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INSIDE

Promising Antiviral Drug in Phase II Studies

By William T. Elliott, MD, FACP

Two new quinolone antibiotics have been approved by the fda. **Bayer's moxifloxacin** (**Avelox**) was approved for once-daily treatment of respiratory infections. The drug is effective against common respiratory pathogens including *pneumococcus*, *H. influenzae*, and *Moraxella catarrhalis*. Moxifloxacin is given as a 400-mg dose, once a day for 5-10 days, and is approved for the treatment of acute bacterial exacerbations of chronic bronchitis, community acquired pneumonia, and bacterial sinusitis. **Bristol-Myers Squibb** is also launching **gatifloxacin** (**Tequin**) for the treatment of upper and lower respiratory infections, urinary tract infections, and gonorrhea. Gatifloxacin is available in both an oral and intravenous form. Both drugs are only approved for adults age 18 and older.

Real progress has been made on **antiviral drugs** in the last few years. Late 1999 saw the approval of two anti-influenza drugs. Now, **Agouron Pharmaceuticals** has announced progress in the development of an **anti-rhinovirus** medication. Rhinoviruses are the most frequent cause of the common cold. The drug, **AG7088**, is an inhaled rhinovirus 3C protease inhibitor. The company reports "significant improvement in total cold symptoms" in patients deliberately exposed to rhinovirus. Phase II trials of the drug in naturally acquired colds are in progress.

Antiarrhythmic therapy with drugs, even if it is guided by electrophysiologic studies, has no effect on the risk of sudden death in high risk coronary disease. That is the finding of a study of more than 700 patients published in December 1999 (*N Engl J Med* 1999;341:1882-1890). This confirms previous studies that empirical therapy in these patients is of no value. A second part of the study evaluated the role of **implantable defibrillators** in the same role. The survival benefit was significant with these devices, with a reduction in five-year mortality from 37% (no defibrillator) to 9% (implantable defibrillators). All patients in the study had ejection fractions below 40% and asymptomatic, nonsustained ventricular tachycardia.

Protease inhibitors have been associated with lipodystrophy, hypercholesterolemia, insulin resistance, and even premature CAD. Now there is a report that these drugs may also be associated with venous thromboembolism. Researchers from the University of Iowa report 11 episodes of venous thrombosis or pulmonary embolism in seven HIV-infected patients. These patients were otherwise healthy individuals who were receiving protease inhibitors. The drugs used in these

patients were **ritonavir**, **nelfinavir**, **saquiniavir**, and **indinavir** (*Am J Med* 1999;107:624-626). It is felt that the drugs may interfere with hepatic regulation of clotting proteins resulting in a prothrombotic state.

Niacin may increase homocysteine levels in patients who are being treated for **hypercholesterolemia**. Fifty-two patients with peripheral arterial disease were randomized to receive 1-3 g of niacin daily, or placebo. At 18 weeks, the 25 patients in the niacin group averaged a 55% increase in homocysteine levels from baseline (*Am Heart J* 1999;138:1082-1087). The effect may be blunted by a daily dose of folate or vitamin B_6. Elevated homocysteine levels have been implicated as a risk factor in the development of atherosclerosis.

Anecdotal reports have suggested that **secretin** might be effective as a treatment for children with **autism**. The National Institute of Child Health and Human Development recently tested a single intravenous dose of secretin or placebo in 60 autistic children. The drug showed no efficacy in any of the outcome measures (*N Engl J Med* 1999;341:1801-1806). This study was disappointing for many parents of autistic children, but despite the findings, the majority of parents of the children in the study were planning on pursuing further secreting treatments.

FDA News:

Allergan has received clearance to market a new eye drop for **allergic conjunctivitis**. **Nedocromil sodium** (**Alocril**) stabilizes mast cells and decreases activation of other allergic mediators. The agency has also approved the first topical treatment for **onychomycosis**. German manufacturer **Aventis** will market **topical ciclopirox** as **Penlac Nail Lacquer Topical Solution 8%**. Daily application is required for as long as 48 weeks to treat fungal nails.

Pending final FDA approval, **SmithKline Beecham** will market a new **OTC cream** for the treatment of **oral-facial herpes**. **Docosanol 10% cream** is expected to receive final approval early this year. A trade name has not yet been decided. ■

Entacapone Tablets

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

In october, the fda approved entacapone, the second reversible catechol-O-methyltransferase (COMT) inhibitor for the treatment of Parkinson's disease. Inhibition of the COMT enzyme reduces the peripheral metabolism of levodopa, allowing more levodopa to reach the brain. When a COMT inhibitor is used in conjunction with levodopa/carbidopa, the result is more sustained plasma levels of levodopa for a longer time.

The first approved COMT inhibitor, tocalpone (Tasmar) has been associated with acute, severe liver failure (estimated rate of 1 per 20,000), leading to withdrawal of the drug from the market in many countries.

Tocalpone remains on the market in this country, but the FDA has recommended liver function monitoring every two weeks for patients on the drug. Unlike tocalpone, entacapone has not been associated with liver disease and the FDA is not requiring monitoring of liver function tests when patients are treated with this new medication.

Entacapone is manufactured by Orion Pharma in Finland and marketed as Comtan by Novartis Pharmaceuticals.

Indications

Entacapone is indicated as an adjunct to levodopa/carbidopa to treat patients with idiopathic Parkinson's disease who experience the signs and symptoms of end-of-dose "wearing-off."

Dosage

The recommended dose of entacapone is 200 mg taken concomitantly with each dose of levodopa/carbidopa (immediate or controlled release formulations) up to a maximum of eight times daily (1600 mg). The drug may be taken without regard to meals. Entacapone is supplied as 200 mg tablets.

Potential Advantages

In contrast to tolcapone, monitoring of liver enzymes is not required. Although acute, severe (fulminant) liver failure has been reported with tolcapone, hepatotoxicity has not been reported with use of entacapone. The incidence of elevation in liver enzymes is similar between entacapone and placebo.[1]

Potential Disadvantages

Dopaminergic side effects including dyskinesia, nausea, dizziness, hallucinations, vomiting, and insomnia are the most common adverse effects.

The most common nondopaminergic side effects compared to placebo are diarrhea (20% vs 7%), constipation (14% vs 5%), and urine discoloration (up to 37% vs 0-1.2%).[1] Entacapone turns the urine to dark yellow or even orange-red depending on the dose.[2] On a milligram basis, entacapone is less potent than tolcapone in increasing the bioavailability of levodopa.[3]

Comments

Levodopa, combined with dopa decarboxylase

inhibitor (carbidopa), is a mainstay in the pharmacologic management of Parkinson's disease. But since this drug combination is taken orally, it is still subject to peripheral metabolism of levodopa by catechol-O-methyltransferase (COMT), which is found in the gut and liver. The addition of a COMT inhibitor increases the bioavailability of levodopa by 30-60% and increases levodopa concentration in the central nervous system as assessed by positron emission tomography studies.[1,2] Clinical efficacy has been demonstrated in three 24-week multicenter, randomized, double-blind, placebo-controlled trials conducted in Finland, Norway, Sweden, Denmark, United States, Canada, Germany, and Austria involving 678 patients with wearing-off-type motor fluctuations.[4,5] Treatment with entacapone resulted in an increase in mean "on" time of 0.6-1.4 hours, a decrease in "off" time of 0.6-1.3 hours, and an increase from baseline the percent of awake time "on" 3.0-8.7%. There were also significant ($P < 0.05$) improvements in the United Parkinson Disease Rating Scale (UPDRS) total scores, subscores for part II (activity of daily living), and part III (motor disability).[2,4,5] There was generally no improvement in subscore I (mentation, behavior, and mood). Levodopa/carbidopa dosing generally needs to be decreased when starting entacapone by an average of 25%. More than 58% of patients with daily doses equal to or greater than 800 mg require dose reduction.[5] Data were obtained from daily patient 18- or 24-hour diaries. Analyses were based on intent-to-treat using last observation carried forward method. Limited data suggest that the treatment effect may be greater in patients with less than 55% "on-time."[6] Entacapone is $1.68 per tablet with a daily cost of up to $13.44.

Clinical Implications

Parkinson's disease is a progressive neurodegenerative disorder that affects about 1.5 million Americans. Levodopa is an effective treatment for Parkinson's disease, although there is debate when therapy should be initiated. Long-term levodopa therapy combined with disease progression results in changes in the dopaminergic pharmacodynamics leading to the "wearing-off" phenomenon. The addition of a COMT inhibitor, such as entacapone as an adjunct to levodopa/carbidopa, provides another strategy in managing patients with the "wearing-off" phenomenon. ■

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Pioglitazone Tablets (Actos)

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

The fda has approved a new thiazolidinedione for the treatment of type 2 diabetes mellitus. Eli Lilly and Takeda's pioglitazone (Actos) is the third drug in this class, joining troglitazone (Rezulin) and the recently approved rosiglitazone (Avandia). Thiazolidinediones improve insulin sensitivity by acting as potent agonists for the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) that regulate the transcription of insulin-responsive genes.[1] Sites of action include the liver, adipose tissue, and muscle tissue resulting in a decrease in fasting plasma glucose and insulin.

Indications

Pioglitazone is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. The drug can be used as monotherapy or in combination with sulfonylurea, metformin, or insulin when diet and exercise plus the single agent is inadequate in achieving glycemic control.[1]

Dosage

The recommended initial dose for monotherapy is 15 mg or 30 mg once daily. The dose may be increased in increments up to 45 mg once daily. When used in combination with a sulfonylurea, the initial dose is 15 mg or 30 mg once daily. The dose of the sulfonylurea should be reduced if the patient experiences hypoglycemia. A similar initial dose is recommended for use in combination with metformin or insulin. In patients receiving insulin and pioglitazone, the insulin dose can be reduced by 10-25%.[1] The drug may be taken without regard to meals.

Baseline alanine transaminase (ALT) should be determined before initiating therapy and therapy should not be initiated in patients with baseline ALT more than 2.5 × ULN. Therapy should be discontinued if ALT exceeds 3 × ULN or if the patient is jaundiced.

Pioglitazone is supplied as 15 mg, 30 mg, and 45 mg tablets.

Potential Advantages

In clinical trials involving more than 4500 subjects, no evidence of drug-induced hepatotoxicity or elevation of ALT levels has been reported.[1] The incidence of ALT values equal to or greater than 3 × ULN was 0.26% and 0.25% for pioglitazone and placebo, respectively.[1] Due to the chemical similarity between pioglitazone and troglitazone, the FDA is still recommending that serum ALT be evaluated prior to initiation of therapy and every two months for the first year, and periodically thereafter.[1] Pioglitazone has been reported to produce a modest reduction in triglyceride levels (50 mg/dL) and increase in HDL cholesterol (7-8 mg/dL).[8]

Potential Disadvantages

Edema has been reported in 4.8% of pioglitazone-treated patients compared to 1.2% for placebo-treated patients. Edema was more frequently reported in patients on pioglitazone/insulin combinations. Mean hemoglobin values have declined by 2-4%, which generally occurred within the first 4-12 weeks of therapy and may be related to expansion of plasma volume.[1] Pioglitazone is not indicated in heart failure patients with NYHA III or IV cardiac status. In clinical trials, weight gain was associated with pioglitazone therapy (0.5-3.7 kg), with the greatest increase when used in combination with insulin (2.3-3.7 kg). Pioglitazone may cause resumption of ovulation in anovulatory patients with insulin resistance. Contraceptive measures should be considered in these patients. Ketoconazole may inhibit the metabolism of pioglitazone by inhibiting cytochrome P450 isoform 3A4.[1]

Comments

Pioglitazone is the third thiazolidinedione to be approved. Results from clinical trials (16-26 weeks in duration) have not been published. Limited details are available from the manufacturer and abstracts.[1-6] As monotherapy (n = 865), pioglitazone produced a mean reduction in fasting blood glucose of 30-56 mg/dL from baseline (267-281 mg/dL) and reduction in glycosylated hemoglobin (HbA1c) from 0.3 to 0.9% (10.2-10.8%).[1-3] In combination with a sulfonylurea (n = 560) or metformin (n = 328), pioglitazone produced a mean reduction in fasting blood glucose of 34-58 mg/dL from baseline (236-259 mg/dL) and 0.8-1.3% reduction (9.8-10%) in HbA1c.[1,4,5] In combination with insulin (n = 566), pioglitazone produced reductions of 35-49 mg/dL in fasting blood glucose and 0.7-1% in HbA1c.[1,6] A greater HbA1c reduction has been observed in female patients than in male patients (mean difference of 0.5% in HbA1c).[1]

Clinical Implications

Thiazolidinediones are the newest class of antihyperglycemic drugs, providing a different mechanism of action from the sulfonylureas, metformin, insulin, and alpha-glucosidase inhibitors (acarbose, miglitol). As monotherapy, the magnitude of the glycemic control achieved with thiazolidinediones is generally less than that seen with sulfonylureas or metformin, making them more suitable for combination therapy. Due to the natural progressive course of type 2 diabetes, combination therapy is usually unavoidable. In the first three years of treatment, about 50% of patients achieve control with monotherapy but this is reduced to only 25% after nine years.[7]

Troglitazone had wide appeal as a combination drug until reports of drug-induced hepatotoxicity associated with the drug forced it off the market in Europe and led the FDA to impose strict monitoring of liver function tests in this country. Both pioglitazone and rosiglitazone are touted as being safer than troglitazone, as drug-induced hepatotoxicity has not been reported in clinical trials. The two drugs also seemed to be similar in efficacy (the magnitude of reduction in fasting plasma glucose and glycosylated hemoglobin) and in their side effect profiles (e.g., edema, weight gain). Their effect on the lipid profile may offer a point of differentiation. While both drugs increase HDL-cholesterol (7-8 mg/dL), rosiglitazone increased LDL-cholesterol more than pioglitazone (10-15 mg/dL to 5 mg/dL). In addition pioglitazone reduced triglyceride levels by about 50 mg/dL while rosiglitazone had no effect.[8] Since these differences are not from direct comparative studies, the exact magnitude of the difference and clinical significance remains to be determined.

Pioglitazone is priced between $2.85 and $4.95 per day, similar to rosiglitazone. ■

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Beta Blockers for High-Risk Vascular Surgery

Source: *Poldermans D, et al. N Engl J Med 1999;341:1789-1794.*

Although earlier studies have shown a reduction in perioperative cardiac events with prophylactic beta-blocker use, they lacked power to assess such serious events as perioperative death or nonfatal myocardial infarction (MI). Thus, Poldermans and colleagues randomized 112 major vascular surgery patients with positive dobutamine stress echocardiograms (DSE) at multiple centers to one week of bisoprolol (5-10 mg/d) preoperation (pre-op) followed by 30 days post-operation (post-op) vs. usual care. The primary end points were death from cardiac causes or MI for 30 days post-op. Bisoprolol resulted in lower heart rates, but other patient characteristics were similar in the two groups. Perioperative mortality was less in the bisoprolol group (3% vs 17%; P = 0.02), as was nonfatal MI (0 vs 17%; P < 0.001). All but one of the nine MIs occurred post-operatively; the one pre-op MI resulted in cancellation of the surgery. The combined end point was also reduced (3% vs 34%; P < 0.001). The relative risk of the combined end point on bisoprolol was 0.09 (95% CI 0.02-0.37). Because of these results, the trial was stopped prematurely. Among 53 patients who were excluded from the study because they were already on beta blockers, 7.5 died and there were no MIs. Among eight patients excluded because of extensive wall motion abnormalities on DSE (high risk), four underwent bypass surgery and two of these died, but the two survivors later had successful vascular surgery. The remaining four underwent vascular surgery on beta blockers; one had an MI, but none died. Poldermans et al conclude that bisoprolol reduces perioperative death and MI in high-risk patients undergoing major vascular surgery.

Comment by Michael H. Crawford, MD

Many have resisted the move to liberally use beta blockers for major noncardiac surgery in patients with risk factors for or clinical suspicion of coronary artery disease in favor of preoperative testing to select the appropriate candidate for revascularization or beta blockers. Why the reluctance? The mechanism of action of beta blockers for this purpose is not known and if the myocardium lacks adequate blood flow, it seems more reasonable to return blood flow, especially if it can be accomplished percutaneously. Most agree coronary bypass surgery should be reserved for those who need it anyway. Also, the previous large randomized trial of atenolol prophylactically by Mangano and associates was not very impressive.[1] Perioperative deaths and MI were not reduced, but long-term mortality was. However, Mangano et al studied a lower risk group undergoing various surgeries and their study was underpowered for serious perioperative events. The 10-fold decrease in perioperative death or MI in this study (34% vs 3.4%; P < 0.001), even though it was interrupted when half the planned patients were enrolled, is impressive. On the other hand, these were truly high-risk patients with clinical risk factors, such as age older than 70 years, prior MI, heart failure history, undertreatment for ventricular arrhythmias, diabetes, limited exercise ability, and a positive DSE. The latter suggests that they have flow limiting coronary lesions that perhaps could have benefited from a percutaneous intervention (PCI).

Because of the lack of evidence that PCI improves perioperative outcomes in randomized trials and the cost of such an approach, Lee, in an accompanying editorial, suggests that we should de-emphasize testing and revascularization and increase beta blocker use in appropriate patients.[2] The question is how liberal to be? Clearly not everyone should receive beta blockers, but who are the appropriate candidates? The ACC/AHA guidelines[3] suggest that intermediate-risk patients undergoing major surgery should have noninvasive testing, but Lee believes that, based upon this new evidence, this should be modified to read beta-blocker therapy.

There are other issues as well. What about the lower risk patient (i.e., 1 or 2 risk factors and a negative DSE)? Poldermans et al would not treat such a patient because of the high negative predictive value of DSE. Is one week of therapy enough or necessary? Must selective beta blockers be used like bisoprolol or will nonselective agents work? Also, there are limitations to this study such as the lack of blinding. Of course, it is almost impossible to blind a study using beta blockers because of the heart rate response to the drug. In addition, Poldermans et al eliminated very high-risk patients and the intermediate and lower risk patients. Thus, these data only strictly refer to high-risk patients. However, it will be hard to argue that a perioperative major cardiac event rate of 3.4% on beta blockers can be bested by any other therapy or management approach. Finally, would dipyridamole thallium stress testing provide the same predictive power as DSE for the application of beta blockers? ■

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Stroke Prevention in Patients with Atrial Fibrillation

Source: *Hart RG, et al. Ann Intern Med 1999;131:492-501.*

In this paper, hart and associates performed a meta-analysis of data from 16 randomized clinical trials of antithrombotic therapy for patients with nonvalvular atrial fibrillation. The 16 trials included a total of 9874 participants, including 2239 patients who were assigned to placebo.

Six trials involving 2900 patients compared adjusted-dose warfarin with placebo or control. The mean age of participants at study entry was 69 years, with 29% of the patients being women. The control stroke rate was 4.6% and 12.3% per year for primary and secondary prevention trials, respectively. Meta-analysis showed that therapy with adjusted-dose warfarin reduced the relative risk of stroke by 62%. The absolute risk reduction for all strokes was 2.7% per year in primary prevention and 8.4% per year in secondary prevention. All-cause mortality was decreased by 26% in patients who received warfarin.

Six trials compared antiplatelet therapy vs. placebo. Approximately 90% of total follow-up exposure during antiplatelet therapy was with aspirin alone. The aspirin dosage ranged from 25 mg twice daily to 1300 mg daily. The mean age of participants was 70 years, with 38% women. The average rate of stroke among participants assigned to placebo was 5.2% per year for primary prevention and 12.9% per year for secondary prevention.

Meta-analysis of all six trials showed that aspirin reduced the incidence of stroke by 22%. The absolute risk reduction was 1.5% per year for primary prevention and 2.5% per year for secondary prevention.

Adjusted-dose warfarin was compared to aspirin in five trials involving 2837 patients. The mean age of participants was 71 years and 38% were women. The results of these comparisons were variable but meta-analysis showed that adjusted-dose warfarin reduced overall relative risk for stroke by 36%. The paper also lists data from trials that compared adjusted-dose warfarin with fixed doses of warfarin and aspirin and a number of other antithrombotic regimens. However, these trials were sufficiently different to prevent meaningful use of meta-analysis to combine results. Hart et al then present a table giving the estimated size of treatment effects according to risk status. The greatest benefit is seen with warfarin compared to aspirin in high-risk patient groups, with a 48% reduction with warfarin seen for secondary prevention and a 24% reduction for primary prevention in these subgroups.

Hart et al conclude that there is conclusive evidence from a large number of randomized trials that antithrombotic agents reduce the risk of stroke in nonvalvular atrial fibrillation.

Table

ACCP Recommendations

Age	High Risk	Antithrombic
< 65 yrs.	No	Aspirin
	Yes	Warfarin
65-75 yrs.	No	Aspirin or Warfarin
	Yes	Warfarin
> 75 yrs.	All	Warfarin

Comment by John P. DiMarco, MD, PhD

This paper summarizes two decades of clinical trials in the field of stroke prevention among patients with atrial fibrillation. By combining data from these trials in a meta-analysis, Hart et al give physicians a better estimate of the magnitude of treatment effect of such therapy.

The most valuable parts of this meta-analysis are the comparisons of warfarin vs. placebo, aspirin vs. placebo, and warfarin vs. aspirin. It is clear that warfarin is superior to aspirin or aspirin plus low, fixed-dose adjusted warfarin in high-risk populations. Here, the magnitude of treatment effect is substantial and the risk of excess bleeding relatively modest. Controversy about the role of warfarin still exists, however, for relatively low-risk patients. Here, there is only a modest benefit achieved with warfarin over aspirin or even over placebo, but the excess risk of hemorrhage is still present. A possible conclusion from these data is that physicians should still exercise judgment when considering warfarin for patients at low risk for stroke. A conservative approach may be appropriate for patients at low risk but physicians should be aggressive in the use of warfarin in patients at high risk. High-risk factors include: older women, patients with prior stroke or transient ischemic attack (TIA), and those with hypertension and diabetes.

It is disappointing that this meta-analysis does not

allow us to show any regimen superior to adjusted-dose warfarin. Although a large number of alternative antithrombotic strategies have been tested, none has proved to be superior to warfarin. Anticoagulation with warfarin is still difficult and one hopes that in the future some effective alternative strategy may be identified. Until then, the recommendations of the American College of Chest Physicians (*Chest* 1998) (*See Table*) are worth considering. ■

Dr. DiMarco is Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque.

The Hope Trial

Source: *American Heart Association Annual Scientific Sessions, Nov. 7-10, 1999, Atlanta, GA.*

The heart outcomes prevention evaluation (HOPE) trial randomized 9541 high-risk patients to the angiotensin-converting enzyme (ACE) inhibitor ramipril (10 mg/d) or placebo and vitamin E (400 IU/d) or placebo for a mean follow-up period of 4.5 years. This international study was carried out in 267 hospitals and 19 countries, with the majority of patients coming from the United States. The ramipril arm was stopped in early 1999 because of a favorable outcome for the ACE inhibitor; the vitamin E arm has continued. The study population consisted of individuals with documented coronary artery disease (CAD), cerebrovascular, or peripheral vascular disease. In addition, diabetics without vascular disease with at least one additional CAD risk factor were enrolled. All individuals were older than 55 years of age. Patients had no history of heart failure; hypertensives could be enrolled if blood pressure was controlled (46% had hypertension). Thirty-eight percent had diabetes, 11% had a previous stroke, 43% had peripheral vascular disease, and two-thirds had an elevated cholesterol level. Eighty-one percent of all patients had CAD, half with a prior myocardial infarction (MI). The results were striking, with a robust 20-25% reduction in relative risk favoring ramipril for all vascular end points. (*See Table*.) There was a 22% reduction in the primary end point of cardiac death, stroke, or nonfatal MI (17.7% vs 14.1%). There was a major decrease in stroke and in new heart failure as well as for revascularization. Of interest, new onset diabetes was decreased by 32% (P = 0.002). New renal dysfunction/dialysis or microalbuminuria was also decreased by ramipril. An echo substudy of approximately half the entire cohort (mean ejection fraction of 60%) demonstrated comparable risk reductions for all end points as the entire cohort. Higher risk patients had a greater reduction in events than those at lower risk. It was concluded that lowering of blood pressure only accounted for a small proportion of the decrease of MI and other end points; individuals in the highest quartile of baseline systolic blood pressure had the greatest risk reduction. The hypertensive and nonhypertensive patients had no difference in benefit from ramipril. Vitamin E had no effect on total mortality, cardiovascular deaths, or other end points.

Table

HOPE	End Points (Ramipril vs Placebo)			
	RAM (%)	PLAC (%)	P Value	RR
CV death, MI, or stroke	14.1	17.7	0.001	0.78
All MI	9.8	12.0	0.0005	0.80
CV death	6.0	8.0	0.0002	0.75
NMFI	5.9	7.5	0.0002	0.78
Revascularization	16.0	18.6	0.001	0.85
All death	10.3	12.2	0.003	0.83
Stroke	3.4	4.9	0.0002	0.68
Nondiabetes	3.7	5.3	0.002	0.68
CHF	9.2	11.7	0.002	0.77

Note: The *New England Journal of Medicine* has taken the unusual step of premature electronic publication of this trial on its electronic website: (http://www.nejm.org/content/yusuf/1.asp).

Comment by Jonathan Abrams, MD

These data have already achieved considerable attention and were formally announced at the European Cardiac Society Meeting at the end of August. The benefits of the ACE inhibitor in individuals who ordinarily would not be treated with such a drug are impressive and concordant with a large amount of vascular biology research, endothelial function studies, and mechanistic hypotheses regarding prevention or slowing progression of vascular disease. These data raise the question as to whether *all* individuals who meet the HOPE criteria should be treated with an ACE inhibitor. Given that the entire cohort had an event rate of cardiac death, stroke, or MI of greater than 3% per year, it seems reasonable that for patients with documented vascular disease, representing the majority of the HOPE cohort, or individuals at high risk for future events (e.g., diabetics with risk factors or those with multiple CAD risk factors), ACE inhibitor therapy should be considered. There is considerable disappointment regarding the antioxidant hypothesis because of the null effects of vitamin E.

Earlier data this year from the GISSI-3 trial were also negative in a large population given vitamin E. Some believe that the combination of vitamin E and vitamin C, or the use of different antioxidants, will be necessary to really test the oxidation hypothesis. Certainly, HOPE and GISSI-3 deflate the present enthusiasm for routine use of antioxidant vitamins. ■

Dr. Abrams is Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque.

Therapeutics & Drugs Brief

HIV-1 Drug Resistance in Newly Infected Individuals

Source: *Boden D, et al. JAMA 1999;282:1135-1141.*

As many as half of hiv-1 infected individuals treated with antiviral therapy may develop resistance. Contributing factors include serial monotherapy, uninhibited viral replication due to inadequate suppression by less than maximally effective agents, difficulty adhering to complicated regimens often associated with substantial burden of side effects, and therapy begun late in the course of the disease. Transmission of multidrug-resistant HIV-1 virus is a serious concern. To evaluate the demographics of this problem, Boden and associates evaluated mutations in 80 newly HIV-1 infected individuals who acquired the disease between July 1995 and April 1998; during this time, multidrug treatment of HIV had become the standard methodology.

More than 16% of samples analyzed demonstrated resistance to one or more antiretroviral agents and almost twice that number showed a three-fold or greater reduction in susceptibility to at least one retroviral agent. Only about 4% of samples demonstrated multidrug resistance.

Study subjects in this group came primarily from a population of urban homosexual men. Hence, demographics here described may not reflect other community settings and may not be applicable to women or heterosexual men.

Boden et al suggest that clinical trials that evaluate potential virological and immunological benefits achieved by using resistance assay-guided therapeutic regimens are in order. ■

The Therapeutics and Drugs Brief in this issue was written by Louis Kuritzky, MD, Courtesy Clinical Assistant Professor, University of Florida, Gainesville, FL.

CME questions

Testing form inserted in this issue

17. Which of the following is *not* true about entacapone?

a. It blocks peripheral metabolism of levodopa.
b. The FDA is requiring regular liver function monitoring.
c. It is indicated only for use as an adjunct of levodopa/carbidopa.
d. It increases "on" time and decreases "off" time for Parkinson's patients.

18. With regard to Pioglitazone tablets, no evidence of drug-induced hepatotoxicity or elevation of ALT levels has been reported.

a. True
b. False

19. Prophylactic beta blockers are useful for:

a. high-risk surgery in low-risk patients.
b. high-risk surgery in intermediate-risk patients.
c. high-risk surgery in high-risk patients.
d. b and c

20. 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

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