Hishida A, et al. Antimicrob Agents Chemother 1998; 42:1718-1721.*

The most recent of the orally administered antibiotics to receive FDA approval is cefdinir. Approval was awarded in December 1997 for its use in the treatment of skin infections, as well as in upper and lower respiratory tract infections (i.e., acute sinusitis,

otitis media, pharyngitis, acute exacerbations of chronic bronchitis, and community-acquired pneumonia.)

The bioavailability of cefdinir capsules is 20%, while that of the oral suspension is only slightly greater. The drug is excreted, unchanged, in the urine and has a half-life in plasma of approximately 1.7 hours. The recommended adult dose is 300-600 mg q12h; it may be taken without regard to feeding state. Preliminary data suggest that a dose of 100 mg daily may be sufficient in hemodialysis patients.

In terms of its antibacterial spectrum of activity, cefdinir most closely resembles, among the orally administered cephalosporins, cefpodoxime. It is active against *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*, except for those isolates which are fully penicillin resistant. Methicillin-susceptible *Staphylococcus aureus* are susceptible, as are many Enterobacteriaceae, but not *Pseudomonas aeruginosa*. As with other cephalosporins, cefdinir is not active against "atypical pneumonia" pathogens, nor is it active against enterococci.

The following tentative interpretive criteria for determining the susceptibility of *S. pneumoniae* to cefdinir have been proposed: susceptible, MIC less than 0.5 mg/L or inhibition zone diameter greater than 23 mm; intermediate, MIC 1.0 mg/L or inhibition zone, 20-22 mm; resistant, MIC greater than 2.0 mg/L or inhibition zone diameter, less than 19 mm.[1]

Randomized Clinical Trials

Skin and Skin-Structure Infections. A randomized trial comparing cefdinir 300 mg bid to cephalexin given 500 mg qid, each for 10 days, in the treatment of 952 adults with mildly to moderately severe skin and skin-structure infections found no difference in outcome.[2] A similar study in 394 children also found similar outcomes in comparing the results of treatment with these two drugs.[3]

Pharyngitis. Five days of cefdinir therapy appears to be at least as effective as 10 days of penicillin therapy in the treatment of acute pharyngitis due to *S. pyogenes*. A randomized trial involving 558 children found that bacterial eradication was achieved in 81.7% of the cefdinir recipients and in 88.2% of those treated with penicillin ($P = 0.053$).[4]

Acute Community-Acquired Paranasal Sinusitis. Two randomized studies, one involving 1229 patients, 698 of whom underwent antral puncture, and the other with 569 patients, all of whom underwent antral puncture, found similar outcomes between treatment with either cefdinir or amoxicillin-clavulanate.[5]

Acute Otitis Media. Response rates to cefdinir and to amoxicillin-clavulanate, in a randomized trial of 595 assessable children with acute otitis media, were similar.[6]

Community-Acquired Pneumonia. Six hundred ninety patients with community-acquired pneumonia were randomized to receive either cefdinir 300 mg bid or cefaclor 500 mg tid, each for 10 days.[7] Bacteriological eradication rates were, respectively, 89% and 86%. Diarrhea occurred in 13.7% of those assigned cefdinir and 5.3% of those assigned cefaclor.

The wholesale cost of a 10-day course of cefdinir 300 mg twice daily is reported to be approximately $67. Cefdinir has been demonstrated to be an effective agent for the treatment of certain respiratory and skin structure infections. More data are required to determine its efficacy in the treatment of infections caused by pneumococci that are intermediately susceptible to penicillin. The increasing prevalence of high-level penicillin resistance among pneumococci may limit the usefulness of this and other available orally administered beta-lactam agents in the future. ■

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Postmenopausal Hormone Therapy and the Risk of Ovarian Carcinoma

Source: *Garg PP, et al. Obstet Gynecol 1998;92:472-479.*

Garg and associates performed a meta-analysis, examining the relationship between postmenopausal hormone therapy and the risk of epithelial ovarian carcinoma. After identifying 327 pub-

lished citations, seven articles representing 12 analyses of 21 individual studies were included in this meta-analysis. The final conclusion indicated a relative risk of 1.14 (CI = 1.04-1.24) for developing invasive or borderline ovarian cancer among ever-users of postmenopausal hormone therapy. The relationship of invasive ovarian cancer with increasing years of hormone therapy use was derived from data from six studies. Among women who used hormone therapy for more than 10 years, the final relative risk for the development of invasive cancer was 1.27 (CI = 1/00-1.61). Garg et al conclude that the use of postmenopausal hormone therapy, especially for more than 10 years, is associated with an increased risk of developing invasive epithelial ovarian carcinoma.

Comment by Leon Speroff, MD

In my opinion, this meta-analysis illustrates everything that is wrong with the application of this technique to observational studies. Meta-analysis is a technique developed to bring together small, randomized clinical trials in the effort to achieve greater statistical power. When applied to case-control cohort studies, it is subject to the same confounding biases that are present in individual studies. An overall increased risk of 14% in ever-users of hormone therapy in epidemiologic terms is slight and cannot be expected to reflect greater reliability when derived from case-control studies (as in this meta-analysis).

The conclusion that a 27% increased risk is associated with long-term use (more than 10 years) of hormone therapy is based upon six observational studies with data including long-term use. This conclusion, with a C.I. of 1.00-1.61, was by definition not statistically significant. Examining the individual conclusions of each of the six studies reveals that only one of these six reported significant increase with long-term use. This was a report from The Nurses' Health Study in 1995 (Rodriguez, et al. *Am J Epidemiol* 1995;141:828-835) that found no significant increase in the relative risk of fatal ovarian cancer with the ever-use of postmenopausal hormone therapy. The link with long-term use achieved statistical significance with only 18 cases. Thus, the conclusion of this meta-analysis, regarding increased risk with increasing duration of use, is tenuous. Despite this, in the discussion of the meta-analysis, Garg et al imply that this is a risk that should be included in the clinician-patient dialog. I strongly disagree.

A paragraph in the discussion is an excellent example of epidemiologic thinking that is not helpful for clinicians and patients. In making an argument for estrogens in the etiology of ovarian cancer, they cite the publication in the *New England Journal of Medicine* (Rossing, et al. *N Engl J Med* 1994;331:771-776), which concluded there was a two- to three-fold increase in the risk of developing ovarian cancer with the long-term use of clomiphene. They don't share with the reader the fact that this conclusion was based on five cases, and, not surprising, the confidence interval (1.5-82.3) was extremely wide, reflecting the imprecision of their conclusion because of the small number of cases. They further ignore subsequent studies that failed to confirm a link between clomiphene and ovarian cancer. It is precisely studies like the clomiphene study in which clinicians are justified in concluding that statistically significant epidemiologic studies with small numbers and imprecision probably have no clinical relevance.

In view of the controversy in the last few years regarding the appropriate use of meta-analysis, it is disappointing to me that our journals give credibility to conclusions of meta-analyses such as this one based upon weak observational data. I am repeatedly impressed that epidemiologists believe that all data can be presented to patients, allowing objective decision-making on the part of the patients. There are some studies that involve cancer that cannot be separated from the emotions that surround the fear of cancer, and when the studies are incredibly weak, it is better that they do not enter the clinical dialog. This meta-analysis is a prime example. ■

Therapeutics and Drugs Briefs

Fluticasone and Loratadine for Seasonal Allergic Rhinitis Treatment

Source: *Ratner PH, et al. J Fam Pract 1998;47:118-125.*

Intranasal corticosteroids and oral antihistamines are both popular choices for the treatment of allergic rhinitis. Though the former are generally acceded to possess a more favorable effect on nasal blockage than the latter, eye symptoms are typically more favorably affected by systemic antihistamines. This placebo-controlled, randomized, double-blind study compared once daily fluticasone nasal spray (FNS), once daily oral loratadine (LOR), or the combination (FNS/LOR), in 600 seasonal allergic rhinitis sufferers.

On a daily basis, patients recorded nasal symptom scores including nasal blockage, rhinorrhea, sneezing, and nasal itching. After two weeks of treatment, the FNS (and FNS/LOR) recipients had significantly more favorable symptom scores than LOR or placebo.

Surprisingly, LOR did not surpass placebo aqueous vehicle spray, and the FNS/LOR group was no better than FNS alone.

The results of this trial are in accord with several other trials that demonstrate the superiority of FNS over LOR. Indeed, a trial of mometasone nasal spray monotherapy compared to LOR alone or in combination also failed to show a favorable effect of LOR.

Ratner and colleagues conclude that FNS is superior to LOR for management of seasonal allergic rhinitis, and that adding LOR to FNS does not enhance benefits. ■

Orlistat for Weight Loss and Prevention of Weight Regain

Source: *Sjostrom L, et al. Lancet 1998;352:167-173.*

Obesity is a major personal and public health problem throughout the world. After two decades of a relative pharmacotherapeutic vacuum, recently employed agents have been causally implicated in cardiovascular pathology. A new agent that would be efficacious without causing, in particular, serious cardiovascular sequelae would be very welcome.

Orlistat inhibits gastrointestinal lipases, hence reducing absorption of dietary fat. On a typical regimen of orlistat 120 mg tid, a reduction of about 30% fat absorption could be anticipated. The current study enrolled men and women of BMI at least 28 for a double-blind, randomized, placebo-controlled parallel-group study (n = 688). In the first year of the study, patients were assigned to a hypocaloric diet (600 kcal/d deficit). In the second year, patients were placed on a eucaloric (weight maintenance) diet. Active treatment was 120 mg orlistat tid.

At the end of the first year, the active treatment group had lost about nine pounds more than the placebo group. In the second year, patients maintained on orlistat regained only half as much weight as placebo recipients. Surrogate end points such as total cholesterol, LDL, serum glucose, and insulin were more favorably affected by orlistat than placebo. Attesting to the overall tolerability of orlistat, in the first year of therapy, premature withdrawal was almost 30% more common in the placebo group. Gastrointestinal side effects were more common with active treatment. Orlistat may offer an attractive alternative for long-term palliation of obesity. ■

CME questions

Testing form inserted in the January 1999 issue

12. Which of the following is correct?

a. Cefdinir is only available in a form suitable for intravenous administration.
b. Cefdinir is not active against *Pseudomonas aeruginosa*.
c. *Moraxella catarrhalis* is most often resistant to cefdinir.
d. Cefdinir is administered every six hours.

13. Which of the following is correct?

a. Cefdinir is approved for use in the treatment of acute sinusitis.
b. Cefdinir, like other fluoroquinolones, should not be administered together with magnesium or aluminum containing antacids.
c. The oral bioavailability of cefdinir is 90%.
d. Cefdinir is active against "atypical pneumonia" pathogens, such as *Mycoplasma pneumoniae*.

14. The following statements are true of postmenopausal hormone therapy and the risk of epithelial ovarian carcinoma except:

a. All of the epidemiologic data regarding ovarian cancer and the use of hormone therapy are derived from observational case-control or cohort studies.
b. Meta-analysis is a technique that can avoid epidemiologic errors and biases.
c. The majority of data available in the studies thus far have not indicated an increased risk of ovarian cancer associated with postmenopausal hormone therapy.
d. There are no data available from randomized clinical trials regarding the risk of ovarian cancer and hormone therapy.

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