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ACE Inhibitors Reveal a Strong Suit

By William T. Elliott, MD, FACP

November was a good month for **ace inhibitors**. the *New England Journal* of Medicine took the unusual step of publishing an early release of data from The Heart Outcomes Prevention Evaluation (HOPE) on its Web site because of potential therapeutic implications. The study of more than 9000 patients was performed at 129 centers in Canada, 27 in the United States, 76 in Europe, and 35 in Mexico and South America on patients aged 55 years and older with cardiac risk factors such as coronary artery disease, diabetes, or a previous stroke. Patients with heart failure or weak heart function were excluded from the study. In the critical part of the study, 4645 patients were randomized to receive the ACE inhibitor **ramipril** (**Altace**) (**Hoechst—Marion Roussel**) while 4652 received placebo. Treatment with ramipril resulted in a 25% reduction in death from all cardiovascular causes, 20% reduction in MI, and 30% reduction in stroke risk. The proportion of patients who required either coronary or noncoronary revascularization procedures was 16% lower in the ramipril group than in controls. The rates of cardiac arrest, heart failure, and complications of diabetes were 37%, 22% and 16% less with ramipril therapy, respectively. The drug also reduced the new development of diabetes by 30%, the first drug to be effective in this role. The full paper will be published in a January issue of the *New England Journal of Medicine.*

Angiotension receptor blockers (**ARBs**) such as **losartin** (**Cozaar—Merck**) are becoming popular antihypertensive agents because of their effectiveness and lack of cough commonly associated with ACE inhibitors. There has been some suggestion that ARBs may be more effective than ACE inhibitors for treating congestive heart failure as well. Much of this evidence was from the head-to-head, double-blind ELITE trial, comparing losartin to captopril in patients with heart failure. ELITE enrolled only 700 patients and early results suggested a significant survival benefit for patients on losartin. The follow-up ELITE II trial enrolled more than 3000 patients in the same design. The results of ELITE II, reported in November to the 72nd scientific sessions of the American Heart Association, came up with a far different conclusion—the mortality curves were superimposable, with 250 deaths in the captopril group and 280 in the losartin group—a nonsignificant difference. The investigators suggest that the early findings were due to chance and the small number of patients in the original study.

Yet another **ACE inhibitor** study for the treatment of **chronic heart failure**

(**CHF**) suggests that most CHF patients may be receiving subtherapeutic doses. The study, entitled **ATLAS** (**Assessment of Treatment with Lisinopril and Survival**), enrolled 3000 patients with heart failure, all with ejection fractions less than 30%. Two groups were given either low-dose lisinopril (2.5-5 mg/d) or high-dose (32.5-35 mg/d) along with standard CHF therapy. During the five-year study period, the high-dose group had a 12% lower risk of death or hospitalization. There was no improvement in symptoms with high-dose lisinopril and, surprisingly, there was a higher rate of cough in the low-dose group. The results of the study were published as a "rapid track" by the American Heart Association, and the full results are in the December 1999 issue of *Circulation*.

Glaxo's drug **lamivudine** may be effective in preventing liver fibrosis associated with chronic hepatitis B infections. A multicenter, placebo-controlled, randomized trial of 137 patients studied 100 mg of lamivudine daily vs. placebo. The active treatment group was significantly more likely to have a reduction in liver inflammation (64% vs 34%) or progressive fibrosis (5% vs 20%) compared to placebo. HBV DNA levels became undetectable after lamivudine therapy, but quickly returned to half of pretreatment levels within four months (*N Engl J Med* 1999;341:1256-1263). In phase III studies of lamivudine, a lower 25 mg/d dose was also found to be effective (59% reduction in inflammation, and 10% progressive fibrosis). Lamivudine is marketed for HIV treatment under tradenames **Epivir** and **Combivir**, and for HBV therapy as Epivir-HBV.

Do **lipid-lowering medications** cause more accidental injuries? Ever since the Helsinki Heart Study was published in 1987, concern has lingered on whether lipid-lowering medications may increase total mortality even if they reduce cardiovascular events. Some studies seemed to suggest that these medications might increase depression and hostility, thereby leading to an increase in accidental deaths or injuries. A new study suggests that not only is this not the case, but that patients on these drugs may be at a lower risk of accidental injury as nonusers. The population-based, case-control study showed that injured patients are about half as likely to be on lipid-lowering medications as nonusers (*J Clin Epidemiol* 1999;52:1197-1200).

FDA News:

The FDA has approved the combination drug **aspirin/dipyridamole** for the prevention of recurrent CVAs and TIAs. The drug will be marketed as **Aggrenox** by **Boehringer**. Approval of the drug combination was based on data from the European Stroke Prevention Study in which it was compared to 50 mg of aspirin/d, showing a modest benefit.

The Agency has also approved **Teva Pharmaceutical's** generic version of **Glaxo's antidepressant bupropion** (**Wellbutrin**) in the 75 and 100 mg dose form. Bupropion is also marketed under the trade name **Zyban** for smoking cessation.

The FDA's **Gastrointestinal Drugs Advisory Committee** has recommended approval of **alosetron**, a **5-HT3 antagonist**, for the treatment of symptoms of irritable bowel syndrome (IBS). The drug is recommended only for women with IBS who have diarrhea as the predominant symptom. Once approved by the FDA, it will be marketed under the name **Lotronex** by **Glaxo**.

UCB Pharmahas received approval to market their antiepileptic agent **levetiracetam** (**Keppra**). The drug, which is approved for the treatment of partial-onset seizures in adults, should be available this spring. ■

Oseltamivir Phosphate (Tamiflu)

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

In october, the fda approved oseltamivir (Tamiflu—Roche), the second neuraminidase inhibitor for the treatment of influenza. This comes three months after the FDA approved zanamivir (Relenza) (*Intern Med Alert* 1999;21:133). The major difference between these agents is the route of delivery—zanamivir is administered by oral inhalation while oseltamivir is orally active. Neuraminidase inhibitors exert their action by inhibiting viral replication.[1]

Indications

Oseltamivir is indicated for the treatment of uncomplicated acute illness due to influenza infection in adults who have been symptomatic for no more than two days.

Dosage

The recommended dose is 75 mg twice daily for five days. Treatment should be initiated within two days of symptom onset. Oseltamivir may be taken without regard to meals although food may reduce the gastrointestinal side effects.[2,5] No dosage adjustment is necessary in patients with creatinine clearance above 30 mL/min. The dose should be reduced to 75 mg daily for five days in patients with creatinine clearance between 10-30

mL/min.[2] No dose adjustment is necessary for patients with hepatic impairment. Patients should be advised to take any missed doses as soon as possible unless it is within two hours of the next scheduled dose. Oseltamivir is supplied as 75 mg capsules.

Potential Advantages

Oseltamivir is orally active and, thus, is more convenient to administer than zanamivir, which requires administration by oral inhalation using a Diskhaler. In a published trial, about 12% of patients on zanamivir withdrew due to adverse events. In contrast, withdrawal in the unpublished oseltamivir trials were less than 1% due to the major side effects, nausea and vomiting. In addition, unlike zanamivir, the oseltamivir labeling does not contain a precaution for use in patients with underlying respiratory diseases. Bronchospasm or decline in lung function has been reported in some patients treated with zanamivir.[3]

Potential Disadvantages

The most common side effects compared to placebo are nausea (9.9% vs 5.6%) and vomiting (9.4% vs 2.9%).[2] Oseltamivir is approved for use in patients 18 year of age and older. Zanamivir is approved for use in younger teens aged 12 years and older. Post-treatment influenza with reduced susceptibility to oseltamivir has been demonstrated in challenge studies and in studies with naturally acquired infections.[2] These varied from 3% in the challenged studies to 1.3% in the natural studies.

Comments

Oseltamivir is the ethyl ester prodrug of oseltamivir carboxylate. The prodrug is converted to the active drug mainly by hepatic esterases. Clinical study results (n = 849) demonstrated that oseltamivir, initiated within 40 hours of onset of symptoms, produces a reduction of 1.3 days (30%) in the median time-to-symptom improvement. Patients (18-65 years old) were eligible if they had fever higher than 100°F with at least one respiratory symptom (cough, nasal symptoms, or score throat) and one systemic symptom (myalgia, chills/sweats, malaise, fatigue, or headache).[2] Study end points were self-assessed by the patient. Time to improvement was determined from onset of therapy to time when all symptoms were assessed as "none" or "mild." Details of these pivotal trials have not been published. While it is difficult to compare across studies, the magnitude of effect appears to be very similar to those seen with zanamivir.[3,4] Oseltamivir has not been evaluated in high-risk patients such as those with chronic cardiac or respiratory disease or the elderly (> 65 years). These trials are ongoing.

While cross-resistance between zanamivir-resistant strains and oseltamivir-resistant strains has not been adequately studied, cross-resistance may be expected due to their mechanisms of action. Oseltamivir, has been reported to be effective for the prevention of influenza as well.[5,6] However, the FDA has not approved either drug for this indication.

The cost for a five-day course of treatment for oseltamivir is $53 compared to $44.40 for zanamivir.

Clinical Implications

The benefit of the current neuraminidase inhibitors (zanamivir and oseltamivir) are modest, reducing the duration of illness of uncomplicated influenza by 1-1.5 days if initiated within 36-48 hours. Initiating treatment early may be problematic, as most adults may not seek treatment within that time frame. Oseltamivir does offer the advantage of a much more convenient route of administration. There are no indications that these drugs can reduce complications of influenza illness in patients at risk. In addition, the clinical and pharmacoeconomic effects of a modest benefit in illness duration are not known. They are not substitutes for vaccination, which is the primary strategy to control influenza. ■

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Quinupristin and Dalfopristin for Injection

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

The fda has approved a new two-drug antibiotic that promises to be effective against resistant bacteria. Rhône Poulenc Rorer's Synercid pairs the antimicrobials quinupristin and dalfopristin, both members of a new class of antibiotics known as streptogramins. The drugs work synergistically against a range

of bacterium, including vancomycin-resistant *Enterococcus faecium* (VREF) and other gram-positive bacteria.[1] Synercid was given an accelerated approval as it qualified as a product for use in life-threatening conditions when other alternatives are not available.

Indications

Quinupristin/dalfopristin is indicated for the treatment of patients with serious or life-threatening infections associated with vancomycin-resistant *Enterococus faecium* (VREF) bacteremia. It is also indicated for the treatment of complicated skin and skin structure infections caused by *Staphyloccus aureaus* (methicillin susceptible) or *Streptococcus pyogenes*.

Dosage

The recommended dosages are 7.5 mg/kg every 8 hours for VREF and 7.5 mg/kg every 12 hours for complicated skin and skin structure infections. The drug is administered by intravenous infusion over a 60-minute period. The minimum duration of treatment is 7 days for complicated skin and skin structure infections and duration should be determined by the site and severity of VREF infections.[2] In the clinical trials the average duration of therapy of VREF was 14.5 ± 10.7 days.[5]

No dosage adjustment is required in the elderly or in patients with renal impairment. The manufacturer did not have a recommendation for dosage reduction in patients with hepatic impairment since the half life of the two components did not change but the area under curve (AUC) increased by about 180% and 50%, respectively.[2]

Quinupristin/dalfopristin is supplied as 500 mg (150 mg of quinupristin and 350 mg of dalfopristin) in single-dose 10 mL vials.

Potential Advantages

Quinupristin/dalfopristin has demonstrated good activity against a number of resistant gram-positive bacteria including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium*, and penicillin-resistant *Streptococcus pneumoniae*.[1,3,4] Quinupristin/dalfopristin is bacteriostatic against *Enterococcus faecium* and bactericidal against methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*.[2] Cross-resistance to other classes of antibiotics has not been reported.[1]

The FDA approved the drug combination for serious infections caused by vancomycin-resistant *Enterococcus faecium*. Despite the short elimination half-lives of quinupristin and dalfopristin (< 1 hour), the post-antibiotic effect and active metabolites permit dosing every 8-12 hours.[1,2]

Potential Disadvantages

Emergence of resistance to quinupristin/dalfopristin has been reported during treatment of VREF.[1] Quinupristin/dalfopristin is not active against *Enterococcus faecalis*.[1,2] It is important to differentiate these enterococcal species.[1] The drug is an inhibitor of cytochrome P450 isoenzyme 3A4. Drugs metabolized by this pathway may have their plasma levels increased. The most common adverse effects are injection-site-related side effects such as pain (40%), inflammation (42%), and edema (17%). Other side effects include nausea (4%), vomiting (3.7%), arthralgia, and myalgia (7%).

The most common laboratory abnormalities are increases (5 × ULN) of total and conjugated bilirubin (25-35%).[1]

Quinupristin/dalfopristin was approved based on a surrogate marker, clearance of VREF bacteremia, not the cure or improvement of the underlying infection. The validity of this surrogate end point has not been validated.[1] In two open-label comparative trials in patients with complicated skin and skin structure infections, bacteriological success rates for selected bacteria1 suggest that quinupristin/dalfopristin may be less effective against gram-positive pathogens than the comparator drug (66.6% vs 77.7%; P = 0.004). This difference was largely explained by lower success against methicillin-sensitive *S. aureus* (64.3% vs 76.%).[6]

Comments

Quinupristin/dalfopristin is a mixture of two semisynthetic derivatives of pristinamycin at a 30:70 mixture. These two drugs act synergistically against gram-positive bacteria by inhibiting protein synthesis at different sites on the bacterial ribosomes.[1] The drug was given an accelerated approval by the FDA permitted for drugs to be used for life-threatening conditions with limited or no alteratives. Quinupristin/dalfopristin was studied in noncomparative emergency use settings in infections caused by vancomycin-resistant *Enterococcus faecium*.[5] In a published report of two prospective studies, the overall success rate (clinical and bacteriologic cure) was 65.8% (95% CI, 57.9%, 72.9) in 156 evaluable patients. However, this may be misleading as only 24.4% of the total 1222 patients in four studies were evaluable due to variability in data collection. When all the evaluable patients were considered (n = 298) the overall success was 52.3%. FDA approval was based on a 90% clearance of VREF bacteremia within the first 48 to 72 hours.[1] In two randomized, open-label trials in patients with complicated skin and skin structure infections (*S. aureus* most commonly isolated) quinupristin/dalfopristin produced comparable success rates compared to oxacillin or cefazolin (68% vs 71%).[6] Vancomycin may be substituted if MRSA is suspected or confirmed, or if the initial comparator is not appropriate. These studies did not assess the drug against

methicillin-resistant *S. aureus*, as only 2.7% of the infections were caused by MRSA. The FDA approval for this indication only included methicillin-susceptible *S. aureus*.

Quinupristin/dalfopristin is priced at $103 per 500 mg vial or roughly $200-300 per day.

Clinical Implications

Treating infections caused by vancomycin-resistant *E. faecium* has been problematic due to the limited number of therapeutic options. In vitro data suggest that quinupristin/dalfopristin is active against VREF. However, clinical data are limited due to emergency-use protocols severely limiting the number of evaluable patients. This is further complicated by the use of a surrogate end point that has not been validated in VREF infections, making clinical results difficult to evaluate. Given the lack of viable therapeutic options for VREF however, quinupristin/dalfopristin becomes a reasonable option. Findings from published data on skin and skin structure infections suggest that quinupristin/dalfopristin was no better than oxacillin/vancomycin or cefazolin/vancomycin. As for infections caused by methicillin-resistant *S. aureus*, more clinical data are needed to establish clinical efficacy. ■

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PTCA vs. Thrombolytic Therapy for Acute MI

Source: *Zijlstra F, et al. N Engl J Med 1999;341:1413-1419.*

Prompt revascularization of the infarct-related artery (IRA) in acute myocardial infarction (MI) by thrombolytic therapy or direct angioplasty is proven to decrease mortality and morbidity. In 1993, two small, randomized trials of thrombolytic therapy vs. percutaneous transluminal coronary angioplasty (PTCA) suggested a benefit for PTCA, but other data were conflicting. This important report represents a five-year follow-up of the original Netherlands trial,[1] and confirms a robust advantage of PTCA over streptokinase (SK). The PTCA group manifest increased survival, had fewer hospitalizations and invasive procedures, better LV function, less heart failure, and a lower clinical angina class compared to the SK cohort over a mean of 5 ± 2 years. Of the original 395 randomized subjects (194 PTCA, 201 SK), 16 of the angioplasty group received no procedure or coronary artery bypass graft (CABG). TIMI-3 flow was confirmed in 90% of the PTCA group vs. 65% of the SK cohort. This translated into better LV function at discharge in the PTCA patients (only 14% with LVEF < 40% vs 26% of the SK cohort). Late (5 ± 2 years) follow-up demonstrated a persistent advantage for primary angioplasty: total long-term mortality was 13% vs. 24%; nonfatal MI occurred in 6% vs. 22% (RR = 0.27). All recurrent infarcts were documented to occur in the IRA. The primary end point of death and nonfatal MI was markedly reduced during long-term follow-up; reinfarctions were considerably higher in the SK patients, as were readmissions for ischemia or heart failure. Interestingly, total medical charges per patient were comparable, and actually lower in alive PTCA subjects at the end of follow-up.

Zijlstra and colleagues conclude that the major factor explaining the results is the higher early patency rates in PTCA subjects, resulting in better LV systolic function, less reinfarction, and improved survival. Reinfarction rates in the IRA were high in the lytic therapy subjects.

Comment by Jonathan Abrams, MD

These data are impressive and confirm the findings of a (short-term) meta-analysis of 10 trials assessing early morbidity and mortality,[2] and a new long-term meta-analysis.[3] Moreover, the long-term results are reassuring, indicating that the PTCA patients do not develop an increased late hazard. The Kaplan-Meier survival curves are relatively parallel for mortality and nonfatal reinfarction after the first 30 days. While not discussed by Zijlstra et al, anterior infarction was an independent risk factor for death or MI; although data are not provided, it is possible that the benefits of PTCA are somewhat less in inferior infarcts. Other analyses have not been consistent regarding outcomes in anterior vs. inferior MI.

There are several caveats. Streptokinase does not result in TIMI-3 flow at 90 minutes in the majority of

patients. Front-loaded t-PA vs. angioplasty would be likely to produce a smaller difference in outcomes. On the other hand, the use of stents during primary angioplasty, as well as therapy with platelet IIb-IIIa inhibitors, might result in even better PTCA outcomes.

Nevertheless, long-term cardiac mortality was threefold greater in the SK patients vs PTCA (2% vs 7%; P < 0.001); this outcome is impressive. Of the subjects initially randomized to PTCA, nine were treated conservatively and seven underwent urgent CABG. The intention to treat analysis does not allow one to know the possible influence of these 16 subjects who did not receive a PTCA on short- and long-term events.

It now seems clear that, in experienced hands, within an appropriate time window, direct or primary angioplasty is preferred in most patients. One recent report suggests that time to intervention may be more critical to outcome in lytic patients than direct PTCA. New thrombolytic agents and lytic combinations with IIb-IIIa inhibitors, as well as the increasing use of stents, will keep this subject on the front burner for years to come. ■

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Benefit of Short-Course Steroids in COPD Exacerbations Demonstrated

Source: *Niewohner DE, et al. N Engl J Med 1999;340:1941-1947.*

This large-scale clinical trial of the use of systemic corticosteroids in acute exacerbations of chronic obstructive pulmonary disease (COPD) was carried out at 25 VA medical centers across the United States. To be eligible, patients had to have COPD both clinically and by pulmonary function tests when available, have no prominent findings suggesting asthma, have no other imminently life-limiting diagnoses, be admitted because of an acute exacerbation, and not have used systemic corticosteroids in the preceding month.

All patients were treated with oxygen, antibiotics, and aerosolized beta-agonist and anticholinergic bronchodilators. They were randomized within 12 hours of admission to receive either eight weeks of systemic steroids (125 mg methylprednisolone IV every 6 hours for 72 hours, followed by a tapering course of oral prednisone that started with 60 mg daily for 4 days), two weeks of steroids (same regimen, truncated at 2 weeks), or placebo. All of the patients also received inhaled steroids beginning on day four of hospitalization. Theophylline was not used. Outcomes studied prospectively included death, the need for intubation, duration of hospitalization, and serial spirometry, with follow-up standardized over the six months following admission.

One thousand eight hundred forty patients were screened for the study, of whom 271 were enrolled. The main reasons for exclusion were recent systemic steroid use (50%), refusal to participate (23%), and the presence of severe comorbidity (18%). There were 80 patients in each of the steroid groups and 111 received placebo. The patient groups were reasonably matched. Rates of nonadherance to the protocol were low and comparable among the groups.

Overall, 26 of the 271 patients died during the six-month follow-up period, and there were no differences among the groups. Lung function, as measured by forced expired volume in the first second (FEV_1), improved faster in the steroid-treated patients than in those who received placebo; the maximum difference was about 0.10 L, and this difference disappeared by two weeks. The average length of hospitalization was significantly longer in the placebo group than in the combined corticosteroid groups (9.7 days vs 8.5 days; P = 0.03). Data on deaths during hospitalization and the need for intubation are not explicitly provided in the paper, but these outcomes involved only small numbers of patients and were apparently not different in the treatment groups. About half of all the patients experienced a treatment failure, defined as death from any cause, the need for intubation, readmission because of COPD, or intensification of pharmacologic therapy, during the six-month follow-up period. Placebo-treated patients had more treatment failures than steroid-treated patients (33% vs 23% at 30 days, P = 0.04; 48% vs 37% at 90 days, P = 0.04). Duration of steroid treatment (2 vs 8 weeks) had no significant effect on treatment failures. More steroid-treated patients developed hyperglycemia that required treatment (15% vs 4% in the placebo group; P = 0.002).

Comment by David J. Pierson, MD, FACP, FCCP

Only a minority of patients with severe COPD (10-15%) benefit physiologically from systemic corticosteroids when clinically stable. However, the situation changes during acute exacerbations of the disease, when bronchospasm and inflammation presumably intensify, and short courses of systemic steroids have long been a cornerstone of therapy. A landmark 1980 study by Albert and associates, also conducted in a VA population, showed that steroid-treated patients with acute exacerbations of chronic bronchitis and/or COPD experienced more spirometric improvement in the first 72 hours of hospitalization than patients who received placebo.[1] That study did not address length of stay or the patients' subsequent clinical course. The present study, much larger in scope and involving many more patients, confirms and extends the findings of Albert et al. It shows that unselected, nonasthmatic COPD patients requiring emergency hospitalization for an acute exacerbation improve more rapidly, get out of the hospital faster, and do better clinically over the next six months if they are treated with systemic corticosteroids.

An overall management strategy for patients with COPD has evolved by which all patients with acute exacerbations are treated with short-course systemic steroids, but only those who demonstrate a substantial improvement in FEV1 during a two-week prednisone trial while clinically stable receive this drug long-term. Such a strategy should avoid most steroid-associated complications, while maximizing potential clinical benefit for the patient. Inhaled steroids are widely used in patients with COPD, as they were in this study. However, this expensive and intrusive therapy is based on unimpressive and, in my opinion, debatable evidence and I do not often prescribe these agents for my own patients. ■

Reference

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Therapeutics & Drugs Briefs

Aspirin Revisited in Light of the Introduction of Clopidogrel

Source: *Gorelick PB, et al. Stroke 1999;30:1716-1721.*

Aspirin is currently the standard of care for stroke prevention in patients with identified atherothrombotic disease. Ticlopidine (Ticlid), a potentially more efficacious drug than aspirin, has been available as alternative therapy, but serious side effects such as neutropenia limit its usefulness. Now, clopidogrel (Plavix), a thienopyridine derivative similar to ticlopidine, offers similar efficacy with fewer side effects.

Clopidogrel was recently compared with aspirin in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial. Among patients with recent MI, stroke, or significant peripheral vascular disease, CAPRIE found an event rate of 5.83 events per year in the aspirin-treated groups vs. 5.32 events per year in the clopidogrel-treated group (P = 0.043), an 8.7% relative risk reduction. CAPRIE used a combined end point of ischemic stroke, MI, or vascular death.

A secondary subgroup analysis in CAPRIE showed that not all patients benefited equally. The largest benefit of clopidogrel, accounting for 75% of its therapeutic advantage, occurred in the group with peripheral arterial disease. The relative risk reduction in these patients was 23.8% compared to 7.3% for those with stroke (95% CI-5.7-18.7; P = 0.26, a nonstatistically significant difference).

Gorelick and colleagues review the safety profiles of clopidogrel compared with aspirin. Clopidogrel does not cause significant neutropenia, although long-term data are not available for this drug. Observations are limited to three years. By contrast, aspirin has been in use for more than 100 years. The CAPRIE study used 325 mg of plain aspirin. Enteric-coated aspirin (the most commonly prescribed form) or low-dose aspirin (probably of equal efficacy) may have compared even more favorably with clopidogrel.

Clopidogrel is considerably more expensive than aspirin (45-fold cost differential) and remains 5- to 7-fold more costly when costs to prevent an event or save a life are calculated. Patient compliance may also be influenced by the higher drug cost of clopidogrel.

Analyzing efficacy, safety, and cost, Gorelick et al conclude that aspirin should remain first-line therapy in this setting. As Gorelick et al observe, however, clopidogrel is a viable alternative, particularly for patients who fail aspirin or cannot tolerate it. ■

SSRIs and Breastfeeding

Source: *Ohman R, et al. J Clin Psychiatry 1999;60:519-523.*

Depression affects 13% of women after childbirth, a period with a four-fold higher risk for depression. Although appropriate treatment of depression in the post-partum period is important to both the mother and infant, many women and physicians

shy away from medication because of concern about adverse events to infants who are exposed to antidepressant medications in breast milk.

The current article describes seven patients with depression or panic disorder, who received a constant 20 mg morning dose of paroxetine for eight days. In six subjects, trough and peak serum and breast milk levels were determined. The seventh subject had samples drawn at steady-state, 0, 1, 2, 3, 4, 6, 8, and 24 hours after paroxetine intake, on two occasions (at 20 mg/d and 40 mg/d) with an interval of seven weeks. A total of 58 milk/serum samples were analyzed. Concentrations varied in milk from 5.3-145 ng/mL and serum from 11-188 ng/mL. There was a mean increase of 61% in the paroxetine concentration from the time of the daily dose to six hours after the dose. The estimated individual mean relative dose to the infants was 1.4% (0.7%-2.9%) of the weight-adjusted maternal dose. Single milk/serum ratios varied from 0.31 to 2.00, with a mean of 0.69. Ten pairs of foremilk and hindmilk samples were collected; the concentration of paroxetine was 78% higher in hindmilk compared to foremilk. In summary, the study demonstrated a considerable time-dependent, dose-dependent, and interindividual variability in the excretion of paroxetine in breast milk. Data on other antidepressants reveal that the relative dose to the infant is 1.2%-6.5% for fluoxetine, 0.7%-9% for citalopram, 0.5% for fluvoxamine, and 0.45%-1.04% for sertraline, compared to 1.4% for paroxetine in this study.

The small sample size of the current study limits definitive conclusion and precludes the ability to detect adverse events in the infants. In addition, the validity of the data is limited because serum levels were not measured in the infants.

This preliminary study sets the stage for larger studies that may help us determine the safety of SSRIs for infants during breastfeeding. It is premature to conclude that one SSRI may be more safely used than another, given small sample sizes and the lack of head-to-head comparison. However, data regarding fluoxetine indicate that children followed for up to seven years following intrauterine exposure had no evidence of alteration in development or cognition. If a SSRI is clinically indicated in a mother who is breastfeeding, the overall risk of exposure to the infant may be reduced by not breastfeeding during the period of time in which peak levels of medication will be in the milk, or if possible, by maximizing the use of foremilk rather than hindmilk. ■

The Therapeutics & Drugs Briefs in this issue were written by Alan Z. Segal, MD, Assistant Professor, Department of Neurology, Weill-Cornell Medical College, Attending Neurologist, New York Hospital; and Donald M. Hilty, MD, Assistant Professor of Clinical Psychiatry, University of California—Davis, Sacramento, CA.

CME questions

Testing form inserted in the January 2000 issue

14. Long-term follow-up of patients in a primary angioplasty vs. streptokinase for acute MI trial showed:

a. increased survival in the angioplasty group.
b. better LV function in the angioplasty group.
c. fewer recurrent MIs in the angioplasty group.
d. All of the above

15. Patients with COPD who receive systemic corticosteroids during acute exacerbations:

a. have a mortality rate 33% less than those treated with placebo.
b. have a hospital length of stay on average 1.2 days less than those treated with placebo.
c. require intubation and mechanical ventilation only half as often as those treated with placebo.
d. All of the above
e. None of the above

16. Which antidepressant is believed to expose the infant to the lowest percent of the weight-adjusted maternal dose?

a. Citalopram (Celexa)
b. Fluoxetine (Prozac)
c. Paroxetine (Paxil)
d. Sertraline (Zoloft)
e. Fluvoxamine (Luvox)

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