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INSIDE

FDA Issues Warning on Cisapride

By William T. Elliott, MD, FACP

The fda has issued a warning regarding "serious cardiac events" associated with the drug **cisapride** (**Propulsid-Janssen**) and has required the drug manufacturer to include a boxed warning on the package insert. Cisapride, a pro-motility agent, is used to treat **gastroesophageal reflux disease**. Janssen has issued a "Dr. Letter" warning about the incidence of cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation. Through May 1999, more than 270 cases of cardiac arrhythmias occurred spontaneously, including 70 fatalities. Almost all these cases occurred in patients with known risk factors. Coadministration of drugs that inhibit cytochrome P450 3A4 enzymes is a risk factor as is pre-existing cardiac disease. A partial list of drugs that should not be given with cisapride include: macrolides antibiotics (such as erythromycin, clarithromycin, and troleandomycin), antifungals (such as fluconazole, itraconazole, and ketoconazole), certain protease inhibitors, and phenothiazines. Other drugs that may cause potential interaction include class IA (quiniedine, procainamide) and class III (solatol) antiarrhythmics, tricyclic antidepressants, certain other antidepressants (such as nefazadone and maprotiline), certain antipsychotic medications, and other agents (such as bepridil, sparfloxacin, and grapefruit juice). Janssen is recommending that a 12-lead EKG be performed prior to administration of cisapride and that the drug should not be given if the QTc interval exceeds 450 ms†. Serum electrolytes and serum and creatinine tests should be performed prior to administration of cisapride.

Treatment for ***Helicobacter pylori*** may be getting more simple. Italian researchers have shown that a six-day course of treatment with three drugs has a 90% cure rate. The regimen includes ranitidine bismuth critrate, clarithromycin, and tinidazole all administered three times a day. This combination was safe and well-tolerated by patients. Cure rate was assessed by urea breath test. The study compared the six-day regimen to the same drugs used in a seven-day regimen. Adding an extra day of treatment only increased the cure rate to 92% (*Dig Dis Sci* 1999;44:2386-2389).

In a merger that will form the largest drug company in the world, British pharmaceutical giants **Glaxo Wellcome** and **SmithKline Beecham** announced in January that they are joining forces. The new company will be known as **Glaxo SmithKline**, and have a net worth of nearly $190 billion. This is the second time

the two companies have attempted to merge; however, talks broke down two years ago without an agreement. The new company will have its headquarters in London and its new operational base in the United States. Glaxo's top products include **sumatriptan** and antivirals including HIV drugs. SmithKline's top products include the antibiotic **amoxicillin/clavulantate** (**Augmentin**) and the antidepressant **paroxetine** (**Paxil**).

Congress is getting serious about providing coverage for prescription drugs for **Medicare** beneficiaries. House Speaker Dennis Hastert (R-IL) has asked Republican members of the House Ways and Means Committee to begin working on a plan, an important first-step in what is sure to be a contentious bipartisan process, especially during an election year. House members are looking at a number of options, including a plan to provide coverage outside of Medicare. Both the House Ways and Means and Commerce Committees share jurisdiction over Medicare part B, which provides coverage for outpatient services. President Clinton has made it clear that the **Medicare prescription drug plan** along with a **patient Bill of Rights** are two of his primary objectives for his last year in office.

There is good and bad news for practitioners of alternative therapies. First, the bad news: Popular over-the-counter **antidepressant St. John's wort** is increasingly being associated with photo-toxic reactions. In a recent study of the active ingredient, hypericin, given orally or intravenously for eight weeks to HIV-positive patients, 11 out of 23 patients developed severe cutaneous phototoxicity (*Ann Int Med* 1999;130:510-514). St. John's wort has also been associated with reduced absorption of digoxin, which may lead to a 30% reduction in serum levels of the drug after 10 days of combined therapy (*Clin Pharm Ther* 1999;66:338-345). **Vitamin E** also appears to be a bust in preventing cardiovascular disease. As part of the HOPE study, vitamin E 400 IU daily or placebo was randomly given to nearly 10,000 patients at high risk for cardiovascular disease. Throughout the 4.5 years of the study treatment, vitamin E had no effect on cardiovascular outcomes (*N Engl J Med* 2000;342:154-160). The good news: **Chondroitin sulfate**, available over-the-counter and commonly used for the treatment of osteoarthritis, may be beneficial in this role. A meta-analysis of seven randomized trials totaling 372 patients treated for at least three months showed that patients taking chondroitin sulfate exhibited reduction in pain and a reduction in NSAID use or analgesic consumption compared to those taking placebo (*J Rheum* 2000;27:205-211).

The link between **hormone replacement therapy** (**HRT**) and **breast cancer** has been one of the most contentious issues in medicine during the last 20 years. A recent study is sure to cloud the issue even more with the finding that HRT regimens containing estrogen and progesterone are more likely to increase breast cancer risk than estrogen alone. The data come from follow-up of the **Breast Cancer Detection Demonstration Project** that was conducted from 1973 to 1980. The relative risk of breast cancer increased by 0.01 with each year estrogen alone was used and by 0.08 with each year of progesterone use. The findings, however, are complicated by the fact that estrogen alone was associated with an increased risk for breast cancer in lean women but not in heavy women. The authors conclude that the risks and benefits of HRT should be discussed in the context of the type of hormone replacement regimen and the individual characteristics of the woman, such as body mass index (*JAMA* 2000;283:485-491).

Two separate case reports link the new hypoglycemic agent **rosiglitazone** (**Avandia-SmithKline Beecham**) to severe hepatotoxicity. The case reports, from two different hospitals in Pennsylvania, described diabetic men in their 60s who developed evidence of severe hepatocellular injury within 2-3 weeks of starting rosiglitazone. There was no other obvious cause of hepatotoxicity, and both patients recovered after the drug was discontinued (*Ann Intern Med* 2000;132:118-124). These case reports are important because rosiglitazone is structurally similar to troglitazone, a drug that has been associated with liver failure. In early clinical trials, rosiglitazone was not associated with liver toxicity.

The drug manufacturer, **SmithKline Beecham**, had independent experts review at least one of these cases, and concluded that the liver injury was due to ischemia and not drug-related injury. Their findings were presented in a letter to the editor in the same issue of the *Annals of Internal Medicine* (*Ann Intern Med* 2000;132:164).

Montelukast (**Singulair-Merck**), an oral leukotriene receptor antagonist, has better long-term efficacy than the long-acting inhaled beta-agonist **salmeterol** (**Serevent-Glaxo**) in preventing exercise-induced bronchoconstriction. One hundred ninety-one adults with exercise-induced asthma were randomized to treatment with montelukast, 10 mg once a day, or salmeterol 50 mcg inhaled twice daily.

The bronchoprotective effect of montelukast was maintained throughout the eight weeks of study. In contrast, significant loss of bronchoprotection at weeks 4 and 8 was seen with salmeterol. The authors conclude that long-term administration of montelukast provided consistent inhibition of exercise-induced bronchoconstriction without the development of tolerance (*Ann Intern Med* 2000;132:97-104). ■

Moxifloxacin Tablets (Avelox-Bayer)

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

In december 1999, the fda approved moxifloxacin, a new, once-daily quinolone for the treatment of respiratory tract infections. The new antibacterial agent will be marketed by the Bayer Corporation as Avelox. Moxifloxacin is a 8-methoxyfluoroquinolone with antibacterial activity against gram-positive, gram-negative, and anaerobic bacteria with good activity against common respiratory pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Moraxella catarrhalis*.

Indications

Moxifloxacin is approved for the treatment of adults (≥ 18 years of age) with the following infections caused by susceptible strains of microorganisms:[1] acute bacterial sinusitis caused by *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*; acute bacterial exacerbation of chronic bronchitis caused by *S. pneumoniae*, *H. influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, or *M. catarrhalis*; community-acquired pneumonia (mild to moderate severity) caused by *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, or *M. catarrhalis*.

Dosage

The recommended dose is 400 mg once daily. The duration is five days for acute bacterial exacerbation of chronic bronchitis and 10 days for acute bacterial sinusitis and community-acquired pneumoniae. The tablets may be taken with a liberal amount of fluid without regard to meals. The dose should be taken at least four hours before or eight hours after antacids (magnesium or aluminum based), sucralfate, didanosine buffered tablets or pediatric powder, and metal cations such as iron and zinc, including multivitamins.[1]

Dosage adjustment is not necessary in patients with renal insufficiency. However, moxifloxacin is not recommended in patients with moderate or severe hepatic insufficiency.[1]

Potential Advantages

In vitro data suggest that moxifloxacin is more active than sparfloxacin, levofloxacin, and ofloxacin against *S. pneumoniae* with intermediate resistance to penicillin.[2] These isolates were selected from blood cultures of patients with pneumococcal pneumonia. The MIC90 (0.25 mg/L) was one dilution lower than sparfloxacin, three dilutions lower than levofloxacin, and four dilutions slower than ofloxacin. As with other fluoroquinolones, moxifloxacin achieves good tissue levels. Concentrations three hours post-dose in respiratory tissue (e.g., bronchial mucosa, epithelial lining, alveolar macrophages) and sinus mucosa average at least 1.7 (range, 1.7-21.1) times that of plasma concentrations.[1] Gram-positive microorganisms resistant to other fluoroquinolones may be susceptible to moxifloxacin.[1] Moxifloxacin is approved for a five-day course for the acute exacerbation of chronic bronchitis compared to 7-10 days for other regimens.

Potential Disadvantages

Moxifloxacin has been reported to prolong the QT interval. The effect may increase with increasing concentration.[1] In clinical trials, the mean prolongation of QTc was 6 ± 26 msec. The drug should be avoided in patients receiving Class 1A or III antiarrhythmics, patients with proarrhythmic conditions, or patients taking drugs which can prolong QT intervals (e.g., erythromycin, cisapride).

Common side effects related to moxifloxacin include nausea (8%), diarrhea (6%), dizziness (3%), and headache, abdominal pain, and vomiting each at 2%.[1]

Comments

Moxifloxacin is a new 8-methoxyfluoroquinolone with a broad spectrum of activity including gram-negative and gram-positive anaerobes.[4,5] It is particularly effective against common respiratory pathogens including resistant *S. pneumoniae*. The efficacy and safety of moxifloxacin in these infections were based on several randomized, controlled, double-blind, comparative trials. Moxifloxacin (400 mg daily for 5 days) was compared to clarithromycin (500 mg twice daily for 10 days) for the treatment of acute bacterial exacerbation of chronic bronchitis and (400 mg daily for 10 days) in clinically and radiologically documented community-acquired pneumonia.[1] In the chronic bronchitis trial, clinical success was comparable at 7-17 days post-therapy, 89% (n = 501). Similar results were reported for community pneumonia, 95% clinical success for moxifloxacin and clarithromycin (n = 382), and 89% for moxifloxacin compared to amoxicillin (1 g three times daily) (n = 362).[1,5] In a multinational study (n = 649), moxifloxacin (400 mg for 5 days) was comparable to clarithromycin (500 mg for 7 days) in acute exacerbation of chronic

bronchitis, although bacteriological success favored moxifloxacin.[3] However, bacteriological success was assessed in only 35% of the clinically evaluable patients. In the treatment of acute bacterial sinusitis, moxifloxacin (400 mg for 10 days) and cefuroxime axetil (250 mg twice daily for 10 days) were found to be comparable in clinical cure assessed 7-14 days post-therapy, 90% vs. 89%.[6]

Moxifloxacin is priced at $44 for a five-day course or $87 for a 10-day course.

Clinical Implications

Several new quinolones have been introduced to the market as "ideal agents" to treat various respiratory tract infections with particular focus activity against drug-resistant *S. pneumoniae*. Moxifloxacin is the fifth quinolone to be approved for treating various respiratory tract infections (others being levofloxacin, sparfloxacin, grepafloxacin, and trovafloxacin, with gatifloxacin to follow). None of the older agents has emerged as the "ideal agent." Sparfloxacin has been associated with photosensitivity and prolongation of QT intervals. Glaxo Wellcome has voluntarily withdrawn grepafloxacin from the market due to increased risk of torsade de pointes. The FDA has issued a health advisory to physicians concerning the risk of severe liver toxicity due to trovafloxacin. Levofloxacin, which may be less active against *S. pneumoniae*, is not associated with these toxicities and is recommended by some experts as a good choice for older patients with underlying disease.[9] Moxifloxacin carries the potential to prolong QT intervals, which will bear close watching.

Fluoroquinolones should be prescribed prudently. They should not be prescribed for respiratory syndromes when an antibiotic is not appropriate or in infections where other classes of antibiotics are more appropriate. The increased prevalence of *S. pneumoniae* with reduced susceptibility to fluoroquinolones has been seen in Canada as well as in other countries.[7,8] ■

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Aggrenox

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

Boehringer ingelheim pharmaceuticals has teamed two old staples—aspirin and dipyridamole—to create a new agent for the prevention of stroke in patients who have had a previous stroke or a transient ischemic attack (TIA). The company received FDA approval in November for aspirin and extended release dipyridamole, which will be marketed under the trade name Aggrenox. It joins aspirin, ticlopidine, and clopidogrel on the list of drugs that are used for stroke prevention.

Indications

Aggrenox is approved to reduce the risk of stroke in patients who have had transient ischemia of the brain or complete ischemic stroke due to thrombosis.

Dosage

The recommended dose is aspirin 25 mg and dipyridamole 200 mg (1 Aggrenox capsule) twice daily. Drug-food interaction has not been studied.[1]

Potential Advantages

The fixed combination product offers two different mechanisms of antiplatelet action. Aspirin is a cyclooxygenase inhibitor, while dipyridamole is believed to affect platelet aggregation by inhibiting phosphodiesterase.[2] Results from the two-year European Stroke Prevention Study (ESPS-2) of 6602 patients indicated that this fixed combination reduced the risk of stroke (fatal or nonfatal) by 37% compared to placebo. There was also a 16.3% reduction in stroke end points compared to dypyridamole alone and an 18.1% reduction over aspirin alone (50 mg/day).[6]

Potential Disadvantages

The frequency of common side effects include headache (38.2% vs 33.1% for aspirin only) and diarrhea (12.1% vs 6.6% for aspirin alone). These tend to diminish over time.[2] Aggrenox has been associated with a decline in hemoglobin of 0.25 g/dL, hematocrit of 0.75%, and erythrocyte count of $0.13 \times 106/mm^3$.[1]

Comments

The ESPS-2 trial is the first trial to demonstrate that a fixed combination of aspirin and dipyridamole is more effective than aspirin alone. However, the 50 mg daily

aspirin dose used in the trial was at the low end of the recommended dose range (50-325 mg). The results from previous trials of this combination have generally been unimpressive. After a review of randomized trials involving combinations of aspirin and dipyridamole, the Antiplatelet Trialists concluded that the difference between aspirin and dipyridamole and aspirin alone is likely to be smaller than the difference between antiplatelet and no antiplatelet treatment.[3,4] The ESPS-2 results, based on an intent-to-treat analysis, indicated that the fixed combination, compared to aspirin alone, reduced the risk of all strokes (22%, $P = 0.008$) and frequency of TIAs (24.4%, $P < 0.001$). However, no statistical difference was observed in combined endpoints of stroke or death, death from any cause, or myocardial infarction. The rates of myocardial infarction were, however, low in the study groups.[1] While therapy may lengthen the time to a subsequent stroke, it does not appear to affect the severity of the recurrent stroke.[5]

Aggrenox costs $2.95 per day, which is significantly more than aspirin and and generic dipyridamole (< $1.00). The manufacturer states in Aggrenox labeling that this product is not interchangeable with the individual components of aspirin and dipyridamole, although this claim does not seem to be backed up by scientific evidence.

Clinical Implications

Stroke is the third leading cause of death after heart disease and cancer, and is the leading cause of serious, long-term disability. About 730,000 people have a stroke each year and, of these, more than 80% are first attacks.[8] Risk factors for stroke include increasing age, male gender, hypertension, hyperlipidemia, diabetes, carotid artery disease, heart disease, tobacco, previous stroke, and transient ischemic attacks. Unless contraindicated, antiplatelet therapy is recommended for stroke prevention in persons with a history of transient ischemic attack or a previous thromboembolic stroke.

Aspirin has been the most frequently prescribed drug and is considered the standard. To balance effectiveness and tolerability, a lower dose of aspirin (50-325 mg) has been recommended.[7] Several newer products have been approved by the FDA on the basis of studies compared to aspirin. These include ticlopidine, clopidogrel, and the fixed combination of aspirin/dipyridamole, all of which have shown varying degrees of benefit over aspirin. It is not clear if one of these products would replace aspirin as the standard. There are currently no comparative trials among the newer products. ■

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New vs. Old Drugs for Hypertension

Source: *Hansson L, et al. Lancet 1999;354:1751-1756.*

Concern has been raised about the efficacy of newer antihypertensive agents for the prevention of cardiovascular morbidity and mortality in elderly patients. Thus, the results of the Swedish Trial in Older Patients with Hypertension-2 (STOP-HTN-2) study are of interest. From 312 centers in Sweden, 6614 elderly patients with hypertension (HTN) were randomized to conventional drugs (diuretics, beta blockers) or angiotensin-converting enzyme inhibitors (ACE1) or calcium antagonists. All the patients were older than 70 years of age (average 76) and two-thirds were women. Criteria for HTN were systolic blood pressure greater than 180 or diastolic greater than 105 mmHg or both. End points included stroke, myocardial infarction (MI), and cardiovascular death on an intent-to-treat basis. Blood pressure lowering was similar for the three groups, with an average 35/17 mmHg difference. Compliance at the last visit (24 months) was about 60% for all three groups and 46% were receiving more than one drug. Total adverse events were similar on the three treatments, with about one-quarter of patients experiencing at least one event. The most common side effect of conventional treatment was dyspnea (12%); ACE1 was cough (30%) and calcium antagonist was edema (26%). Cardiovascular death rates were similar in the three groups, as was the combined end point of stroke, MI, or cardiac death. However, fatal or nonfatal MIs were significantly less on ACE1 as compared to the calcium blocker group, as was congestive heart failure. Also, the results in diabetics were similar in the three groups.

Hansson and colleagues conclude that new and old antihypertensive agents were similarly effective in preventing cardiovascular events and death in elderly patients.

Comment by Michael H. Crawford, MD

After concerns were raised about the safety of calcium antagonists, this trial is reassuring that mortality was not higher in the calcium blocker group. That ACE1 would prevent heart failure more than calcium blockers is not surprising, given the action of the two drug classes. That ACE1 prevented MI more than calcium blockers is somewhat of a surprise, but consistent with the recently released HOPE study results. Interestingly, ACE1 did not perform better in diabetics despite theoretic advantages in such patients. Thus, ACE1 seems to hold a slight edge over calcium blockers, but only in the prevention of MI, not total mortality.

There has also been concern about the relative lack of efficacy of conventional therapy vs. newer agents in the prevention of cardiovascular events (both being effective for stroke prevention). However, this study shows equivalent efficacy. One reason for this may be that STOP-HTN-2 included patients with isolated systolic and diastolic HTN; newer drugs may be more effective for the former and conventional drugs for the latter, and cardiovascular events are more closely related to systolic HTN. Thus, on balance, the new and old drugs are equivalent, but a breakdown of the data along the lines indicated above would have been of interest. Also, combinations of drugs from the different classes were permitted to achieve blood pressure control, further complicating the analysis of drug classes and emphasizing the dominant role of adequate blood pressure control. The major message of this study is that blood pressure control is more important for preventing cardiovascular events in the elderly than how it is achieved. ■

Gabapentin vs. Propranolol for Essential Tremor

Source: *Gironell A, et al. Arch Neurol 1999;56:475-480.*

Essential tremor (et), one of the most common movement disorders, is characterized by tremor during the maintenance of posture and active movement. Although ET is commonly perceived to be benign, some patients suffer significant disability, and a larger number suffer substantial embarrassment.

The efficacy of primidone and B-adrenergic antagonists (e.g., propanolol) has been demonstrated, but many patients fail to respond, suffer intolerable side effects, or have contraindications to these medications. Previously, an open-label trial of gabapentin (Neurontin) suggested efficacy for ET,[1] but a double-blind, placebo-controlled study of adjunctive gabapentin in 20 patients found no improvement at a dose of 1800 mg/d compared to placebo.[2] The current study was undertaken in the neurology clinic in Barcelona, Spain. Sixteen patients with moderate to severe bilateral ET and no other neurological disorders were enrolled. Exclusion criteria included cardiac failure, asthma, peripheral vascular disease, diabetes mellitus, and active treatment with tremor-inducing or alleviating drugs.

After a two-week washout period, participants were given gabapentin 400 mg tid or propranolol 40 tid for two weeks in a double-blind, placebo-controlled, crossover trial. A one-week washout period occurred between treatments. Assessment measures included the Tremor Clinical Rating Scale (TCRS), accelerometric (neurophysiological) recordings done on the index finger of the most affected hand, and a 25-item self-reported disability scale. The TCRS includes four examinations rated on a 0-4 scale: 1) tremor of the hands, legs, head, and trunk; 2) motor task performance; 3) functional disability; and 4) subjective assessment by the patient. Analysis of variance (ANOVA) was used to test the effect of medication on tremor. Paired comparisons were analyzed by the test after control for inflation type I errors.

A statistically significant treatment effect was shown for gabapentin and propranolol compared to placebo with regard to tremor, motor task performance, functional disability, and subjective assessment by the patient on the TCRS. No statistical differences were found between gabapentin, propranolol, and placebo in terms of the accelerometric (neurophysiological) recordings; baseline variability may have been too great to see a treatment effect. In terms of the self-reported disability scale, neither drug was statistically better than placebo. All patients completed the study; no serious adverse events occurred. Limitations included a small sample size, fixed dosing (which limited meaningful titration), performing accelerometric recordings only on the most affected hand (potential bias, rather than an average of both hands), and a single study site (which limits generalization of the results).

Comment by Donald M. Hilty, MD

The origin of ET is unknown. A central mechanism involving the inferior olive is incriminated by most experimental data,[3] though some modulation may occur from the cerebellum, thalamus, motor cortex, and brainstem nuclei.[4] Gabapentin may work by increasing

gamma-aminobutyric acid (GABA) levels and reducing intracortical excitability. Gabapentin is extremely well tolerated, even in geriatric patients.[5] A large, multicenter trial is indicated to further study gabapentin for ET. ■

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Therapeutics and Drugs Briefs

Enoxaparin Superior to Unfractionated Heparin for Unstable Coronary Disease

Sources: *Antman EM, et al. Circulation 1999;100:1593-1601; Antman EM, et al. Circulation 1999;100:1602-1608.*

This pair of articles from the thrombolysis in Myocardial Infarction (TIMI) 11b investigators compares enoxaparin, a low-molecular-weight heparin (LMWH), to standard unfractionated heparin in patients hospitalized for unstable coronary artery disease. The TIMI trial enrolled patients presenting within 24 hours of chest pain onset and diagnosed with unstable angina or non-Q-wave myocardial infarction (MI). Patients undergoing urgent revascularization were excluded. Subjects were assigned in a double-blind fashion to receive either conventional therapy with unfractionated heparin (by weight-based bolus and infusion) for 3-8 days, or enoxaparin 30 mg infusion followed by a 1 mg/kg subcutaneous injection every 12 hours during hospitalization and after discharge, up to eight days. All patients received aspirin. Primary study end points were mortality, recurrent MI, and need for revascularization at eight days and 43 days.

The study enrolled 3910 patients. At eight days, 12% of the enoxaparin group had reached the end point of death or serious cardiac event, compared to 15% of patients in the unfractionated heparin group. This difference just reached statistical significance (P = 0.48, odds ratio 0.83 [95% CI, 0.69-1.00]). Enoxaparin's advantage was essentially identical at 14 and 43 days. While there was no difference in major bleeding during the initial phase of the study, enoxaparin carried a higher rate of major bleeds during the outpatient phase of the study (2.9% vs 1.5%, P = 0.02). Antman and colleagues conclude that enoxaparin is superior to unfractionated heparin in the treatment of patients with unstable angina and non-Q-wave MI. They estimate that 21 adverse events would be avoided for every 1000 patients treated with enoxaparin therapy instead of unfractionated heparin.

The companion article is a meta-analysis including the TIMI 11b and ESSENCE 2 phase III studies,[1] both comparing enoxaparin to unfractionated heparin in patients with unstable angina and non-Q-wave MI. Enoxaparin was not administered after hospital discharge in the ESSENCE trial. Pooled results showed that enoxaparin provided a consistent 20% reduction in death or nonfatal MI at all times up to 43 days from presentation. Enoxaparin carried a slightly (but significantly) higher rate of major bleeding during the acute phase (1.3% vs 1.1%, P = 0.03).

Like the glycoprotein IIb/IIIa inhibitors, enoxaparin is a drug with which emergency physicians must quickly become familiar. Both the TIMI 11b and ESSENCE 2 studies favor enoxaparin over unfractionated heparin in patients with unstable coronary syndromes. Enoxaparin appears to be far more effective in this setting than other LMWH preparations such as dalteparin and nadroparin, neither of which appears superior to unfractionated heparin in clinical studies.

Enoxaparin's advantages extend beyond its clinical efficacy, which, while statistically better than unfractionated heparin, is not overwhelming. Unlike standard heparin, enoxaparin does not require constant infusion, and it is not necessary to monitor its anticoagulant effect with laboratory studies. The combination of these advantages makes enoxaparin a far more cost-effective drug. ■

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Initial Antimicrobial Therapy for Hospitalized Elderly Patients with Pneumonia

Source: *Gleason PP, et al. Arch Intern Med 1999;159:2562-2572.*

Gleason and colleagues reviewed records for almost 13,000 Medicare inpatients with pneumonia. An association between initial therapy

and 30-day mortality was assessed incorporating differences in baseline patient characteristics. A nonpseudomonal third-generation cephalosporin alone was the reference standard. Three regimens—a nonpseudomonal third-generation, a second-generation cephalosporin plus macrolide, or a fluroquinolone alone—were independently associated with a lower 30-day mortality. Use of a beta-lactam/beta-lactamase inhibitor plus macrolide and an aminoglycoside plus another agent were associated with an increased 30-day mortality.

Pneumonia remains one of the common problems encountered by internists and family physicians. Each year more than 4 million adults develop pneumonia, resulting in more than 1 million hospital admissions. Because of the substantial morbidity and mortality of this disease, optimal therapy is essential. Current guidelines are based on expert opinion without many studies that examine antibiotic choice and patient outcome.

These two studies shed some light on the outcomes associated with different antibiotic regimens. Both studies suggest there is benefit to either adding a macrolide to a cephalosporin as part of the initial therapy or that using a fluoroquinolone alone improves outcomes. Surprisingly, the commonly used regimen of a beta-lactam/beta-lactamase inhibitor or aminoglycoside in conjunction with another agent did not do as well.

Although further study is needed before there can be a firm recommendation about the best initial therapy, adding a macrolide to the initial therapy for elderly patients with pneumonia seems to reduce mortality. Although future controlled studies will be helpful to confirm what antibiotic regimen yields the best outcome, given the relative safety of macrolides and fluoroquinolones clinicians might consider using these agents as part of initial therapy now, while awaiting corroborating evidence. One caveat pointed out by Gleason et al, regarding the quinolones is that their advantages should be weighed against the risk of developing widespread resistance to these agents. ■

The Therapeutics & Drugs Briefs were written by David J. Karras, MD, FAAEM, FACEP, Associate Professor of Medicine, Temple University School of Medicine, Director of Emergency Medicine Research, Temple University Hospital, Philadelphia, PA; and Martin Lipsky, MD, Professor and Chair, Department of Family Medicine, Northwestern University Medical School, Chicago, IL.

CME questions

Testing form inserted in the July 2000 issue

1. **Compared to older drugs (diuretics/beta blockers), newer drugs (ACE inhibitors/calcium antagonists) for treating hypertension:**
   a. are less well tolerated.
   b. increase total mortality.
   c. reduce stroke rates.
   d. are similar for preventing cardiovascular events.

2. **Which of the following is *not* an FDA-approved indication for the use of moxifloxacin?**
   a. Acute bacterial sinusitis
   b. Pharyngitis and tonsillitis
   c. Acute bacterial exacerbation of chronic bronchitis
   d. Mild to moderately severe community-acquired pneumonia

3. **Which of the following statements is *not* true about aggrenox?**
   a. Therapy does not appear to affect the severity of the recurrent stroke.
   b. A frequent side effect of aggrenox includes vomiting.
   c. No statistical difference was observed in combined end points of stroke or death.
   d. None of the above
   e. All of the above

4. **Based on the current study, which of the following is true?**
   a. Gabapentin is more effective than propranol for the treatment of essential tremor.
   b. Gabapentin is less effective than propranol for the treatment of essential tremor.
   c. Gabapentin and propranol are equally effective for the treatment of essential tremor.
   d. There is no effective treatment for essential tremor.
   e. All of the above

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