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INSIDE

Pharmacology Update

The Latest Information on New Drugs and New Indications

By William T. Elliott, MD, FACP

Duramed has received approval to market a new synthetic conjugated estrogen compound under the trade name **Cenestin**. Initially proposed as a generic form of Wyeth-Ayerst's **Premarin**, the FDA was convinced by Wyeth that the drugs were not identical, and Duramed was denied generic status for the drug. Subsequently, Duramed petitioned the FDA to approve Cenestin as a unique new drug, with approval granted in late March. Cenestin is synthetic and contains nine estrogen compounds that are derived from plant sources. Premarin is derived from pregnant mares' urine.

Searle's COX-2 inhibitor **celecoxib** (**Celebrex**) has been linked to 10 deaths and 11 cases of gastrointestinal hemorrhage since it was released in January. But the FDA is quick to point out that this is based on a denominator of 2.5 million prescriptions in the first three months, a rate that the agency feels is not excessive. The FDA is also looking at reports of dispensing errors associated with the drug. There have been more than 50 errors reported, some of them involving confusion over trade names, especially with the antidepressant **Celexa** and the anti-seizure medication **Cerebyx**, both marketed by **Warner-Lambert**. The irony is that Searle changed the name of celecoxib from Celebra to Celebrex just prior to approval to avoid such confusion. Searle is contemplating another name change for the drug, an option that will become unlikely once the company's aggressive direct-to-consumer advertising campaign begins within the next two months. In other COX-2 news, **Merck's refocoxib** (**Vioxx**) received a recommendation for approval by the FDA's Arthritis Drugs Advisory Committee on April 20, paving the way for full approval by this summer. Merck is seeking, and will likely receive, approval for the treatment of osteoarthritis like Searle's celecoxib, but unlike celecoxib, refocoxib is also likely to get an indication for pain. The committee also said that Merck cannot claim that the drug is less damaging to the GI tract than standard NSAIDs. It has been shown to cause less GI irritation than ibuprofen, but the committee made the recommendation because the drug has not been compared to other NSAIDs.

What is the best approach to the patient with **new nonvalvular atrial fibrillation**? A recent review looked at the long-term health and economic outcomes of treatments designed to restore and maintain sinus rhythm compared with rate control and anticoagulation with warfarin or aspirin.[1] An initial attempt at cardioversion is always the preferred treatment. If patients relapse, those at moderate or high risk of stroke should undergo repeat cardioversion and treatment with low-

dose amiodarone to maintain sinus rhythm. Patients at low risk for stroke may be allowed to fibrillate if they relapse, but daily aspirin therapy should be initiated.

The FDA has given **Hoffman-LaRoche** approval to market **orlistat** (**Xenical**). The drug is a lipase inhibitor that reduces absorption of dietary fat in the intestine by blocking gastro-intestinal lipases from breaking down ingested fat. Orlistat reduces the absorption of dietary fat by 30%. Unabsorbed fats pass from the small bowel to the colon and, eventually, are excreted in feces. The steatorhea that results can be bothersome to some patients. Other side effects include fecal incontinence, explosive diarrhea, and abdominal cramping. When dietary counseling and a low-calorie diet were combined with Orlistat, 57% of patients lost 5% of their baseline weight after one year compared with 31% for placebo. However, the magnitude of weight loss was not great. The average weight loss was 19.3 lb with Orlistat and 12.8 lb with placebo.

The diagnostic accuracy of **colonscopy** is only as good as the prep, but many patients complain that current liquid electrolyte purgative agents are worse than the actual test. **InKine Pharmaceuticals** of Pennsylvania is reporting favorable phase III results with their **tablet purgative agent** (**Diacol**). Their data indicate that the prep is as good as liquid agents, and patient acceptance was much higher. The tablets caused less nausea and vomiting than the electrolyte liquid preps. InKine will file for final FDA approval later this year.

The effects of **estrogen** on the central nervous system of postmenopausal women is the subject of two new studies. Researchers from New York looked at the records of women with early Parkinson's disease. Estrogen users were found to have a slower progression of the disease and significantly lower scores on the Unified Parkinson's Disease rating scale compared to non users of estrogen.[2] Saunders-Pullman and collegues conclude that estrogen should not be avoided in Parkinson's disease, and may be beneficial. In a second study, brain activation studies were evaluated by functional magnetic resonance imaging (MRI) exams in women both on and off conjugated estrogen. While women were taking estrogen, changes were seen in several areas of the brain including areas associated with verbal memory, suggesting that the drug may have a direct effect on the central nervous system.[3]

Despite studies demonstrating similar results using either nebulized bronchodilators or **metered dose inhalers** (**MDI**) with spacers, most hospitals and emergency departments (ED) continue to use only nebulized treatments in the setting of acute asthma. A new study again demonstrates the equivalency of these treatments and even suggests better long-term results with MDIs. Researchers in England looked at children older than 3 years who were brought into emergency departments with acute asthma attacks. The children were randomized to receive salbutamol via nebulizer or MDI with a large volume spacer. The children treated with MDIs had shorter ED stays and showed continued improvement at two weeks, presumably because they were instructed in MDI use during their ED visit. Overall costs were also slightly lower in the MDI group.[4] ■

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Emergency Contraceptive Kit (Preven—Gynetics, Inc.)

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

The fda has approved the first "morning after pill," Gynetics Inc.'s Preven Emergency Contraceptive Kit. Although high-dose oral contraceptives have been used in this role for years, Preven's formulation is the most widely used and now the first approved product in the United States for this indication. The combination of levonorgestrel, progestin, and ethinyl estradiol, an estrogen, was introduced many years ago by AA Yuzpe and is often referred to as the Yuzpe regimen. It has been the standard regimen, in addition to levonorgestrel and ethinyl estradiol. Preven also includes a home pregnancy test to rule out existing pregnancy.

Indications

The tablets in the kit are indicated for the prevention of pregnancy in women after known or suspected contraceptive failure or unprotected intercourse.

Dosage

The initial two tablets must be taken as soon as possible but within 72 hours of intercourse. The remaining two tablets are taken 12 hours later. If the patient should vomit within one hour of taking either dose, she should contact her physician and may consider repeating the tablets.[1] An anti-nausea drug such as meclizine may be considered pro-

phylactically one hour before the first dose.[2] Patients should be advised that emergency contraceptive kits do not protect against sexually transmitted infections such as HIV.

Preven is supplied as four tablets each containing 50 mcg of ethinyl estradiol and 0.25 mg of levonorgestrel. In addition, a pregnancy test is included that detects the presence of human chorionic gonadotropin in the urine.

Potential Advantages

Several oral contraceptives have been regarded as safe and effective as emergency contraceptive regimens. However, Preven is the only product available in a convenient dosage form. Preven works to delay or prevent ovulation, thereby preventing fertilization. It is, therefore, fundamentally different and perhaps more acceptable to some patients than abortifactients such as RU486.

Potential Disadvantages

While Preven is safe and effective, it may be less effective then levonorgestrel (0.75 mg) alone, which is not available in the United States. Results from a large (n = 1998) randomized trial indicated that ethinyl estradiol (100 mcg) and levonorgestrel (0.50 mg) are less effective than levonorgestrel (0.75 mg) alone.[3] The crude pregnancy rate was 1.1% (11/976) in the levonorgestrel group and 3.2% (31/976) in the levonorgestrel/ethinyl estradiol group. The proportion of prevented pregnancy was 85% for levonorgestrel and 57% for the combination. In addition, nausea and vomiting were higher in the combination group (50.5% vs 23.1% and 18.8% vs 5.6%, respectively). A slight delay in the time to next menses has also been reported.[3]

Comments

Preven is an effective form of emergency contraception. While the precise mechanism of action is not clear, it is believed that this product may act by inhibiting ovulation, alter tubal transport of sperm and/or ova, and inhibit implantation.[1] Use of the kit is expected to reduce the expected incidence of pregnancy by about 75%, with a confidence interval of 66-82%.[4] This is based on an analysis of seven studies. A recent study, however, suggested that the efficacy may be lower, 57%.[3] Efficacy may be greatest if the tablets are taken within 24 hours of unprotected intercourse and declines with time.[1,3] Preven should be started within 72 hours. The probability of pregnancy depends on the timing of intercourse and ovulation. There is a 15% chance of pregnancy when unprotected intercourse occurs three days before ovulation, 30% one or two days before, and 12% on the day of ovulation. The probability approaches zero more than two days after ovulation.[4]

Preven is a safe, effective, and convenient form of emergency contraception. It costs about $20 per kit. Other dosage forms used for emergency contraception include Ovral (2 tablets per dose), Lo-Ovral (4 tablets per dose), and Nordette, Triphasil, Levlen, or Trilevlen (4 tablets per dose). One study suggests that Preven may not be as effective as levonorgestrel. Unfortunately, levonorgestrel at emergency contraceptive doses is not available in the United States. The closest would be 20 tablets per dose of Ovrette.[2]

Clinical Implication

There are an estimated 3.5 million unintended pregnancies occuring in the United States annually and about one-half of them are believed to be the result of contraceptive failure. Current products for emergency contraception include various oral contraceptives, emergency insertion of an intrauterine device, and now, Preven. Emergency contraception provides a cost-effective method to reduce the incidence of unintended pregnancies. Greater availability of emergency contraception may reduce the considerable medical and social costs of unintended pregnancies.[5] A recent study indicated that emergency contraceptive options are underused. This is primarily due to lack of awareness among younger patients presenting for pregnancy termination. Jamieson and associates estimated that 38% of the surgical pregnancy terminations could have been avoided with the use of emergency contraceptive pills.[6] ■

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Miglitol Tablets (Glyset-Pharmacia Upjohn)

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

Pharmacia upjohn recently began marketing the second alpha-glycosidase inhibitor, miglitol (Glyset), joining acarbose in this class. These drugs are not hypoglycemic agents; rather, they inhibit

carbohydrate digestion in the brush border of the gut, delaying the absorption of glucose that attenuates postprandial hyperglycemia.[1,2] Miglitol and acarbose were both developed by Bayer. Miglitol was approved by the FDA in 1996 and subsequently licensed to Pharmacia Upjohn.

Indications

Miglitol is indicated as monotherapy as adjunct to diet to improve glycemic control in patients with type 2 diabetes whose hyperglycemia is not adequately managed with diet alone. It is also indicated in combination with a sulfonylurea when diet plus a sulfonylurea or sulfonylurea alone does provide adequate glycemic control.

Dosage

The recommended starting dose is 25 mg three times daily with the first bite of each meal. Due to gastrointestinal side effects, some patients may start with 25 mg once daily and gradually increase to three times daily. The suggested titration regimen is 25 mg at the start of dinner for two weeks, 25 mg at breakfast and dinner for two weeks, then 25 mg three times a day at each meal. Patients should remain on 25 mg three times a day for 4-8 weeks. The dose should then be increased to 50 mg three times a day for about three months. Hemoglobin A1c should be measured periodically to assess the effectiveness of the drug. If the response is inadequate, a dose of 100 mg three times a day may be considered. If no improvement in glycosylated hemoglobin is observed, a reduction in the dose should be considered. The usual maintenance dose is 50 mg three times a day.[1]

Should a patient experience hypoglycemia (e.g., when miglitol is used with a sulfonylurea), glucose, not sucrose (table sugar), should be used to correct this condition since miglitol will inhibit the breakdown and absorption of sucrose.

Miglitol is supplied as 25 mg, 50 mg, and 100 mg tablets.

Potential Advantages

Similar to acarbose, miglitol does not cause hypoglycemia, hyperinsulinemia, or weight gain. When used with sulfonylureas, alpha-glycosidase inhibitors enhance glycemic control as well as attenuate sulfonylurea-associated weight gain and postprandial serum insulin concentrations.[2] An unpublished 24-week study provided by the manufacturer suggests that miglitol is more potent than acarbose on a mg basis. Miglitol at 50 mg three times daily produces similar reduction in glycosylated hemoglobin as 100 mg three times daily of acarbose. An even greater reduction was achieved with miglitol 100 mg three times a day.[1]

Potential Disadvantages

Gastrointestinal side effects are common with alpha-glycosidase inhibitors. In U.S.-based placebo-controlled trials, the incidence of GI side effects compared to placebo were: flatulence (41.5% vs 12%), diarrhea (28.7% vs 10%), and abdominal pain (11.7% vs 4.7%). Flatulence is primarily caused by the gas production resulting from the metabolism of unabsorbed carbohydrates by the intestinal microflora. In these trials, the incidence of discontinuation due to adverse events was 12% compared to 7% for placebo. Low serum iron was reported in 4.3% of the patients treated with miglitol compared to 2.4% for placebo.[2] In contrast to acarbose, miglitol is a smaller molecule (molecular weight of 207 vs 646) and shows dose-dependent systemic absorption. A 25 mg dose is completely absorbed while a 100 mg dose is 50-70% absorbed.2 The significance of this systemic absorption is not known. However, since miglitol is excreted primarily by the kidneys, its use in patients with renal impairment is not recommended. Miglitol is less effective than sulfonylureas in reducing glycosylated hemoglobulin. Reduction in glycosylated hemoglobulin is generally 25-50% less than that achieved with a sulfonylurea.[3,4] Miglitol is contraindicated in patients with inflammatory bowel disease, colonic ulceration, predisposition to intestinal obstruction, and chronic intestinal disease associated with digestion or absorption disorder.[1]

Comments

Alpha glucosidase inhibitors, such as acarbose and miglitol, inhibit membrane-bounded intestinal brush border alpha glucoside hydrolase enzymes. This action inhibits the breakdown of dietary polysaccarides to absorbable monosaccarides resulting in a blunting of postprandial glucose excursion. Several placebo-controlled trials have demonstrated that miglitol significantly reduces glycosylated hemoglobin and one-hour postprandial glucose levels compared to placebo.[1] The placebo-subtracted reduction of HbA1c ranged from 0.26% to 0.81% with doses of 25 mg to 100 mg three times a day with a study duration of three months to one year. One-hour, placebo-subtracted, postprandial glucose levels were reduced by 28 to 87 mg/dL. Compared to a sulfonyurea, miglitol was about 25-50% less effective in terms of reduction in HbA1c.[3,4] The addition of miglitol to a sulfonylurea resulted in additional reduction of HbA1c by 0.30 to 0.82%.[2] Two recently published one-year studies reported that miglitol was efficacious in Hispanics as well as African-Americans with type 2 diabetes.[5,6] Gastrointestinal side effects and frequent dosing (with each meal) are potential limitations for adherence with dosing regimens. Efficacy has also been reported in the elderly and also in type 2 patients treated with insulin.[4,7]

The potential advantages of alpha glucosidase inhibitors are lack of hypoglycemia, hyperinsulinemia, and lack of weight gain. Unpublished data suggest that miglitol may be more potent than acarbose. The clinical relevance of significant systemic absorption of miglitol is not known.

The daily wholesale cost ranges from $1.50 to $2 per day and is similar to that of acarbose.

Clinical Implications

Miglitol provides another option for the management of diabetes mellitus. These drugs may be considered for monotherapy in newly diagnosed mild type 2 diabetics and as adjunctive therapy with oral agents or insulin in type 2 patients, especially where weight gain or hyperinsulinemia are problematic. ■

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Antibiotic Resistance in Uncomplicated UTIs

Source: *Gupta K, et al. JAMA 1999;281:736-738.*

Prevalence and trends in antimicrobial resistance among the narrow spectrum of organisms responsible for acute uncomplicated cystitis were examined in this study from Washington state. Included were those patients with a positive urine culture (≥ 103 CFUs/mL) from a population of women, ages 18-50, in a health maintenance organization, who sought treatment at an outpatient clinic or ED. The study spanned five years, controlled for seasonal variation, and included 4342 urine isolates. Selected chart review confirmed that more than 95% of the study population included visits for uncomplicated cystitis.

The distribution of causative uropathogens was not surprising: *Escherichia coli*, 86%; *Staphylococcus saprophyticus*, 4%; *Proteus* species, 3%; *Klebsiella* species, 3%; *Enterobacter* species, 1.4%; *Citrobacter* species, 0.8%; *Enterococcus*, species 0.5%; and others, 1.3%. More than 20% of *E. coli* isolates were resistant to ampicillin, cephalothin, and sulfamethoxazole. Alarmingly, resistance among *E. coli* to trimethoprim/sulfamethoxazole doubled over the course of the study, rising from 9% to 18%. A significant increasing linear trend in resistance was found for all isolates to ampicillin, cephalothin, trimethoprim, and trimethoprim/sulfamethoxazole. Ciprofloxacin, nitrofurantoin, and gentamicin faired the best with regard to limited resistance. Recognizing that in vitro resistance may not directly translate to altered patient outcome, Gupta and colleagues concluded that the days may be numbered when trimethoprim/sulfamethoxazole should be used for empiric therapy for uncomplicated UTI.

Comment by Richard A. Harrigan, MD, FAAEM, FACEP

And so, more evidence of emerging antimicrobial resistance is published; important news, but is it time to stop using trimethoprim/sulfamethoxazole as the first-line antibiotic for uncomplicated UTI? Not yet. As Gupta et al caution, this is not a clinical outcomes study, but rather a report of a microbiological trend. Moreover, trimethoprim/sulfamethoxazole is concentrated in the urine, achieving higher concentrations than in the blood;1 thus, the pathogen might still be eradicated. Finally, a treatment failure in cases of uncomplicated UTI generally does not result in life-threatening illness, but, rather, persistence of symptoms. Thus, treatment failures should make us think not only of an alternative diagnosis, but also of the anitmicrobial resistance issue. ■

Reference

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Pravastatin Reduces Strokes

Source: *Plehn JF, et al. Circulation 1999;99:216-223.*

The relationship between cholesterol levels and stroke is controversial. The Cholesterol and Recurrent Events (CARE) trial is the first sec-

ondary prevention trial of "statins" after myocardial infarction (MI) that included stroke as a secondary end point. The 4159 patients in this study had average cholesterol levels (mean 209 mg/dL) and LDL levels (139 mg/dL). The primary end point of reduction in cardiac events was reduced 24% in the pravastatin vs. placebo patients. Also, strokes were reduced 32%. The patients were well matched and antiplatelet drug use was 85% in each group. Pravastatin lowered cholesterol 20%, LDL 32%, and triglycerides 14%; HDL was raised 5%. Strokes or TIAs occurred in 92 patients on pravastatin and 124 on placebo—a 27% reduction. There was no increase in intracerebral hemorrhage on pravastatin and no difference in fatal strokes (6 total). Subgroup analysis showed equally beneficial effects for groups based on age, sex, hypertension, smoking, left ventricular ejection fraction, and baseline lipid levels. Plehn and colleagues conclude that pravastatin reduced strokes/TIAs in postmyocardial infarction patients with average cholesterol levels despite concomitant use of antiplatelet agents by most of the patients.

Comment by Michael H. Crawford, MD

Stroke following MI is mainly cardioembolic in the early recovery phase (< 3 months) but is more ischemic later due to the relationship between coronary and cerebrovascular disease. The CARE patients were randomized from three to 20 months (mean 10) postinfarction and only 15% of the strokes were considered embolic. However, the benefit was observed in all types of strokes. The reduction in stroke/TIA rates paralleled the reduction in coronary events, but the point where the event curves separated between the groups was different: 3.5 years for stroke and about 1.5 years for coronary events. Similar results were seen with the 4S secondary prevention study, with a 30% stroke reduction starting after three years. Although the percent reduction is impressive, the P value was not robust at 0.02, but considering that 85% of patients were on antiplatelet drugs, the results are noteworthy.

The mechanism of pravastatin's benefit is unknown, but a relationship was noted with serum LDL levels; the higher the level, the more the benefit. Stroke reduction was a nonsignificant 14%, with LDL less than 125 mg/dL and 54% with LDL more than 150 mg/dL ($P < 0.001$). However, in the West of Scotland primary prevention trial of patients with similar lipid levels, but no prior MI, stroke reduction was an insignificant 11% despite similar reductions in cholesterol on pravastatin treatment. Thus, the mechanism of stroke reduction may involve effects of the statins beyond lipid lowering. Also, the West of Scotland study suggests that the results of this trial in postmyocardial infarction patients may not be transferable to patients with less disease. Whatever the mechanism, it appears that stroke reduction should be another expected benefit of lowering LDL cholesterol in postmyocardial infarction patients with LDL more than 130 mg/dL. ■

Review of Herb-Drug Interactions

Source: *Miller LG. Arch Intern Med 1998;158:2200-2211.*

Herbal medicinals are being used by an increasing number of patients who typically do not advise their clinicians of current use. Known or potential drug-herb interactions exist and should be screened for. For example, feverfew, garlic, ginkgo, ginger, and ginseng may alter bleeding time and should not be used concomitantly with warfarin sodium. Ginseng should not be used with estrogens or corticosteroids because of possible additive effects. Valerian should not be used with barbiturates because excessive sedation may occur. Kava when used with alprazolam has resulted in coma.

Comment by John La Puma, MD, FACP

In this unusual review article, Miller catalogs commonly used herbal medicinals and associated drug-herb interactions, both theoretical and actual. She first briefly recounts evidence for the effectiveness of chamomile, echinacea, feverfew, garlic, ginger, ginkgo, ginseng, saw palmetto, St. John's wort, and valerian. She then identifies drugs with a narrow therapeutic window and several herbal interactions with them. Finally, she lists more drugs, herbs, and minerals "with known or potential drug-herb interactions with commonly used herbal medicinals."

This article reads like an impatient life sciences catalog: Miller has a lot of information and wants to get it all out. But it's often difficult to differentiate between basic science and clinical cases without referring to the 171 references, which are largely bench laboratory observations and single case reports. ■

Dr. La Puma is Adjunct Professor of Nutrition, Kendall College, Director, C.H.E.F. Clinic, C.H.E.F. Skills Research, Alexian Brothers Medical Center, Elk Grove, IL.

Sustained Release Bupropion, a Nicotine Patch, or Both for Smoking Cessation

Source: *Jorenby DE, et al. N Engl J Med 1999;340:685-691.*

Among the 20 million smokers who attempt cessation each year, more than 90% fail to maintain abstinence for longer than one year. Even in patients who use nicotine patches or gum, only 20-30% will remain nonsmokers long term. Seven-week courses of bupropion have demonstrated as much as 23% efficacy at 12 months for smoking cessation. In this placebo-controlled study, Jorenby and colleagues compared sustained release bupropion (n = 244), nicotine patch (n = 244), and the combination of the two (n = 245).

Bupropion was dosed at 150 mg for the first three days, followed by 150 mg bid for nine weeks; nicotine patches were dosed as 21 mg daily for six weeks, followed by 14 mg daily for one week, then 7 mg daily for one week.

Successful abstinence at one year was achieved by 35.5% of the combination therapy group, compared with 30.3% in the bupropion alone group, and 16.4% in the nicotine patch alone group.

Weight gain, a daunting deterrent to cessation for many smokers, occurred in all groups but was least in the combination treatment group (1.1 kg over 7 weeks). Adverse events caused medication discontinuation in less than 10% of subjects.

In this trial, the combination of bupropion with nicotine patches demonstrated a trend toward greater efficacy than bupropion alone, with less weight gain at seven weeks. ■

Echinate Purpurea on the Incidence and Severity of Colds and Respiratory Infections

Source: *Grimm W, Muller H. Am J Med 1999;106:138-143.*

Up until the advent of antibiotics, echinate was the most prominently sold American medical plant in the United States. Echinate-related products remain extremely popular in Europe, particularly in Germany. Echinate products have been used to treat chronic arthritis, cancer, Candida infection, chronic fatigue syndrome, and chronic pelvic infections. The current study examined the efficacy of Echinate purpurea fluid extract on colds and respiratory infections.

Adults (n = 109) were enrolled for an eight-week, placebo-controlled treatment period during which they received either 4 mL placebo juice twice daily or fluid extract of Echinate purpurea. Each subject had a history of at least four respiratory infections in the previous year. Primary outcome measures were the incidence and severity of colds and respiratory infections.

During the eight-week study period, there were no significant differences in incidence, severity, or duration of respiratory infections. Adverse events trended toward greater frequency in the Echinate group, as did treatment dropouts, but adversities were mild and reversible. So, the drug commission of German physicians recommends against the use of Echinate as an immunostimulator pending further data. ■

Long-term Efficacy and Tolerability of Sibutramine

Source: *Apfelbaum M, et al. Am J Med 1999;106:179-184.*

Although low-calorie diets (< 800 calories daily) have proven beneficial over the short term, maintenance of weight loss remains problematic. There have been few trials of pharmacotherapy combined with a low-calorie diet. The current study is a 12-month, double-blind trial of sibutramine in addition to a very low calorie diet for obesity.

Study subjects (n = 160) were required to have a baseline body mass index greater than 30. After a four-week, low-calorie diet, subjects were given sibutramine 10 mg daily, and their diet was changed to a reduced calorie intake calculated to be 20-30% less than their pre-study diet. Subjects were followed monthly for one year.

The placebo recipients gained an average of 0.5 kg over 12 months, compared with a 5.2 kg loss in recipients of sibutramine. Also, sibutramine treatment was associated with favorable changes in triglyceride and HDL levels when compared with placebo. Sibutramine treatment was associated with greater likelihood of maintaining more than 50% of initial weight loss than placebo. Withdrawal from treatment was infrequent (4%) but twice as common among placebo recipients. Apfelbaum and colleagues conclude that sibutramine is effective in main-

taining, and even enhancing, weight loss after a low-calorie diet. ■

Weight Control in Obese Subjects Treated with Orlistat

Source: *Davidson MH, et al. JAMA 1999;281:235-242.*

Traditional nonpharmacological methods for weight reduction based upon diet and exercise show poor long-term performance. Since unchecked obesity contributes to consequences of diabetes, cardiovascular disease, and overall mortality, the need for more efficacious tools is substantial.

Orlistat (Xenical) is an agent that blocks activity of pancreatic and gastric lipases, resulting in about a one-third reduction in absorption of ingested fat. This randomized, double-blind, placebo-controlled study (n = 892) prospectively evaluated patients receiving orlistat, 120 mg three times daily for one year; a second year of the study randomized subjects to 60 mg or 120 mg orlistat three times daily. A controlled-energy diet was used for all study subjects.

At the end of the first year, subjects receiving orlistat had lost an average of 8.76 kg, compared to 5.81 kg in the placebo group; during the second year of the trial, persons who continued either dose of orlistat regained less weight than those on placebo, but the higher dose had a significantly better maintenance effect. Blood pressure, lipids, glucose, and insulin were favorably affected in the active treatment group when compared with placebo. Adverse events, the most common of which were gastrointestinal, were similar in placebo and treatment groups. The withdrawal from treatment rate was actually higher in the placebo group than in the active treatment group in the first year, but both groups had equal withdrawal rates in the second year.

Orlistat can produce sustained weight loss, as well as improvements in lipids and insulin, and is well tolerated by most patients. ■

The Therapeutics and Drugs Briefs were written by Louis Kuritzky, MD, Courtesy Clinical Assistant Professor, University of Florida, Gainesville.

CME questions

Testing form inserted in the July 1999 issue

11. With regard to *Escherichia coli* as a uropathogen, which of the following antibiotics has been linked to increasing resistance in uncomplicated UTI?
a. Trimethoprim/sulfamethoxazole
b. Ciprofloxacin
c. Nitrofurantoin
d. Gentamicin

12. Which of the following statements is true regarding Preven?
a. Preven may act by inhibiting ovulation.
b. Preven may alter tubal transport of sperm and/or ova.
c. Preven may inhibit implantation.
d. All of the above

13. Which is *not* true about miglitol?
a. It does not cause hypoglycemia when used as monotherapy.
b. If used in combination therapy, sucrose should not be used to treat hypoglycemia.
c. It does not need to be titrated.
d. It may attenuate sulfonylurea associated weight gain.

14. The CARE study results showed that Pravastatin reduced the rate of strokes by:
a. 10%.
b. 26%.
c. 32%.
d. 43%.
e. 48%.

15. Which herbal supplement has not been shown to alter bleeding when used concomitantly with warfarin sodium?
a. Feverfew
b. Garlic
c. Kava
d. Ginseng
e. Ginger

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