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INSIDE

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FDA Approves Zanamivir

By William T. Elliott, MD, FACP

The fda has approved glaxo wellcome's **zanamivir** (**relenza**), an inhaled antiviral for the treatment of influenza A and B. Zanamivir is a neuraminidase inhibitor that works to prevent viral dissemination within lung tissue. The drug is delivered via a hand-held, breath-activated device called a Diskhaler. The delivery system was a concern of the FDA because adequate instruction is required for proper use. Relenza needs to be started within two days of symptoms to be effective, and needs to be continued twice a day for five days. The drug should be available by autumn, before the beginning of flu season in this country.

TAP pharmaceuticals has submitted a new drug application to the FDA for **apomorphine** for the treatment of erectile dysfunction. Originally used as a treatment for Parkinson's disease, apomorphine was found to cause erections through both CNS and local mechanisms. The drug, which may be used concomittantly with sildenafil, will be tested in 2 mg, 3 mg, and 4 mg sublingual tablet doses. Higher doses have been found to be effective in early clinical trials. The trade name has already been chosen—"**Uprima.**"

Cytokine tumor necrosis factor (**TNF**) seems to be associated with numerous deleterious actions from joint inflammation in rheumatoid arthritis to organ failure in septic shock. Now it appears that TNF may even play a role in left ventricular dysfunction in congestive heart failure. After a single infusion of **etanercept**, an anti-TNF drug, TNF levels remained depressed for two weeks, ejection fractions were improved, as was exercise tolerance and quality-of-life measures compared to placebo injections (*Circulation* 1999;99:3224-3226). Etanercept recieved approval in January for the treatment of rheumatoid arthritis under the name **Enbrel** (**Immunex Corp**) (See Feb 1999 *PTDA*).

Two vaccines are effective when given in more patient-friendly intervals. **SmithKline Beecham's Lyme disease vaccine** (**LYMErix**) was approved at a schedule of 0,1, and 12 months, thus, it was a full year before maximum protection is achieved. A recent study randomized 800 healthy volunteers to the standard regimen or a shorter schedule of 0, 1, and 6 months. No difference in levels of protective antibodies was noted in the two groups suggesting that the shorter regimen is effective (*Clin Infect Dis* 1999;28:1260-1264). In contradistinction, The hepatitis B vaccine was recently found to be effective in a longer than standard dosing interval. Hepatitis B vaccine is given at 0, 1, and 6 months. This schedule generally requires extra visits, especially to pediatric clinics, where visits are usually yearly. A recent study compared the efficacy of the standard regimen to three annual injections of the vaccine. No difference was found in the efficacy of the two regimens suggest-

ing that children can receive their injections at three yearly physicals (*Pediatrics* 1999;103:1243-1247).

The FDA has approved the second **thiazolidinedione** in three months for the treatment of type 2 diabetes. Following on the heels of **SmithKline Beecham's rosiglitazone** (**Avandia**) which was approved in May, **Takeda and Lilly** are launching **pioglitazone** (**Actos**). Both drugs are similar to **troglitazone** (**Rezulin**), which has recently been linked to more than 40 cases of liver failure. Pioglitazone is approved for monotherapy, or for use in combination with metformin, sulfonylureas, or insulin. Like rosiglitazone, pioglitazone was not associated with hepatoxicity, but also like rosiglitazone, the FDA is recommending periodic liver function testing while on the drug, at baseline, then every two months for the first year, and periodically thereafter.

The **febrile neutropenic** patient represents a challenge to all but the most experienced infectious disease or oncology specialists. Now a study supports a more conservative approach for treating these patients, including the use of oral antibiotics (*N Eng J Med* 1999;341:305-311). One hundred and sixteen febrile chemotherapy patients with average neutrophil counts of 81 were randomized to treatment with intravenous **ceftazidime** or oral therapy with **ciprofloxacin** plus **amoxicillin-clavulanate**. All patients were considered "low-risk" in that they had no other underlying conditions and the neutropenia was expected to last no more than 10 days. All patients were hospitalized until fever and neutropenia resolved. Treatment was successful (no need for treatment modification) in 71% of the oral therapy group vs. 67% of the IV treatment group. The authors conclude that empiric oral therapy with ciprofloxacin and amoxicillin-clavulanate is safe in this group of patients. A second study in the same issue looked at the same oral combination vs. intravenous therapy with ceftriaxone plus amikacin in hospitalized patients (*N Engl J Med* 1999;341:312-318). Again, oral therapy proved as efficacious as intravenous therapy. An accompanying editorial cautions that these findings cannot be extrapolated to treating such patients as outpatients, but many centers are already doing so.

The second "**morning after pill**" has been approved by the FDA. **Women's Capital Corp.'s levonorgestrel** (**Plan B**) is a progestin-only pill to prevent pregnancy after a contraceptive accident or unprotected sex. The product comes in a kit with two levonorgestrel tablets, the first to be taken within 72 hours of unprotected sex, and the second 12 hours later. Efficacy is increased if it is started as soon as possible. Overall rate of pregnancy is decreased from approximately 8% to 1% when taken as directed. The progestin-only regimen is touted as having less side effects, especially nausea, than other morning after regimens containing an estrogen/progestin combination.

Johnson & Johnson will seek approval for a **contraceptive patch** for women. The patch, which contains ethinyl estradiol and norgestimate, is worn for one week, obviating the need to remember to take a daily pill.

Merck is attempting to take its popular muscle relaxant **cyclobenzaprine** (**Flexeril**) over the counter. Ironically, initial concerns on the FDA's part were less about the safety of the drug than about its efficacy. They cited a lack of evidence that muscle relaxants work. Ten million prescriptions were written for Flexeril last year.

The FDA website has published a copy of the "Dear Doctor" letter from **Abbott** regarding **pemoline** (**Cylert**), their CNS stimulant used for treating **attention deficit hyperactivity disorder** (**ADHD**). Because of the risk of hepatotoxicity, the company is now recommending a signed consent prior to initiating therapy and liver function tests every two weeks throughout the duration of therapy. The drug is no longer recommended as first-line therapy for this indication.

For anyone who has been involved with managed care, pharmacy benefits, or formulary management, the federal government's first real look at these issues must seem ironic. As budget surpluses swell, President Clinton has made adding a drug benefit to Medicare a high priority. But Congress has had a rude awakening as cost estimates have swelled to upwards of $90 billion per year by 2008. Various proposals and bills have been tempered by the reality of soaring drug costs and difficult treatment choices. Pharmaceutical corporate boardrooms are, no doubt, sweating out the eventual outcome amidst words and phrases such as "price controls," "guaranteed discounts," "PBM based system," and "formulary." Meanwhile congressional aides are studiously listening to the same buzz words that the industry unsuccessfully approached managed care with in the early 1990's—phrases such as "pharmacoeconomics" and "outcomes-based research." ■

Rofecoxib Tablets and Oral Suspension

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

The cox-2 class of anti-inflammatory/pain relievers now has two entries with the May 21 approval of Merck's rofecoxib (Vioxx). It joins celecoxib (Celebrex—Searle) in this class of "safer"

NSAIDs. Selective cyclooxygenase-2 inhibitors reduce inflammation and produce analgesia without inhibiting COX-1 dependent prostaglandins that protect the gastric mucosa and affect platelet aggregation. Thus, these drugs have a much lower propensity to cause endoscopically detected ulcers and do not cause platelet dysfunction. COX-2 inhibitors, however, do have the same effect on renal blood flow as traditional NSAIDs.

Indications

Rofecoxib is approved for the relief of the signs and symptoms of osteoarthritis, for the management of acute pain in adults, and for the treatment of dysmenorrhea.

Dosage

Rofecoxib is available as 12.5 mg or 25 mg tablets and as an oral suspension containing 12.5 mg or 25 mg per 5 mL. The recommended initial dose for osteoarthritis is 12.5 mg once daily. Some patients may achieve added benefit at a dose of 25 mg once daily, which is considered the maximal dose for this indication. The recommended dose for the management of acute pain or the treatment of primary dysmenorrhea is 50 mg once daily. It may be taken without regard to meals.

Rofecoxib should not be taken by patients who have experienced allergic-type reactions to aspirin or other NSAIDs.

Potential Advantages

Rofecoxib, 25 mg or 50 mg daily, has been reported to produce a lower percentage of endoscopic gastroduodenal ulcers than ibuprofen 2400 mg daily. Difference was statistically significant at 12- and 24-week assessments.1 Rofecoxib also appears to be well tolerated in terms of GI adverse events. In a clinical trial, the percent of patients experiencing diarrhea was 6.8% vs. 6.5% for placebo, 3.5% vs. 2.7% for dyspepsia, 3.8% vs. 2.8% for epigastric discomfort, and 4.2% vs. 3.6% for heartburn.[1] The metabolism of rofecoxib does not involve the cytochrome P450 enzymes, thus minimizing potential drug interactions. A general enzyme inducer, rifampin, has been reported to produce a 50% decrease in the plasma concentration of rofecoxib.[1] Rofecoxib has no effect on platelet function. Dosages up to 375 mg given daily for up to 12 days did not affect bleeding time relative to placebo.[1]

Potential Disadvantages

Rofecoxib is approved for osteoarthritis but not for rheumatoid arthritis. The renal effects of rofecoxib are similar to those of other NSAIDs.[1] The use of rofecoxib for the relief of pain at the 50 mg dose is not recommended beyond five days.[1] Coadministration of rofecoxib and warfarin have resulted in an increase of 8-11% in INR. Monitoring of INR is recommended with coadministration.[1]

Comments

Rofecoxib is a highly selective inhibitor of COX-2. In vitro studies using Chinese hamster ovary cell lines to express COX-1 and COX-2 showed that at doses up to 1000 mg (20 times the maximum recommended dose) no evidence of COX-1 inhibition was seen.[2]

Refocoxib was approved almost six months after the first COX-2 inhibitor, celecoxib, which was approved on Dec. 31, 1998. Merck took extra time to seek a pain indication for its drug, an indication that celecoxib does not have. In various acute pain models, the analgesic effect of rofecoxib 50 mg was similar to that of naproxen sodium 550 mg to ibuprofen 400 mg.[1,2] In osteoarthritis, rofecoxib (12.5-25 mg) has been reported to be similar in effectiveness as ibuprofen 800 mg tid over six weeks or diclofenac 50 mg tid over six months.[1,4,5] Study patients included patients with osteoarthritis of the hip or knee. Ninety percent had an increase in pain following withdrawal of NSAIDs and 10% had moderate symptoms while taking acetaminophen. Rofecoxib, ibuprofen, and diclofenac all showed about a 50% reduction in the WOMAC (Western Ontario and McMaster Universities osteoarthritis index) visual analog scale walking on a flat surface. This is a composite of pain, stiffness, and functional measures in osteoarthritis. Like celecoxib, rofecoxib (25 mg-50 mg) has been associated with fewer endoscopic ulcers (³ 3 mm) than ibuprofen (2400 mg daily) (4.1-8.8% vs 27.7-29.2%). This compares favorably to placebo (5.1-9.9%).[1] However, endoscopic ulcers may not be reliable predictors of severe GI events.[7,8]

Merck will likely seek approval of the drug for treating rheumatoid arthritis; however the effective dose, 50 mg, may be associated with higher adverse events.[9] Rofecoxib is priced competitively with celecoxib for osteoarthritis used (12.5-25 mg daily). For pain, rofecoxib is about $5 per day (2 × 25 mg).

Clinical Implications

Osteoarthritis is the most prevalent form of arthritis, and acute pain and dysmenorrhea are common problems. Pharmacologic management of osteoarthritis includes acetaminophen, topical capsacin, other analgesics, and NSAIDs.[6] Gastrointestinal toxicities are problematic with the use of NSAIDs, especially for patients who have a history of gastritis, peptic ulcer disease, or GERD. COX-2 inhibitors are an attempt to find "safer" NSAIDs.

While the frequency of drug-induced endoscopic ulcers appears to be less with rofecoxib, it is not clear if

long-term serious events are reduced. In addition, it is not known if there are any deleterious effects with prolonged COX-2 inhibition and how it would affect the homeostasis of other body systems such as the balance of prostacycline and thromboxane in blood vessels.[10] ■

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Rosiglitazone

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

The fda has approved smithkline beecham's rosiglitazone for the treatment of type 2 diabetes mellitus. The drug is the second thiazolidinedione to be approved by the FDA. The first drug of this class is troglitazone (Rezulin), which has recently been associated with rare, but highly publicized hepatotoxicity. In clinical trials in about 5000 patients, rosiglitazone has not been associated with drug-induced hepatoxicity or elevation of liver enzymes, but whether rosiglitazone represents a safer thiazolidinedione remains to be established.

Rosiglitazone is marketed as Avandia by SmithKline Beecham and Bristol-Myers Squibb. A third drug in this class, Lilly and Takeda's pioglitazone (Actos), is expected to be approved soon.

Indications

Rosiglitazone is approved for monotherapy, as an adjunct to diet and exercise, to improve glycemic control in type 2 diabetes. It is also indicated for use in combination with metformin when diet, exercise, and either drug alone do not provide adequate control.[1]

Dosage

The recommended starting dose for rosiglitazone is 4 mg daily administered qid or bid. The dose may be increased to 8 mg if there is insufficient glycemic control after 12 weeks of therapy.[1] Higher doses of rosiglitazone tend to be more effective administered twice daily compared to once daily. The difference in glycosylated hemoglobin was significantly greater with 8 mg qid vs. 4 mg bid but not statistically different at 4 mg qid vs. 2 mg bid.[1]

Rosiglitazone may be taken without regard to meals. No dosage adjustment is required in patients with mild to severe renal impairment or in the elderly.[1]

Rosiglitazone is supplied as 2-mg, 4-mg, and 8-mg tablets.

Potential Advantages

Clinical trial results reported no significant difference between placebo in the frequency of ALT elevations more than three times the upper limits of normal (0.2% for both groups).[1] The manufacturer reported no evidence of drug-induced hepatotoxicity in 4598 patients (3600 patient years). However, due to the chemical similarity between rosiglitazone and troglitazone, the FDA is recommending that liver enzymes be checked prior to initiation of therapy and monitored every two months for the first 12 months and periodically thereafter.[1] In vitro data suggest that rosiglitazone does not inhibit any of the major cytochrome P450 enzymes.[1]

Potential Disadvantages

Edema has been reported in 4.8% of patients administered rosiglitazone; thus, the drug should be used with caution in patients with heart failure.[1] Dose-related decreases in hemoglobin (£ 1.0 g/dL) and hematocrit (£ 3.3%) have also been reported.[1] Anemia has been reported in 1.9% of patients compared to 0.7% for placebo and 0.6% for sulfonylurea.[1] Mean weight gains of 1.75-2.95 kg were reported in patients treated with 4-8 mg of rosiglitazone for 52 weeks.[1] Rosiglitazone increases LDL-cholesterol mainly during the first 1-2 months of therapy. HDL-cholesterol is also elevated and continues to rise over time. The net result is an increase in the LDL to HDL ratio, which peaks after two months and tends to decrease over time.[1] The FDA's analysis of the data showed an increase in VLDL-cholesterol of 11.5 mg/dL from a baseline of 20.6 after 26 weeks.[7] Contraception may need to be considered in premenopausal anovulatory women with insulin resistance as rosiglitazone may cause resumption of ovulation.[1]

Comments

Rosiglitazone and troglitazone are both members of the thiazolidinedione class of antihyperglycemic drugs. These agents are thought to improve insulin sensitivity by acting as a potent agonist for the peroxisome prolifer-

ator-activated receptor-gamma (PPARg). These receptors are expressed primarily in tissues such as liver, skeletal muscle, and adipose tissue and regulate the control of glucose production, transport, and use.[1] In animal adipose tissue models, thiazolidinedones may act by increasing the number of small adipocytes and decreasing the number of large adipocytes.[2]

Results from clinical trials on the drug have not been published and limited data are available from the manufacturer and/or in abstract forms only.[1,4,5,6,8] In placebo-controlled 26-week studies (n = 1400), rosiglitazone (4-8 mg daily) produced a reduction (difference from placebo) in fasting plasma glucose (FPG) of 31-76 mg/dL in patients with a baseline FPG of 220-229 mg/dL.[1] Corresponding reductions of glycosylated hemoglobin were 0.8-1.5% with baseline values of 8.9-9.0%. Rosiglitazone was generally more effective when administered twice daily compared to once daily.[1] In a 52-week comparative trial (n = 587) with glyburide (mean dose of 7.5 mg/d), rosiglitazone (4 mg bid) produced a mean change from baseline of 41 mg/dL vs. 30 mg/dL in FPG and 0.53-0.72% in glycosylated hemoglobin. Initial reductions in FPG and glycosylated hemoglobin were greater with glyburide; however, values at 52 weeks appeared to be comparable. In contrast to placebo-controlled trials, patients in the active-controlled trial had lower baseline FPG (190-196) and glycosylated hemoglobin (8.07-8.21). Unpublished data indicate that the addition of rosiglitazone to metformin, sulfonyurea, and insulin in type 2 patients has resulted in added improvement in glycemic control.[4-6] Currently only the combination with metformin is FDA approved.

The daily cost of rosiglitazone (4-8 mg) ranges from $2.50 to $5 per day. This compares favorably to troglitazone (200-800 mg/d), which ranges from $3 to $9.50 per day.

Clinical Implications

Thiazolidinediones are the newest class of antihyperglycemic agents approved for use in type 2 diabetics. Members of this class, which currently include troglitazone and now rosiglitazone, seem to work by increasing insulin sensitivity. These agents offer a different mechanism of action from the sulfonylureas, metformin, insulin, and acarbose. Thiazolidinediones also offer the potential for combination therapy with these other agents. Toxicity is a concern, with liver toxicity leading the FDA to recently change the labeling for troglitazone. On the other hand, animal studies have suggested that these drugs may protect the vasculature from diabetes-enhanced injury.[3] While clinical trial data are encouraging, whether rosiglitazone will be safer for the liver than troglitazone remains to be determined. ■

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Meta-Analysis of Trials for Stable Angina

Source: *Heidenreich PA, et al. JAMA 1999;281:1927-1936.*

Despite many years of use of the three traditional classes of anti-anginal medications, none has emerged as distinctly superior. Because of demonstrated reductions in post-MI mortality with beta-blockers, consensus has generally suggested them as first-line therapy. Since some patients, especially those with bronchospastic lung disease, tolerate calcium channel blockade better than beta blockade, this class of agents also sometimes holds first-choice status. This study analyzed by meta-analysis all randomized trials (1966-1997) of at least one week duration, which compared at least two of the three different drug classes.

Most of the analyzed studies were beta blocker vs. calcium antagonists. Comparing outcomes of cardiac death, MI, angina episodes, use of nitroglycerin, and exercise time, neither class of drug emerged significantly superior. The only statistically significant difference between the classes was in respect to withdrawal for adverse events, for which beta blockers fared more favorably than calcium antagonists.

Studies comparing nitrates with calcium antagonists did not show any significant between-class differences; similarly, although comparisons between beta-blockers and nitrates were the least frequent, no clear advantage of either class emerged.

Comment by Louis Kuritzky, MD

Since all three classes are equally efficacious, the fact that beta-blockers enjoyed more favorable withdrawal rates suggests that they remain first-choice therapy. ■

Does Aspirin Attenuate the Beneficial Effects of ACE Inhibitors?

Source: *Leor J, et al. J Am Coll Cardiol 1999;33:1920-1925.*

For the past several years, there has been a contradiction regarding a possible adverse reaction between the use of aspirin and ACE inhibitors regarding major clinical end points. Several important clinical trials, including SOLVD, CONSENSUS II, GUSTO-I, and GISSI-3, all demonstrated in retrospective analyses a reduction of benefits when aspirin was used with ACE inhibitors. Furthermore, several hemodynamic studies in patients with congestive heart failure demonstrate attenuation of the beneficial effects of ACE inhibitors on a variety of renal and cardiac parameters; on the other hand, other small studies have not shown a negative interaction. Investigators from the Bezafibrate Infarction Prevention (BIP) study performed a retrospective analysis on a large BIP registry cohort. A total of 1196 subjects were identified who were treated with ACE inhibitors and were followed for at least five years. These patients represented 11% of the entire cohort registry. ACE inhibitors and aspirin were given to 618 subjects, whereas 579 received only an ACE inhibitor. A subgroup analysis was also done on 464 patients with clinical congestive heart failure, NYHA Class II or greater. Total and cardiovascular mortality as well as adjusted survival for age, gender, and a variety of other clinical conditions were calculated. The results indicated a substantial difference in total and cardiovascular mortality for the entire cohort, as well as for approximately 50% of individuals with heart failure. Thus, the five-year mortality for those on combination therapy was 19% vs. 27% for the patients on ACE inhibitors alone ($P = 0.002$). Cardiovasvcular mortality was 12% vs. 18%, respectively. These differences remained robust after adjustment for a variety of parameters. In the heart failure cohort, similar findings were noted, with 35% total mortality in the nonaspirin users compared to 24% in the combination therapy cohort. Cardiovascular mortality was 17% in aspirin users vs. 26% in nonaspirin users. Again, there was a significant risk reduction after adjustment for age, gender, diabetes, and various medications. Leor and colleagues conclude that in coronary artery disease subjects treated with both an ACE inhibitor and aspirin, survival is enhanced and the "beneficial association" is even more prominent in subjects with heart failure.

Leor et al emphasize the classic pharmacophysiologic rationale for a potential negative interaction, which is impairment of bradykinin generation due to use of aspirin (or nonsteroidals), resulting in a decrease in production of vasodilator prostaglandins and nitric oxide. Several studies from Europe have demonstrated inhibition of the hemodynamic effects of ACE inhibitors when aspirin is co-administered. Furthermore, a report suggests that enalapril may reduce the formation of thromboxane A2, resulting in an independent antithrombotic effect of ACE inhibitors that might attenuate the beneficial effects of aspirin. On the other hand, a recent study suggests that aspirin may improve endothelial function. Thus, there are a number of conflicting mechanisms that could explain both a positive and negative interaction of these two agents.

The BIP investigators recognize that major clinical trials do not support a favorable interaction or association between ACE inhibitors and aspirin. They point out the limitations of their study being a post hoc analysis, with the therapeutic designation based on a single report form. They believe that possible crossover between the groups regarding aspirin use might underestimate the benefits associated with combination therapy. They call for further research in this area and suggest that low-dose aspirin (most patients received less than 250 mg/d) are safe and can be given with an ACE inhibitor in patients with heart failure and coronary artery disease (CAD).

Comment by Jonathan Abrams, MD

This controversy is very important. Because all currently support the use of aspirin in patients with CAD, it is inappropriate to preclude this compound. It is known that the majority of patients with heart failure have CAD as the primary etiology. Thus, the potential downside of a negative interaction between two commonly used agents is of widespread interest. Adequate data are clearly not available to resolve this question. The BIP registry experience data are reassuring; however, it is unclear how and when the diagnosis of heart failure was made, how long the patients were treated with an ACE inhibitor and aspirin or ACE inhibitor alone, or why an ACE inhibitor was chosen. The indications for ACE inhibitors are

increasing beyond patients with abnormal ventricular systolic function. The unreported results of the HOPE Trial indicate that an ACE inhibitor may improve survival in high-risk subjects who do not have overt CAD. Other data are concordant with a beneficial effect of ACE inhibitors in postinfarction patients regarding recurrent myocardial infarction and unstable angina.

Given the absence of prospective data, the differences in patient populations, and drug use among the various studies, it seems prudent not to withhold aspirin from patients with CAD with or without congestive heart failure who are taking an ACE inhibitor. The data from BIP do not prove that there is no negative interaction, but they are inconsistent with an adverse association. Whether individuals treated with ACE inhibitors should be given a lower dose of aspirin, as suggested by the BIP investigators, is unresolved but seems like a harmless and prudent strategy. ■

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

Abciximab for Unstable Angina in Patients with Elevated Troponin T

Source: *Hamm CW, et al. N Engl J Med 1999;340:1623-1629.*

This study is an important subgroup analysis from the c7E3 Fab Antiplatelet Therapy in Unstable Refactory Angina (CAPTURE) trial. In the earlier study, the glycoprotein IIb/IIIa-receptor blocker abciximab (ReoPro) was shown to reduce the risk of myocardial infarction (MI) in patients with refractory unstable angina.[1] This study looks more closely at the prognostic value of troponin T and the effect of abciximab on risk of adverse outcome in relation to troponin T level. The patients had recurrent chest pain at rest associated with ECG changes consistent with ischemia and continued to have chest pain despite treatment with IV heparin and nitroglycerin. All patients had significant coronary artery disease documented by angiography. Patients were excluded if they had sustained an MI within the prior two weeks.

Suitable patients were given abciximab 0.25 mg/kg IV bolus followed by a 10 mcg/min infusion or a matching placebo. Subjects were scheduled for percutaneous transluminal coronary angioplasty (PTCA) the day after study medication was given. Study end points were death, MI, unscheduled PTCA, and coronary bypass surgery.

Of the 1265 patients in the CAPTURE trial, 890 met criteria for inclusion in this study. Subjects were grouped according to troponin T levels at study entry. Among the 615 patients with normal troponin T levels, the risk of death or MI was 8% and was not improved by abciximab treatment. However, the effect of abciximab was striking among the 275 patients with elevated troponin T levels (> 0.1 ng/mL): 7.5% of abciximab-treated patients experienced death or MI within six months, compared to 24% of placebo-treated patients. The relative risk of death or MI associated with abciximab treatment was 0.32 in patients with elevated troponin T levels. The authors conclude that troponin T elevation identifies a subgroup of patients at high risk of death or MI and that this group will benefit considerably from treatment with abciximab.

Comment by David J. Karras, MD, FAAEM, FACEP

Unstable angina carries with it a high risk of MI and/or death within several months of onset. The rate of adverse events in placebo-treated patients (despite therapy with heparin and nitroglycerin) in this study is strikingly high and consistent with earlier studies. Furthermore, this study confirms that troponin T elevation greatly increases the risk of mortality and infarction. Troponin T is an extremely sensitive and specific marker of myocardial injury. Elevated troponin T levels in patients without a rise in creatine kinase is thought to reflect focal myocyte necrosis from embolization of thrombi released from a disrupted coronary plaque. Since such plaque disruption precedes coronary occlusion, troponin T elevation often heralds an impending major infarction or sudden cardiac death.

Certain caveats must be condidered before applying this study's finding to patients in the ED. Most importantly, abciximab was not used as primary therapy for unstable angina. The patients in this study all had recurrent chest pain despite management with heparin and nitroglycerin. All subjects were demonstrated to have significant coronary artery disease; the results may not be applicable to "all comers" presenting with angina-like chest pain to the ED. Nonetheless, it is important that emergency physicians be familiar with the glycoprotein IIb/IIIa-receptor blockers. Several articles discussing the role of these drugs from an ED perspective appear in a recent issue of *Journal of Emergency Medicine* (1999;17:565-595). ■

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Therapeutics and Drugs Brief

A Cure for the Common Cold?

Source: *Turner RB, et al. JAMA 1999;281:1797-1804.*

In randomized, double-blind, placebo-controlled trials conducted in humans, experimental rhinovirus type 39 inoculation was tested with preinoculation or postinoculation administration of tremacamra or placebo. Tremacamra was associated with decreased incidence of clinical colds (44% ± 11% vs 67% ± 9%), improved total symptom scores (9.6 ± 2.9 vs 17.6 ± 2.7), and decreased nasal mucus weight (14.5 ± 9.4 vs 32.9 ± 8.8 g) ($P < 0.001$ for all comparisons). Tremacamra was not associated with any adverse effects or evidence of absorption through the nasal mucosa and did not interfere with development of neutralizing antibody to rhinovirus.

We continue to search for the cure for the most common human infection, the common cold. Strategies that have been attempted include antivirals, which show some promise when used prophylactically but not once symptoms develop, and symptomatic treatments such as antihistamines, decongestants, and anti-inflammatory agents, all of which have limited efficacy and on only some but not all of the typical cold symptoms.

Of the 101 types of rhinoviruses, which account for 70% of upper respiratory tract infections, 90 types use intercellular adhesion molecule 1 (ICAM-1) as the cellular receptor for cell entry. This is the basis for this particular strategy to attempt to prevent or treat rhinovirus infections by intranasal administration of the soluble extracellular portion of the ICAM-1 molecule to compete with virion binding.

This study included both preinoculation and postinoculation administration, but both were actually prophylactic since clinical symptoms had not yet appeared. Thus, this strategy is not curative, but rather preventive. Tremacamra has been studied with one rhinovirus type 39, which appears to be particularly susceptible to the effects of tremacamra. The effects on the other rhinoviruses remain to be proved. Soluble tremacamra is cleared rapidly from the nasal mucosa. In these studies, two formulations were used—one solution and the other a mannitol-based powder with carboxymethylcellulose to retard clearance of the drug from the nasal cavity. Unfortunately, the carboxymethylcellulose was associated with nasal irritation. It is enticing that a strategy such as this actually shows efficacy, but we remain a long way from being able to use this clinically. ■

The Therapeutics and Drugs Brief was written by Hal B. Jenson, MD, FAAP, Chief, Pediatric Infectious Diseases, University of Texas Health Science Center, San Antonio.

CME questions

Testing form inserted in the January 1999 issue

23. Which of the following is *not* true about refocoxib?

a. It is approved for the treatment of pain.
b. It is approved for the treatment of rheumatoid arthritis.
c. It does not affect platelet function.
d. Its effect on renal blood flow is similar to traditional NSAIDs.

24. Which of the following is *not* true for rosiglitazone?

a. It raises LDL and HDL cholesterol
b. Higher doses are more effective administered twice a day
c. It has not been associated with liver dysfunction in clinical trials
d. The FDA is not recommending monitoring liver functions when the drug is started.

25. Abciximab reduces the risk of MI and death associated with unstable angina when administered:

a. upon patients' ED presentation.
b. regardless of serum troponin T level.
c. to patients with or without known atherosclerotic disease.
d. concomitantly with heparin.

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