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SmithKline Beecham Issues 'Dear Doctor Letter' for Ropinirole

By William T. Elliott, MD, FACP

Ropinirole (**requip**), **smithkline beecham's parkinson's drug,** is the subject of a "Dear Doctor" letter regarding a tendency of treated patients to suddenly fall asleep while performing various activities, even driving a car. To date, 60 cases of sudden sleep onset have been reported, and there have been reports of fatal car accidents. Similar reports have been seen with **pramipexole** (**Mirapex**), also a **dopamine agonist** used for the same indication. Although somnolence is a known side effect of these drugs, many patients have noted sleep onset suddenly without warning signs. The onset of these sleep episodes may occur as late as one year after starting the drug. Patients need to be assessed for safety and drowsiness during activities. Patients may need to be warned not to drive or perform other potentially hazardous activities.

Glaxo Wellcome has received FDA approval to market **alosetron** for the treatment of **irritable bowel syndrome** (**IBS**) in women. The drug is the first in a new class of drugs for this indication—the **selective 5HT3 antagonists**. Alosetron will be marketed under the trade name **Lotronex**. Other pharmaceutical manufacturers are rushing to develop similar drugs for this indication, which affects as many as 20% of Americans, and for which no current treatment provides consistent relief. The drug is only approved for use in women for whom diarrhea is the primary symptom. It should not be used in women with constipation as their primary symptom. It is most effective at reducing pain and urgency to defecate. Constipation is the most common side effect.

Johnson & Johnson's levofloxacin (**Levaquin**) is the first agent to be approved for **penicillin-resistant *Streptococcus pneumonia*** in community-acquired pneumonia. Although it is the only drug to have received this indication, the other two new fluoroquinolones, **moxifloxacin** (**Avelox**) and **gatifloxiacin** (**Tequin**), may also be effective in this role. Because of this coverage and their coverage of gram-negative as well as atypical organisms such as *mycoplasma* and *chlamydia*, these antibiotics are becoming the drug of choice for community-acquired pneumonia over the macrolides such as azithromycin.

The FDA has approved a new **proton pump inhibitor** (**PPI**). **Wyeth-Ayerst's pantoprazole** (**Protonix**) is the fourth entry into this competitive and lucrative drug

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class. The dominant PPI remains **omeprazole** (**Prilosec**) which is the top selling prescription drug in the world. **Rabeprazole** (**Aciphex**) and **lansoprazole** (**Prevacid**) round out the class. Pantoprazole may try to position itself in the market by touting its favorable drug-drug interaction profile since, unlike omeprazole, no dose adjustment is needed with concomitant administration of other drugs metabolized by the cytochrome P450 system. Pantoprazole is available as a delayed released tablet and is seeking FDA approval for an intravenous (IV) form as well.

Mifepristone, the French **abortion pill**, has received an "approval" letter from the FDA. However, this was a disappointment for the Population Council, the group that holds the rights to the controversial drug formerly known as **RU-486**. The letter raises several questions about the manufacture and use of the pill, questions that may be answered by the end of the year. Mifepristone is taken with a **prostaglandin** (usually misoprostol) to terminate pregnancy and is about 97% effective. It could eventually take the place of 50% of abortions in this country, as it has done in Europe where is has been available for 10 years.

Researchers from the University of Naples have reported success with **fluoxetine** (**Prozac**) in preventing **migraine**. Fifty-two patients with migraine without aura were randomized to 20 mg of fluoxetine or placebo for six months of therapy. Fluoxetine resulted in a significant reduction in total pain index, but only after three months of therapy. No change was noted with placebo. This suggests that serotonin disregulation may play a role in the pathogenesis of migraine (*Headache* 2000;39:716-719).

Based on research from the University of California at Irvine, **estrogen** does not appear to benefit women with **Alzheimer's disease** (**AD**). A total of 97 women with mild to moderate AD completed the one-year study after being randomized to conjugated estrogen (0.625 mg/d or 1.25 mg/d) or placebo. The women were assessed using the Clinical Global Impression of Change 7-point scale. Estrogen showed no benefit in either primary or secondary outcomes (*JAMA* 2000;283:1007-1015). Despite these findings, the role of **estrogen replacement therapy** (**ERT**) in the prevention of AD is still unclear. A recent study from Columbia seems to suggest that women with low estradiol levels may be predisposed to developing AD. Fifty postmenopausal women with mild AD were compared to 93 nondemented controls, none of whom were taking ERT. The women with AD had significantly lower estradiol levels than the controls. The authors consider many potential explanations for this finding, but conclude that a cause and effect is likely, suggesting that low estradiol levels may predispose women to AD (*Neurology* 2000;54:833-837). Studies are ongoing to evaluate the role of estrogen in the prevention of AD. ■

Ciclopirox Topical Solution 8% (Penlac Nail Lacquer)

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

The fda has approved ciclopirox, a topical broad-spectrum antifungal agent, for the treatment of fungal infections of the fingernails and toenails. Ciclopirox is formulated in a 8% topical solution and will be marketed as Penlac Nail Lacquer by Dermik. It is manufactured by Aventis in Germany where it is already available. The vehicle contains volatile (flammable) solvents such as isopropyl alcohol and ethyl acetate that vaporize after application. Daily application results in a build up on the nail which must be removed on a weekly basis. Ciclopirox has also been marketed worldwide for years in cream, lotion, and gel formulations.

Indications

Ciclopirox topical solution is approved as topical treatment of mild to moderate onchomycosis of fingernails and toenails without lunular involvement, due to *Trichophyton rubrum*. Treatment should be a component of a comprehensive management program that includes removal of the unattached, infected nails as frequently as monthly by a trained health care professional.[1]

Dosage

Ciclopirox should be applied once daily evenly over the entire affected nail plate. Application is preferable at bedtime or eight hours before washing. Where possible, the solution should be applied to the underside of the nail and to the skin beneath it.[1] Daily application should be applied over the previous coat. Layers should be removed with alcohol every seven days.

Potential Advantages

Bioavailability studies in human volunteers suggest that ciclopirox formulated as an 8% nail lacquer can penetrate the nail.[2] In vitro studies demonstrated penetration up to a depth of about 0.4 mm.[1] Efficacy with nail lacquers appears to be better than other topical therapy.[3] Microbiologic cure has been reported in the range of 29-36% after 48 weeks of therapy.[1]

Potential Disadvantages

Complete clear nail may not be achieved with ciclopirox nail lacquer even after 48 weeks of therapy along with the comprehensive nail care program which includes weekly trimming of the nails by the patient and monthly removal of unattached nail by a professional.[1] Less than 12% of patients with oychomycosis of the great toenail achieve either a completely clear or almost clear toenail. Common side effects include rash-related side effects (periungual erythema and erythema of the proximal nail fold), 5%.[1]

Comments

Ciclopirox is a hydroxy-pyridone that is chemically distinct from the azoles or other antifungals. It has a broad spectrum of action including fungicidal activity against *T. rubrum*.[4] Ciclopirox has been available as a cream and solution for many years as a 1% strength. The 8% nail lacquer has been available in Europe and has now been introduced in the United States. The nail lacquer appears to improve nail penetration and is well tolerated. However, in patients with 20-65% involvement of the great toenail plate, complete cure was less than 10% and mycological cure ranged from 29% to 36% after 48 weeks based on intent-to-treat and last observation carried forward. Relapse rates have not been reported. There does not appear to be any published comparative trials with other topical or oral regimens. Dermik is expected to launch Penlac within the next few months.

Clinical Implications

Onychomycoses, or infections of the nail, are common, and can be caused by a number of organisms including dermatophytes, yeast, or molds. Dermatophytes with *T. rubrum* as the major pathogen are responsible for about 90-95% of the infections.[3] Pharmacologic treatment involves oral and topical routes.

Topical therapy, which has the advantage of few systemic side effects, is generally limited by diffusion of the drug through the horny layers of the nail which may be enhanced with lacquer formulations. Ciclopirox in a nail lacquer formulation is reported to enhance nail penetration, but its long duration of therapy may be problematic. Oral therapy with antifungals such as fluconazole, itraconazole, and terbinafine are more effective and involve shorter courses of therapy. For example, the cure rates for terbinafine (250 mg daily) range from 60% to 80% after three months of therapy and that of fluconazole (150-450 mg weekly) 77-86%.[3] A recent comparative study (n =137) suggested that terbinafine (250 mg for 12 weeks and evaluated at week 60) was more effective than fluconazole (150 mg weekly for 12 or 24 weeks).

Mycological cure was 89% vs. 51% and 49% and complete clinical cure was 67% vs. 21% and 32%.[5] As for topical therapy, it may be reasonable for less severe infections (e.g., involvement of < 30% of the nail).[3]

Combined topical and systemic therapy is also being evaluated. ■

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Dofetilide—Tikosyn

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

In october, the fda approved a new anti-arrhythmic drug for the maintenance of, and conversion to, normal sinus rhythm in patients with highly symptomatic atrial fibrillation/atrial flutter. Dofetilide, marketed as Tikosyn by Pfizer, is a Vaughan Williams Class III antiarrhythmic agent that prolongs action, potential duration, and the effective refractory period.

Indications

Dofetilide is indicated for the maintenance of normal sinus rhythm in patients with atrial fibrillation/atrial flutter of longer than one week duration who have been converted to normal sinus rhythm. It is also indicated for the conversion of atrial fibrillation and atrial flutter to normal rhythm. Due to the potential for life threatening ventricular arrhythmias it should be reserved for patients in whom atrial fibrillation/atrial flutter is highly symptomatic.

Dosage

The dose must be individualized according to calculated creatinine clearance and QTc. The usual dose is 500 mcg twice daily. Prior to the administration of the first dose, the QTc must be determined using an average of 5-10 beats. The drug is contraindicated if the QTc is greater than 440 msec or 500 msec in patients with ventricular conduction abnormalities. If the heart rate is less than 60 beats per minute, QT interval should be used. Use in

patients with more than 50 beats per minute has not been studied. The QTc should be monitored 2-3 hours after the first dose and adjusted for QTc prolongation and monitored after each subsequent dose for a minimum of three days.[1] This requires initiation of the drug in a monitored inpatient setting.

Dofetilide is available as 125 mcg, 250 mcg, and 500 mcg capsules.

Potential Advantages

Results from pooled data of randomized trials in patients with supraventricular arrhythmias (n = 2023) indicated that treatment with dofetilide does not adversely affect survival compared to placebo (hazard ratio 1.1, 95% CI 0.3-4.3).[2] In patients with congestive heart failure and left ventricular dysfunction (n = 1518), dofetilide, compared to placebo, reduced the risk of hospitalization for worsening heart failure (odds ratio 0.75, 95% CI, 0.63-0.89).[3] Patients with atrial fibrillation (AF) at baseline (n = 391) had a higher overall rate of conversion at 12 months (44% vs 13%; $P < 0.001$) and were less likely to have recurrence (hazard ratio 0.35, 95% CI 0.22-0.57). In sinus rhythm at baseline, fewer patients developed atrial fibrillation (2% vs 6.6%; $P < 0.001$). Dofetilide does not appear to adversely affect survival in patients with heart failure with or without a recent MI, or AF at study entry.[1,3]

Potential Disadvantages

Dofetilide does not appear to reduce mortality. It prolongs QT interval in a dose-dependent manner and can cause serious ventricular arrhythmias (i.e., torsades de points).[1] In the supraventricular tachycardia study population, the incidence of torsades de pointes was 0.8% while in the heart failure population it was 3.3%.[1,2] The majority, 76%, of these episodes have been reported to occur within the first three days of therapy.[3] Dofetilide should be initiated in the hospital with three days of cardiac monitoring. The concomitant use of dofetilide and other drugs that can prolong the QT interval should be avoided. These include macrolides, cisapride, tricyclic antidepressants, and phenothiazines. Cimetidine has been reported to increase dofetilide plasma levels by 58%.[1]

Comments

Dofetilide is a selective inhibitor of the rapid component of the delayed rectifier potassium current, which results in prolongation of the action potential duration and the effective refractory period. It does not affect repolarizing potassium channels, sodium channels, adrenergic alpha-receptors, or beta receptors.[1,4] The drug does not affect AV node conductance, sinus node function, or cardiac output. In patients with chronic atrial fibrillation and/or atrial flutter, dofetilide had a conversion rate of about 30% at a dose of 500 mcg twice daily and an estimated probability of 58-66% of remaining in normal sinus rhythm for 12 months.[1] In the two survival studies, the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND), dofetilide did not appear to increase the risk of mortality in patients with structural heart disease.[1,3] Dofetilide can cause torsade de pointes and the dose must be carefully initiated and titrated based on creatinine clearance and QTc. Therapy should be initiated in the hospital or an equivalent setting with appropriate EKG monitoring. Pfizer is developing a comprehensive educational program for health care professionals on the required in-hospital initiation of therapy and the use of the dosing algorithm. Their marketing suggests that the drug will only be available to physicians and hospitals that have participated in the educational program.

Dofetilide costs $3.60 per day for 250 mcg or 500 mcg taken twice daily.

Clinical Implications

AF is the most common form of cardiac arrhythmia. Its incidence increases with age and is associated with cardiovascular disorders such as coronary heart disease, valvular heart disease, or cardiomyopathy.[5] Management of AF is generally divided between conversion and maintenance of sinus rhythm or control of ventricular rate and prevention of thromboembolic events. Management strategies depend on the clinical presentation and the patient's need for restoration and maintenance of sinus rhythm.[5] Antiarrhythmics have been used to convert as well as to maintain sinus rhythm, but their effect on survival has generally not been favorable, especially in patients with heart failure or post-myocardial infarction. Post-MI patients treated for premature ventricular beats with encainide, flecainide, or moricizine have increased risk of mortality compared to placebo in the Cardiac Arrhythmia Suppression Trials (CAST, CAST II).[6,7] D-sotalol and class I antiarrhythmics have been shown to increase mortality compared to placebo in patients with AF and heart failure in the Stroke Prevention in Atrial Fibrillation trial (SPAF) and the Survival with Oral D-Sotalol trial (SWORD).[8,9] Amiodarone, on the other hand, may have neutral or slightly improved mortality.[10] In the Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT), amiodarone showed improved survival in patients who converted to sinus rhythm compared to those who did not convert.[11] Amiodarone has not been approved by the FDA for the management of AF. Dofetilide appears to be neutral with regard to mortality and, thus, is an option for patients with AF and heart failure. Implantable car-

dioverter defibrillators may be another treatment option in the future. ■

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Menopausal Estrogen and Progestin-Estrogen Replacement Therapy and Breast Cancer Risk

Source: *Schairer C, et al. JAMA 2000;283:485-491.*

Schairer and colleagues reported the results of a cohort study. The population base was 46,355 postmenopausal women followed as part of the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. Data from this study were previously analyzed. To increase statistical power, Schairer et al added subjects and then reanalyzed the data for this report. To increase the size of the study population, they relaxed the inclusion and exclusion criteria. Therefore, not all data points were available for all study subjects. For instance, if age of menopause was not known, it was estimated to have occurred at age 57. If a hysterectomy was done, but there was no information on ovarian status, the age of menopause was assigned as the age at the time of hysterectomy. If women were known to have used a nonoral hormonal preparation, they were excluded. In phase 1 of the study (original cohort), no information on hormone type was collected. In phase 2, information on breast cancer screening was not included. In phase 3, Schairer et al attempted to collect missing information by interview, thus making part of the study retrospective. Using the relaxed criteria, Schairer et al expanded the population to 46,355 women. In this cohort, there were 2082 breast cancers. Pathology reports were obtained for 82%. Nodal status was available for 86%. Tumor size was available for 71%. The mean age at the start of follow-up was 58 years and the mean duration was 10 years, but some were followed for only one year and others for 16 years. A majority (86%) of the population was white. Hormone use was classified as follows: none, 42%; ERT, 38%; PERT 4%; both ERT and PERT, 6%; uncertain, 10%; and progestin-only use, 1%. The most commonly used estrogen was conjugated equine estrogen and the primary progestin was medroxyprogesterone acetate.

The main limitation of the study was the paucity of cases of breast cancer for each category. There were 1209 cases of breast cancer among ever-users of any type of hormone, 112 cases in whom hormone use was unknown, and 761 cancers among never-users. Despite the few number of cases, subanalyses were done.

For ERT users, the greatest number of cases of breast cancer (309) was in the category of more than six years use. The relative risk (RR) of breast cancer in this category was 1.1 and the confidence interval was 0.9-1.2. While a relative risk of 1.1 could mean a slight increase in risk because the confidence interval includes 1.0, the "increase" is not statistically significant. For all current users of ERT, the RR was also 1.1, but the confidence interval was 1.0-1.3, again indicating that the "increase" was not statistically significant.

There were only 77 cases of breast cancers among PERT users. When taken together, the RR of breast cancer was 1.4, with a confidence interval of 1.1-1.8. This is barely significant. Needless to say, with so few cases and only 10% of the population having ever taken PERT, subanalysis by duration of use yielded RR that were not statistically significant, but the trend was for the RR to fall with increasing duration of use, such that in the category of more than six years PERT use, the RR was 0.6 (decreased risk), with a confidence interval (CI) of 0.3-1.6.

Another subanalysis partitioned risk according to body mass index (BMI). Based on 72 cases who had used estrogen 16 or more years and 82 cases who had used estrogen more than eight and less than 16 years, Schairer

et al conclude that there is an increase in risk in thin women (those in the bottom two quartiles, i.e., with a BMI ≤ 24.4 kg/m^2). There was no increase in thin women with less than eight years of use and no increase in risk in women with BMI more than 24.4 regardless of duration of ERT use. Although there were only 26 cancers in "thin" women who had used PERT for four or more years, Schairer et al interpreted a RR of 2.0 and a CI of 1.3-3.0 as showing that there was an increased risk in lean, long-term PERT users, but not in heavier PERT users. Furthermore, the biological mechanisms that would make thinness a risk factor for hormone-induced breast cancer were not discussed.

Comment By Sarah L. Berga, MD

The day after this *JAMA* article appeared in my mail, the newspaper headlines read, "Progestin-estrogen use increases the risk of breast cancer more than estrogen use alone." *The Wall Street Journal* featured this on its front page. The implication is that both PERT and ERT increase the risk of breast cancer, that the increase is definitive and of a biologically relevant magnitude, and that hormone use is therefore dangerous. By the time I got to the office that day, I already had one phone call from a patient taking PERT who now wondered if she should have a hysterectomy.

The newspaper headlines were derived from the last line of the structured abstract that read, "Our data suggest that the estrogen-progestin regimen increases breast cancer risk beyond that associated with estrogen alone." At best, this sentence is a great example of overstating the study findings. On reflection, however, I think that the conclusion is simplistic to the point of being both wrong and irresponsible. Most newspaper reporters missed the word "suggest." That this would happen is entirely predictable. Now millions of women are needlessly anxious and many are deciding to quit taking hormones, vowing never to start, or signing up for an unnecessary hysterectomy. While there is an understandable tendency to prefer to report "positive findings ," we must demand better reporting from our medical journals. We must not allow ourselves and our patients to be victimized by misinformation. Sadly, the editorial that accompanied the source report did little to dispel the hype.[1]

To review, the limitations of the study are many. Certainly, there is ascertainment bias regarding hormone use, age of menopause, and disease status. Thus, subject classification may be in error. Adding subjects was done to increase the statistical power, but it may have compromised the validity of the data set. Schairer et al acknowledge in their discussion that the associations were smaller when subjects for whom age of menopause was unknown were removed from the analysis. They kept them in because excluding them would result in "a substantial loss of information." Does this mean that the borderline statistical significance of the subanalyses was lost altogether? Nonetheless, despite the increase in the study population size, the number of events is still too few to expect the subanalyses to yield meaningful conclusions.

Importantly, the overall analysis is limited to determining risk for incidence of breast cancer rather than mortality from breast cancer. As Schairer et al acknowledge in their discussion, mortality from breast cancer is lower in HRT users, although they cannot explain it based on earlier-stage disease or more favorable histology (see also Willis DB. *Maturitas* 1997;27:105-108). In addition, the study population included only those women who apparently took oral medications. While there is no reason to suspect that other HRT regimens will yield substantially different risks in a general population, the study results are specific to those using oral medication.

Given the multiple limitations of the data set, I do not believe there was a basis for drawing firm conclusions. If there is an increase in risk, it is small and it would not translate into a risk for death from breast cancer. It is this last point that patients so desperately deserve to understand.

The accompanying editorial suggested that women consider omitting hormones and rely instead on a combination of statins to decrease the risk of cardiovascular disease and bisphosphonates to prevent osteoporosis. SERMs were also suggested as a second line of defense. However, none of these medications, alone or in combination, yields a comprehensive strategy for chemoprevention of aging. None of these will ameliorate urogenital atrophy. None of these has any significant short- or long-term benefits for the brain. None will relieve hot flashes and night sweats or buttress speed of processing. Consider that a statin and a bisphosphonate will not an undemented mind make! The benefits of estrogen use are multiple and so critical that it is truly a crime to simplistically conclude that ERT and PERT pose an important risk for breast cancer.

What if PERT but not ERT increases the risk of breast cancer? Progestins do seem to have untoward effects on the brain and the endothelium. Should we do more hysterectomies? The approach I would like to see become more widely available is a progestin-containing intrauterine device that confines the progestin exposure to the endometrium. Sadly, the development of this technology has received far more attention in Britain and Europe than here.

As a consequence of this article and its reiteration in the media, practitioners will have a lot of explaining to do. Sadly, much hand wringing could have been avoided by more responsible reporting. It is difficult to read all that one must. It is tempting to just read the last line of an abstract. Even though we all want a short bottom line, conclusions need to be more than overly reductionistic soundbites. Not every one of us has the time and skills to tease apart the data and draw independent conclusions. I hope this analysis helps those of you seeking a second opinion. ■

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Another Promising New Antistroke Treatment

Source: *Furlan A, et al. JAMA 1999;282:2003-2011.*

Thrombolysis with intravenous tissue plasminogen activator (tPA) has been shown to be beneficial when given within three hours of acute ischemic stroke. These data from the PROACT study suggest that intra-arterial (IA) recombinant prourokinase (r-proUK) may extend this therapeutic window to six hours.

A total of 180 patients were randomized in a ratio of 2:1 to receive up to 9 mg of IA r-proUK plus heparin (n = 121) or heparin only (n = 59). In the primary analysis, 40% of r-proUK patients and 25% of control patients had a modified Rankin score of 2 or less (P = 0.04). This was a 58% relative benefit.

Recanalization rates were 66% for the r-proUK group and 18% for the control group (P < 0.001). Other secondary outcome measures at 90 days, such as Barthel Index of 90 or more or NIH Stroke Scale of 1 or less showed insignificant trends toward benefit. The overall hemorrhage rate was 35% with r-proUK compared to 13% in controls, while symptomatic hemorrhage occurred in 10% and 2%, respectively. There were no differences in mortality.

Comment by Alan Z. Segal, MD

Although total hemorrhage rates were high for r-proUK (often small and seen on a mandatory post-procedure CT scan), the symptomatic rate was only 10%. This is not enormously higher than in the NINDS-tPA trial (6.3%). Furthermore, the r-proUK patients were treated later and had larger strokes, both factors known to increase hemorrhage risk.

IA thrombolysis should be strongly considered for patients presenting with MCA occlusion within 3-6 hours of symptom onset. IA therapy for basilar artery occlusion might be considered up to 12 hours post-stroke. In the 0- to 3-hour time window, IV tPA remains the standard of care. However, in centers where it is available, combination IV followed by IA therapy should be considered.

r-proUK is not currently FDA approved. Current options for IA therapy include nonrecombinant urokinase (which is currently out of production) or tPA (which may be given in IA doses of approximately 20-30 mg). ■

Dr. Segal is Assistant Professor, Department of Neurology, Weill-Cornell Medical College, Attending Neurologist, New York Presbyterian Hospital.

Amiodarone for Shock-Refractory Ventricular Fibrillation

Source: *Kudenchuk PJ, et al. N Engl J Med 1999;341(12):871-878.*

Kudenchuk and associates at the university of Washington and the Seattle Fire Department performed this study to determine whether the administration of amiodarone to patients with cardiac arrest due to ventricular fibrillation (VF) or pulseless ventricular tachycardia (PVT) who had not responded to initial measures improved initial survival. Study patients comprised 504 persons out of a total of 3954 consecutive patients treated in the field for cardiac arrest during the 29-month study period. Patients with nontraumatic cardiac arrest were eligible for the study if they had been endotracheally intubated

and remained in VF or PVT after receiving three or more precordial shocks and other therapy according to the American Heart Association's Guidelines for Advanced Cardiac Life Support. In a randomized, double-blind fashion, after administration of 1mg epinephrine intravenously, paramedics on the scene gave the patients either 300 mg amiodarone or placebo intravenously.

The patient groups receiving amiodarone and placebo, respectively, were well matched for age (mean 66 vs 65), gender (76% vs 79% male), cardiac and other medical history, whether bystander CPR was administered, initial cardiac arrest rhythm, and mean time from dispatch to response or procedure (4.3 vs 4.4 min).

Of the 246 patients who received amiodarone, 44% survived to hospital admission, as compared to 34% of the 258 patients who received placebo (P = 0.03), a 29% improvement.

After adjustment for other independent predictors of outcome (e.g., location of arrest, paramedic response time, initial rhythm, presence or absence of bradycardia or hypotension prior to study drug administration, and previous therapy), the odds ratio for survival to admission to the hospital was 1.6 (95% CI, 1.1-2.4; P = 0.02) in favor of amiodarone. Of the 504 study patients, 67 survived to hospital discharge, 13.4% of the patients receiving amiodarone vs. 13.2% of those who got placebo. The trial did not have sufficient statistical power to detect significant differences in patient survival to hospital discharge.

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

This study was conducted in the field, using Seattle's superb multitiered prehospital emergency response system. It could not have been carried out in most cities in the world—even in most large North American cities—and it may be a while before a similar study is performed on patients who suffer ventricular fibrillation in the hospital. Thus, although its clinical setting and patient population differed from those encountered in the ICU, this study's data are unlikely to be augmented by findings more directly applicable to critical care practice.

As a result of this study's findings, amiodarone seems certain to see wider use during shock-refractory cardiac arrest in other clinical settings, including the ICU. Especially in the latter setting, better patient characterization, response times, and dose adjustment should be possible, and thus outcomes could be better than observed in the field. On the other hand, outside the settings of the operating room and the coronary ICU, critically ill patients who suffer cardiac arrest in an ICU tend to have underlying medical conditions, rendering the prognosis unfavorable. Still, the availability of amiodarone may make it possible to successfully resuscitate some patients in whom efforts would otherwise be unsuccessful, at least initially, if the results of this study prove valid. ■

CME questions

Testing form inserted in the July 2000 issue

5. **Which of the following statements is *not* true regarding ciclopirox topical solution (Penlac)?**
   a. It must be applied daily.
   b. Unattached, infected nails do not need to be removed.
   c. Treatment may be needed for 48 weeks or more.
   d. Layers should be removed once a week.

6. **Which of the following is *not* true about dofetilide?**
   a. It is a beta blocker.
   b. It should be started only in a monitored setting.
   c. It prolongs QT intervals.
   d. It is not associated with adverse survival compared with placebo.

7. **When given in the field to patients suffering nontraumatic cardiac arrest, amiodarone improved:**
   a. survival to hospital admission.
   b. survival to hospital discharge.
   c. neurologic outcome at six months.
   d. All of the above
   e. None of the above

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