

CLINICAL CAPSULES

BMI Risk: 19th vs. 20th Century

Experts should periodically revise the risk limits for body mass index among ethnically similar populations, as well as among different populations and ethnicities, to keep abreast of changing height, weight, and nutritional intake, reported R. Max Henderson of the University of Chicago.

Among 9,509 white Civil War veterans of the Union Army, the healthiest range of body mass index (BMI) was approximately 2 kg/m² below that for white men studied in the first National Health and Nu-

trition Examination Survey (NHANES I) (Econ. Hum. Biol. 2005;3:339-66).

Union Army veterans with BMIs in the range of 20-26 kg/m² had the lowest risk of death, whereas NHANES I subjects with BMIs in the range of 22-28 kg/m² had the lowest risk of death. The upward shift in BMI risk cut-off points may be explained by the theory that Union Army veterans were underweight and lived in unhealthy environments with poorer nutrition in their formative years, compared with NHANES I subjects a century later.

Anger, Eating Disorders, and College

Anger management may help in treating eating disorders in obese, college-age students of both sexes, reported Jeanne L. Edman, Ph.D., of Cosumnes River College, Sacramento, Calif.

Compared with the 88 male subjects, the 102 female subjects reported higher levels of eating disorders, body dissatisfaction, and self-dissatisfaction and more frequent dieting, while males reported higher activity levels (Eat Behav. 2005; 6:308-17).

Multiple regression analyses were used to determine which variables best predicted subjects' drive for thinness and in-

teroceptive awareness. Anger discomfort and dieting significantly predicted drive for thinness in males, accounting for 46% of the variance.

Among females, anger discomfort and self-dissatisfaction were significant predictors of the drive for thinness, accounting for 47% of the variance. The only predictor of interoceptive awareness in both males and females was anger discomfort, accounting for 28% and 36% of the variance, respectively.

Weight Loss in Fibromyalgia

Behavioral weight loss treatment benefited overweight and obese women with fibromyalgia syndrome, reported Jennifer R. Shapiro, Ph.D., and her colleagues at the University of Albany, State University of New York.

In a 20-week pilot study, 31 overweight or obese Caucasian women with fibromyalgia syndrome lost an average of 9.2 lbs, or more than 4% of their initial body weight. Most who lost weight shed at least 5% of their initial body weight (J. Psychosomatic Res. 2005;59:275-82).

The intervention entailed small group meetings every week for 1.5 hours, along with use of guidelines for diet and exercise.

Weight loss treatment at week 20 was significantly associated with improvements in depression, anxiety, pain, body concerns, support, and quality of life, the investigators said. "The amount of weight loss, as opposed to both absolute weight and treatment participation in general, is a better predictor of pain improvement," the researchers said.

Pregnancy After Bariatric Surgery

Women who have undergone laparoscopic adjustable gastric banding have similar pregnancy outcomes as women in their general community, and they have better outcomes than severely obese women, reported John B. Dixon, MBBS, Ph.D., of the Monash Medical School, Melbourne, Australia.

Dr. Dixon and his associates prospectively examined 79 consecutive pregnancies in women who had had laparoscopic adjustable gastric banding (LAGB) and compared the data with these patients' previous pre-LAGB pregnancies (n = 40); pregnancies in 79 matched, severely obese subjects; and community outcomes in Victoria (n = 61,000).

In LAGB subjects, the mean maternal weight gain was 9.6 kg, versus 14.4 kg for the 40 pre-LAGB pregnancies and 15.5 kg for the matched obese controls. Birth weights were similar after LAGB (3,397 g) and before LAGB (3,350 g), and both were within the normal range of community birth weights (Obstet. Gynecol. 2005; 106:965-72).

The rate of pregnancy-induced hypertension was similar after LAGB and in the community (10% and 10%-13%, respectively), but was much higher in pre-LAGB pregnancies (45%) and in matched, obese controls (38%).

Rates of gestational diabetes were nearly the same in women who underwent LAGB (6.3%) and in the community (5.5%), but were 19% in the obese controls and 15% in pre-LAGB pregnancies. Neonatal outcomes were also similar for LAGB subjects and the overall community.

—Kevin Foley

Levofloxacin (levofloxacin) is a registered trademark of Ortho-McNeil Pharmaceutical Inc.

Reference: 1. Breen J, Chandra R, Herbig S, Lo J, Appel L. Zmax: a novel microsphere-based azithromycin dosage form. Poster for presentation at the American Association of Pharmaceutical Scientists: November 6-10, 2005; Nashville, Tenn.

Zmax™
(azithromycin extended release) for oral suspension
BRIEF SUMMARY

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Zmax™ and other antibacterial drugs, Zmax should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

INDICATIONS AND USAGE

Zmax is indicated for the treatment of patients with mild-to-moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. (Please see **DOSAGE AND ADMINISTRATION** for specific dosing recommendations.)

Adults:

Acute bacterial sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*.

Community-acquired pneumonia due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* in patients appropriate for oral therapy.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Zmax and other antibacterial drugs, Zmax should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to Zmax. Therapy with Zmax may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

CONTRAINDICATIONS

Zmax is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, or any macrolide or ketolide antibiotic.

WARNINGS

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy using other formulations. Although rare, fatalities have been reported. (See **CONTRAINDICATIONS**.) Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen has not been determined.

If an allergic reaction occurs, appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General: Because azithromycin is principally excreted via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. Due to the limited data in subjects with GFR <10 mL/min, caution should be exercised when prescribing azithromycin in these patients.

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes*, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out at increased risk for prolonged cardiac repolarization.

Prescribing Zmax in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients: Patients should be instructed to take Zmax on an empty stomach (at least 1 hour before or 2 hours following a meal).

The patient should be instructed to contact a physician immediately if any signs of an allergic reaction occur. Patients who vomit within the first hour should contact their health care provider about further treatment.

Keep bottle tightly closed. Store at room temperature. Use within 12 hours of constitution. Shake bottle well before use. The entire contents of the bottle should be consumed.

Patients should be advised that Zmax may be taken without regard to antacids containing magnesium hydroxide and/or aluminum hydroxide.

Patients should be counseled that antibacterial drugs including Zmax should only be used to treat bacterial infections. They do not treat viral infections (eg, the common cold). Not taking the complete prescribed dose may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Zmax or other antibacterial drugs in the future.

Drug Interactions: Co-administration of nelfinavir at steady-state with a single dose of azithromycin (2 x 600 mg tablets) results in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted. (See **ADVERSE REACTIONS**.)

Azithromycin did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

Drug interaction studies were performed with azithromycin and other drugs likely to be co-administered. When used in therapeutic doses, azithromycin had a modest effect on the pharmacokinetics of atorvastatin, carbamazepine, ceftriaxone, didanosine, efavirenz, fluconazole, indinavir, midazolam, rifabutin, sildenafil, theophylline (intravenous and oral), triazolam, trimethoprim/sulfamethoxazole, or zidovudine. Co-administration with efavirenz or fluconazole had a modest effect on the pharmacokinetics of azithromycin. No dosage adjustment of either drug is recommended when azithromycin is co-administered with any of the above agents.

Interactions with the drugs listed below have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products. Until further data are developed regarding drug interactions with azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised:

Digoxin—elevated digoxin concentrations

Ergotamine or dihydroergotamine—acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia

Cyclosporine, hexobarbital, and phenytoin concentrations

Laboratory Test Interactions: There are no reported laboratory test interactions.

Repeat Treatment: Studies evaluating the use of repeated courses of Zmax have not been conducted.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. No evidence of impaired fertility due to azithromycin was found in rats given daily doses up to 10 mg/kg (approximately 0.05 times the single 2.0 g oral adult human dose on a mg/m² basis).

Pregnancy: Teratogenic Effects. Pregnancy Category B. Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose concentrations (ie, 200 mg/kg/day). These daily doses in rats and mice, based on mg/m², are estimated to be approximately equivalent to one or one-half of, respectively, the single adult oral dose of 2.0 g. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman.

Geriatric Use: Data collected from the azithromycin capsule and tablet formulations indicate that a dosage adjustment does not appear to be necessary for older patients with normal renal function (for their age) and hepatic function receiving treatment with Zmax.

In clinical trials of Zmax, 16.6% of subjects were at least 65 years of age (214/1292) and 4.6% of subjects (59/1292) were at least 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Zmax 2.0 g oral suspension contains 148 mg of sodium.

ADVERSE REACTIONS

In controlled Phase 3 clinical trials with Zmax, the majority of the reported treatment-related adverse reactions were gastrointestinal in nature and mild to moderate in severity.

Overall, the most common treatment-related adverse reactions in adult subjects receiving a single 2.0 g dose of Zmax were diarrhea/loose stools (11.6%), nausea (3.9%), abdominal pain (2.7%), headache (1.3%), and vomiting (1.1%). The incidence of treatment-related gastrointestinal adverse reactions was 17.2% for Zmax and 9.7% for pooled comparators.

No other treatment-related adverse events occurred in subjects on Zmax with a frequency of ≥1%.

Treatment-related adverse reactions following Zmax treatment that occurred with a frequency of <1% included the following: **Cardiovascular:** palpitations, chest pain. **Gastrointestinal:** constipation, dyspepsia, flatulence, gastritis, oral moniliasis, loose stools. **Genitourinary:** vaginitis. **Nervous System:** dizziness, vertigo. **General:** asthenia. **Allergic:** rash, pruritus, urticaria. **Special Senses:** taste perversion.

Laboratory Abnormalities: In subjects with normal baseline values, the following clinically significant laboratory abnormalities (irrespective of drug relationship) were reported in Zmax clinical trials:

—with an incidence of ≥1%: reduced lymphocytes and increased eosinophils; reduced bicarbonate

—with an incidence of <1%: leukopenia, neutropenia, elevated bilirubin, AST, ALT, BUN, creatinine, alterations in potassium

Where follow-up was provided, changes in laboratory tests appeared to be reversible.

Post-Marketing Experience with Azithromycin Immediate Release

Adverse events reported with azithromycin during the post-marketing period for which a causal relationship may not be established include:

Allergic: arthralgia, edema, urticaria and angioedema. **Cardiovascular:** palpitations and arrhythmias including ventricular tachycardia and hypotension. There have been rare reports of QT prolongation and *torsades de pointes*. **Gastrointestinal:** anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis, pancreatitis, oral candidiasis and rare reports of tongue discoloration. **General:** asthenia, paresthesia, fatigue, malaise and anaphylaxis (rarely fatal). **Genitourinary:** interstitial nephritis, acute renal failure, moniliasis and vaginitis. **Hematopoietic:** thrombocytopenia, mild neutropenia. **Liver/Biliary:** abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, some of which have resulted in death. **Nervous System:** convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation and syncope. **Psychiatric:** aggressive reaction and anxiety. **Skin/Appendages:** pruritus, rash, photosensitivity, rarely serious skin reactions including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. **Special Senses:** hearing disturbances including hearing loss, deafness and/or tinnitus and rare reports of taste perversion.

DOSAGE AND ADMINISTRATION (See INDICATIONS AND USAGE.)

Zmax should be taken as a single 2.0 g dose. Zmax provides a full course of antibacterial therapy in a single oral dose. It is recommended that Zmax be taken on an empty stomach (at least 1 hour before or 2 hours following a meal).

In the Phase 3 program, no patient vomited within 5 minutes of dosing Zmax. In the event that a patient vomits within 5 minutes of administration, the health care provider should consider additional antibiotic treatment since there would be minimal absorption of azithromycin. Since insufficient data exist on absorption of azithromycin if a patient vomits between 5 and 60 minutes following administration, alternative therapy should be considered. Neither a second dose of Zmax nor alternative treatment is warranted if vomiting occurs ≥60 minutes following administration, in patients with normal gastric emptying.

Instructions for Pharmacist: Constitute with 60 mL of water and replace cap. Shake bottle well before dispensing.

Special Populations:

Renal Insufficiency: No dosage adjustment is recommended for patients with renal impairment (GFR 10-80 mL/min). Caution should be exercised when Zmax is administered to patients with end-stage renal disease (GFR <10 mL/min).

Hepatic Insufficiency: The pharmacokinetics of azithromycin in patients with hepatic impairment have not been established. No dose adjustment recommendations can be made in patients with impaired hepatic function.

For more detailed professional information please refer to the full prescribing information.

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