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Inflammation not the main suspect in the case of osteoarthritis

Research now points finger at chronic joint degeneration

In the search for the best treatment for patients with osteoarthritis (OA), evidence is mounting against a different enemy — shifting the blame away from inflammation. The change in focus is bringing dramatic changes to how caregivers think about the disease and how it should be treated.

With ongoing research suggesting chronic joint degeneration, not inflammation, is responsible for causing the disease and its associated pain, researchers argue the primary treatment goal should be to fight the pain and not the inflammation.

The new interest in pain relief is leading experts to take another look at the basic first-line treatment, such as exercise and lifestyle changes. There is also concern over some serious mortality and morbidity issues that can come with treating patients with first-generation nonsteroidal anti-inflammatory drugs (NSAIDs). With the return to the basics comes renewed interest in the simple analgesics that do not reduce inflammation.

Relieving the inflammation still is important, however, and the newly available COX-2 inhibitors have provided physicians and patients with a popular new drug treatment without much of the gastrointestinal (GI) side effects associated with other NSAIDs. **(See related story, p. 135.)**

There is an inflammation component to OA, says **Joseph Golbus**, MD, head of the division of rheumatology at Evanston Northwestern Healthcare and an associate professor of medicine at Northwestern University Medical School in Evanston, IL. “But inflammation is no longer the primary mechanism.”

Golbus says that fundamentally, OA is a mechanical process of the joints. Doctors can treat the inflammation, but it will not prevent the overall progression of the disease. “What you’re really after is pain relief, comfort,” he says.

Another argument against treating inflammation is the toll some of the drugs take on the patients. “We’ve realized the toxicity is a bigger issue than we thought in terms of the mortality [from] the ulcers and bleeding, . . . and that’s the turning point. The number of deaths from the anti-inflammatories are far greater than earlier appreciated. If the

disease is not life-threatening, and NSAIDs don't alter the course of the disease, why should we expose patients to the risks? If pain control is really the issue, we ought to rethink [drug regimens]," he says.

Data from epidemiological studies compiled by The American College of Rheumatology (ACR) show that among OA patients over 65, 20% to 30% of all hospitalizations and deaths due to peptic ulcer disease were attributable to NSAID therapy. The same studies show that patients also taking oral corticosteroids and anticoagulants are at higher risk. Overall, the studies found that 30% of all NSAID users will suffer GI side effects, which are likely to begin within three months of therapy. The studies also found that women are more likely to develop GI bleeding than men.

In a related survey of OA patients conducted by the Arthritis Foundation in Atlanta, 58% said they have either changed their medication or stopped taking it because of side effects.

But Golbus says he is not ready to discount the use of NSAIDs and notes that so far, he is a proponent of the new COX-2 inhibitors. The bottom line, he says, is NSAID use is not likely to stop.

Currently, more than a dozen first-generation NSAIDs are on the market, and physicians long have taken a trial-and-error approach to prescribing, based on patient reactions. According to the research firm IMS Health in Westport, CT, sales of anti-arthritics totaled $1.7 billion for 1998, accounting for 70.5 million prescriptions.

"The COX-2s are for real and are probably one of the best-studied drugs in the history of drug development," Golbus says. "That's why there's been the push over the last year for the simple analgesics or the selective COX-2 inhibitors."

Of the two cyclooxygenases (or COX enzymes) known to exist, COX-1 protects the stomach lining, while COX-2 causes inflammation. Blocking both enzymes with traditional NSAIDs exposed the stomach to toxicity. The selective COX-2 inhibitors work by blocking only the inflammation response.

Golbus says if patients can get safe relief from inflammation, which the majority of patients still believe is the cause of OA, and can be convinced to maintain analgesic therapy for pain, then new treatment goals can be satisfied.

ACR is revising its 1995 treatment guidelines to emphasize pain relief and to overhaul recommendations on NSAID therapy.

OTC compliance, interactions

Physicians believe the new focus on pain relief and the advent of the COX-2 inhibitors will bring greater patient compliance, especially if side effects decrease during new NSAID regimens. They note, however, the need to improve compliance with analgesic therapy, which traditionally has been erratic.

"Achieving compliance with acetaminophen as first-line pharmacologic therapy is more challenging than it seems," says **Stephen Brunton**, MD, clinical professor of family medicine at the University of California College of Medicine in Irvine. "Even though acetaminophen is available without a prescription and is less expensive than many other drugs, those factors can be a disincentive because the drugs are not reimbursed by plans, and patients feel like they aren't getting their money's worth from a physician when they are told to take what they perceive to be a headache remedy," he says.

Additionally, if the focus on pain relief over anti-inflammation leads to even more reliance on analgesic-only, first-line regimens, patients will need more education on the merits of OTC therapy. "Patients may not understand why they do not need an anti-inflammatory agent when conventional wisdom has labeled OA as an inflammatory condition."

Golbus notes he is concerned that the COX-2 inhibitors already are popular and could replace the first-line analgesic therapy that continues to be a mainstay of treatment guidelines. The allure of a new drug can be so great that patients get wrapped up in it, hoping for a panacea instead of

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A second COX-2 inhibitor

In July, the Food and Drug Administration approved Merck's Vioxx (rofecoxib), which will join Pfizer's Celebrex (celecoxib) as the second selective cyclooxygenase type 2 (COX-2) inhibitor on the market within the new class of nonsteroidal anti-inflammatory drugs (NSAIDs) available for the treatment of osteoarthritis (OA). Celebrex was approved in December 1998.

Rofecoxib's approval indicates use for OA, the management of acute pain, and for the treatment of dysmenorrhea. The label indications for celecoxib are for the management of OA and rheumatoid arthritis. Merck's ability to obtain labeling information for acute pain is timely and potentially advantageous, based on the newly recognized shift in OA treatment from decreased inflammation to simple pain relief **(see cover story)**.

Joseph Golbus, MD, however, head of the division of rheumatology at Evanston (IL) Northwestern Healthcare, says both drugs achieve the desired effect of pain relief without the gastrointestinal (GI) side effects of the widely used first-generation NSAIDs.

The COX-2 inhibitors breakthrough came when researchers found two forms of the cyclooxygenase enzyme that NSAIDs are used to block. The COX-1 enzyme protects the stomach lining, while the COX-2 enzyme causes inflammation.

Traditional NSAIDs block both enzymes, making the body vulnerable to GI toxicity that can result in bleeding and ulcers. The selective COX-2 drugs attack only the inflammatory enzyme, leaving the COX-1 enzyme to protect the stomach lining. Both COX-2 inhibitors are recommended at a dose of between 12.5 mg and 25 mg once daily.

In clinical trials of celecoxib, the recommended dosage proved similar in efficacy to 800 mg of ibuprofen or 50 mg of diclofenac.

In terms of the decreased toxicity of the COX-2 inhibitors, trials of rofecoxib as high as 50 mg daily were associated with lower rates of ulcers than the standard dosage of 2,400 mg of ibuprofen daily. Approval of rofecoxib followed trials of approximately 3,300 patients.

Interaction cautions include its use with rifampin, methotrexate, and warfarin. Like celecoxib, rofecoxib's label will carry a warning concerning GI ulcers and bleeding, though few cases were documented during trials.

The drug is expected to be on the shelves by this fall, supplied as 12.5 mg and 25 mg tablets in bottles of 30, 100, 1,000, and 8,000, and in an oral suspension at 12.5 mg or 25 mg per 5 mL. The drug is expected to be priced at $2.02 per tablet and $3 per 5 mL suspension.

[For more on rofecoxib, contact Merck in West Point, PA, at (800) 672-6372. For more on celecoxib, contact Pfizer in New York City at (800) 438-1985 and see the July 1999 issue of Drug Utilization Review.*]* ■

following diet and exercise recommendations.

"Particularly, physicians fall down on the lack of application of the nonpharmacologic therapies, then they are quick to write a prescription," he says. (The Arthritis Foundation, which in May published a national report card on the state of OA therapy, gave physicians an overall grade of C on their use of a comprehensive treatment approach for arthritis. Golbus says the assessment is fair.)

If the COX-2 inhibitors overshadow other regimens, then drug-drug interactions can become a treatment factor. Even the COX-2 drugs, like all NSAIDs, should be used carefully with high-blood-pressure drugs, particularly beta-blockers and ACE inhibitors. "The NSAIDs can cause salt and water retention, which affect high blood pressure and interfere with how the antihypertensives work," says Golbus, who adds that more post-market surveillance needs to occur before the specific interactions between the selective COX-2 inhibitors and antihypertensives are known.

Even acetaminophen therapy has its side effects. The drug is linked to liver toxicity, but mainly in patients using alcohol excessively while taking the analgesic, a factor pharmacists can investigate during patient profiles or in clinics.

Long-term use of acetaminophen also has been associated with renal failure when taken in combination with NSAIDs. Rheumatologists will be watching that combination closely if it becomes more popular than NSAID monotherapy after the new treatment goals and COX-2 inhibitors gain popularity.

Although the American College of Rheumatology is revising its 1995 OA treatment guidelines, much of what is already published will remain. Revisions will focus on strengthening the message of pain relief throughout the stages of treatment. A more substantial change will be adding provisions for the use of COX-2 inhibitors in high-dose second- or third-line therapies for OA of the hip or knee, for example.

The guidelines stress initiating drug-free

therapy to gauge any response to exercise, physical therapy, or weight control as needed, before beginning any drug therapy.

For first-line drug therapy, 4,000 mg of acetaminophen daily is generally recommended. (In specific cases of OA of the knee, aspiration or injections of the intra-articular steroid triamcinolone hexacetonide 40 mg is recommended for consideration prior to the administration of acetaminophen. Also in cases of OA of the knee, the topical analgesics methyl salicylate or capsaicin cream are recommended in combination with acetaminophen.)

In general drug therapy, the lack of response to acetaminophen is followed by the use of low-dose over-the-counter ibuprofen, aspirin, naproxen sodium or non-aceylated salicylates.

The guidelines then move to prescription, or full-dose, NSAIDs. "This is where the guidelines need to be changed the most, as to where the COX-2s will come in," says Golbus. The existing provisions for the combined use of NSAIDs and misoprostol, which is recommended for patients who have risk factors for GI bleeding or ulcers also need to be revised, he says. In general, he says it's premature to speculate on whether the traditional crop of NSAIDs will be phased out of the guidelines in favor of the COX-2 inhibitors.

Guideline time line

Representatives from the ACR also say it's too early to reveal much detail about the new guidelines, but they say official interim guidelines or fact sheets concerning the use of COX-2 inhibitors should be published by the end of this year. Postmarket surveillance of the COX-2 inhibitors also will be necessary, they add.

Following the use of prescription NSAIDs, current guidelines go on to address different types of elective surgery when drug therapy has failed.

Also this year, the National Institutes of Health is embarking on a comprehensive study of glucosamine therapy, which has not been approved by the Food and Drug Administration for OA.

Glucosamine is an endogenous compound synthesized from glucose believed to work by repairing joints and cartilage through the relief of inflammation and pain. Small studies have alluded to pain relief and increased long-term mobility. Glucosamine is given either orally or by injection into muscle or blood vessel.

Viscosupplementation, the injection of synovial fluid directly into affected joints to replace or boost the viscoelasticity of synovial fluid, is available by the product names Hyalgen and Synvisc, which have been approved by the FDA for OA treatment.

[For additional information, contact the Arthritis Foundation at 1330 W. Peachtree St., Atlanta, GA 30309. Telephone: (404) 872-7100. Web: www.arthritis.org. American College of Rheumatology, 60 Executive Park S., Suite 150, Atlanta, GA 30329. Telephone: (404) 633-3777. Web: www.rheumatology.org.] ■

ADA Conference Highlights

New studies and warnings unveiled at CA meeting

Attendees at the 59th annual scientific sessions of the American Diabetes Association (ADA) in San Diego learned that a new trial is coming on the heels of the landmark United Kingdom Prospective Diabetes Study (UKPDS), which followed the treatment of patients with Type 2 diabetes for two decades.

The UKPDS found that 22% of incidences of myocardial infarction (MI), stroke, or angina occurred within first 10 years after Type 2 diabetes diagnosis. A next step is to determine whether a combination of statin and fibrate therapy to lower lipid levels can prevent cardiovascular incidents in these patients (who have not had a stroke, MI, or angina).

The Lipids in Diabetes Study will recruit 5,000 subjects with Type 2 diabetes. The new study will randomize a daily dose of 0.4 mg of the HMG-CoA reductase inhibitor cerivastatin and a 200 mg dose of fenofibrate vs. placebo.

The research is co-sponsored by the ADA and statin manufacturer Bayer (Lipobay and Baycol) and will include researchers from the UKPDS study.

According to the Centers for Disease Control and Prevention (CDC) in Atlanta, 98% of adults with Type 2 diabetes either suffer from cardiovascular disease (CVD) or are carrying risk factors. Yet the CDC says that just one in five patients are regularly taking a simple daily dose of aspirin. The ADA began recommending aspirin therapy

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in 1997, after published studies dating back to 1988 showed the positive effects of aspirin in patients with CVD or risk factors.

The CDC and the National Center for Health Statistics surveyed 1,503 patients over age 20 who were statistically eligible for aspirin therapy in terms of having a history of MI, stroke, angina, or claudication, or risk factors such as hypertension, obesity, abnormal lipid levels, smoking, or a family history of coronary disease. The survey found that only 37% of patients with cardiovascular disease and 13% of patients with risk factors used aspirin regularly.

According to **Deborah Rolka** of the CDC's Diabetes Statistical Division, only patients with aspirin allergy, recent GI bleeding, or active liver disease should not take aspirin as part of diabetes treatment. She says the survey found that demographics played a large role in who was informed about aspirin therapy. Most likely to be taking aspirin were white, non-Hispanic patients age 40 or older who already were suffering from cardiovascular disease. Rolka says more resources and clinic time need to be spent educating younger, poorer, minority patients.

The ADA recommends a daily dose of 81 to 325 mg of an enteric-coated aspirin as a secondary prevention for patients with cardiovascular disease (CVD) and as a primary prevention for patients with CVD risk factors. The ADA also says it has completed a study showing that regular aspirin therapy does not increase the risk for diabetic retinopathy, a bleeding in the eye which was thought to be a condition of aspirin therapy by diabetics.

Four separate studies presented at the scientific sessions warned that adolescents were developing Type 2 diabetes at alarming rates; until recently, the disease mainly has affected overweight adults 45 and older. Obesity is blamed for much of the problem in children, considered part of a generation suffering from poor diets and too little exercise. Diagnosis also has become a factor because most physicians do not expect diabetes to show up in young patients.

"Type 2 diabetes was practically unheard of in young people until the last few years," says **Robin Goland**, MD, of the Naomi Berrie Diabetes Center at Columbia Presbyterian Hospital in New York City. "Because of the long-term damage that high blood sugar levels can do to blood vessels throughout the body, we might see the devastating complications of diabetes very early, such as heart attack, stroke, blindness, and amputations in 30-year-olds if they are not properly diagnosed and treated early."

Goland submitted a paper detailing a study of 19 patients ages 10 to 17, all of whom were obese and had acanthosis nigricans, and most of whom had relatives with diabetes. "The average blood glucose level of these children was 397 mg / dl, which is extraordinarily high," Goland says. "Because physicians are not expecting to see Type 2 in youngsters, the diagnosis is not made until severe hyperglycemia has developed."

Goland emphasizes that in terms of diagnosis, obesity in children (defined as more than 20% above desired body weight) should be associated with insulin resistance, which is the first step toward the development of Type 2 diabetes.

A similar patient assessment at the University of California at San Diego School of Medicine detailed the cases of 58 patients, of whom 83% were obese, 74% had acanthosis nigricans, and 100% had type 2 diabetes. Studies from Canada and Japan also spelled out an increase in the cases of adolescent Type 2 diabetes.

Depressed patients at greater risk

Patients with Type 2 diabetes also suffering from depression need an interdisciplinary treatment approach in order to treat both conditions successfully, according to research submitted by **Patrick Lustman**, PhD, professor of medical psychology in the department of psychiatry at Washington University School of Medicine in St. Louis.

"Because of physiologic and behavioral interactions between diabetes and depression, each becomes more difficult to control, which increases the risks of cardiovascular disease, diabetic retinopathy, neuropathy, and other problems," says Lustman.

He says his research has found that up to 20% of diabetics suffer from clinical depression, based in part on the unhappiness over the obesity associated with the disease. Depression can lead to poor compliance with diabetes treatment, which makes a patient sicker and, therefore, more depressed.

"But when you treat the depression with psychotherapy or medication or both, it's easier to control blood sugar levels, and when you treat blood sugar levels, it becomes easier to treat depression. The two conditions are ideal candidates for intensive interdisciplinary treatment."

The hormonal impact of depression, which

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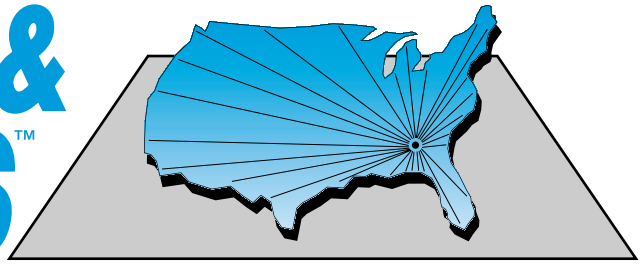

Thrombolytic therapy for acute myocardial infarction

By **Edgar R. Gonzalez**, PharmD, FASHP, FASCP
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Introduction

Coronary artery disease, the leading cause of death in the United States, affects approximately 12 million Americans. The medico-economic impact of cardiovascular disease is astronomical; estimated direct and indirect costs for cardiovascular disease and stroke will exceed $250 billion a year, with $111.5 billion of these dollars spent on hospital costs and nursing home services.

Despite a 54% decrease in age-adjusted mortality between 1963 and 1990, 50% of deaths in Americans older than 65 are due to coronary artery disease. Each year 1.25 million Americans suffer an acute myocardial infarction (AMI), causing 500,000 deaths annually. Experts estimate that AMI occurs about once for every 160 persons.

Approximately 50% of patients with AMI die within the first few hours due to electrical instability leading to ventricular fibrillation. Mortality among AMI survivors ranges from 10% to 15% in the first year and is 3% or 4% per year thereafter. Patients with anterior wall infarction, left ventricular dysfunction, and complex ventricular ectopy have the highest one-year mortality rate after AMI (20%). AMI patients without these risk factors have a 3% one-year mortality rate.

The primary goal of therapy for AMI is to reduce mortality. Management of AMI is designed to relieve pain and anxiety, to recognize and control life-threatening arrhythmias, to limit infarct size, and to prevent complications.

Thrombolytic therapy is central in the treatment of AMI for these reasons:

- 85% to 90% of transmural infarctions are caused by a coronary thrombus.
- Thrombolytic agents can effectively lyse coronary thrombi.
- Myocardium can be salvaged if thrombolytics are initiated within six hours of symptom onset.
- AMI-related morbidity and mortality are reduced when thrombolytics are administered no later than six to 12 hours after symptom onset.

Effective management of AMI can save both lives and health care dollars. Because lasting ischemia means more myocardial damage, clinicians must learn to recognize and treat patients with AMI promptly to reduce the duration of electrical instability.

Prompt attention to symptoms of myocardial ischemia is mandatory; ventricular fibrillation is 15 times more likely to occur during the first hour after symptom onset than during the next 12 hours. Successful myocardial salvage is most likely during the first three hours after symptom onset. Any unnecessary delays in treatment place the patient at risk for life-threatening complications and increase the long-term mortality rate.

Open-artery principle

The basic pathophysiologic process leading to an AMI is rupture of an atherosclerotic plaque and the acute formation of a thrombus in a coronary artery. Infarction occurs after prolonged ischemia (i.e. 30 minutes or more), irreversibly damaging the myocardium.

The basic tenet of the open-artery principle is "time saved is muscle saved." The earlier a thrombus-obstructed coronary artery can be opened and kept open, the smaller the infarct, the better the healing of damaged muscle and the lower the probability of post-infarction complications. By reducing the infarct-at-risk zone and salvaging more myocardium, early reperfusion reduces short-term AMI-related morbidity and preserves left-ventricular function.

The current standards of care in AMI center on recognizing symptoms more quickly, initiating emergency cardiac care more quickly, and administering an appropriate thrombolytic agent within 30 minutes of presentation to the treatment facility. Animal studies first demonstrated how early reperfusion limited infarct size. Angiographic studies show that speed is critical in opening the occluded coronary vessel. Treatment in the first hour after symptom onset is an ideal goal for patients with ST-segment elevation AMI because it helps achieve maximum myocardial salvage.

After the first two hours, the incremental benefit of thrombolytic treatment is less, although some benefit can be derived up to at least 12 hours after symptom onset.

Data from the national Myocardial Infarction Triage and Intervention (MITI) trial at the University of Washington in Seattle show a 1% mortality rate when thrombolytics are initiated within 70 minutes vs. a 10% mortality rate when they are initiated after 70 minutes. In the MITI trial, an "abortive effect on the AMI" was observed in approximately 40% of patients. This observation suggests that very early thrombolysis (within one hour) dissolves the clots more rapidly: The clot's architecture has not yet become fully organized. Therefore, rapid thrombolysis (within 30 to 60 minutes of symptom onset) may prevent further damage.

Controlled randomized clinical trials confirm that the earlier the thrombolytic agent is given, the greater the benefit. Pooled data from mortality studies suggest that a one-hour reduction between symptom onset and thrombolysis produces a 17% reduction in mortality.

Data from a similar trial, the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial at Baylor College of Medicine in Houston also show important differences between clot-selective and non-clot-selective agents with respect to the open-artery principle. Angiographic studies comparing streptokinase with recombinant tissue plasminogen activator (t-PA) showed that t-PA opens the occluded artery faster.

Data from the GUSTO-1 angiographic trial provide the link between a higher percentage of early vessel patency and significantly better survival by demonstrating that t-PA is superior to streptokinase when administered within the first four hours of symptom onset. Angiographic patency rates at 90 minutes were significantly lower with streptokinase with subcutaneous heparin (54%) and with intravenous heparin (60%) compared with accelerated t-PA.

Clinical pharmacology of thrombolytic agents

Thrombolytic agents activate the conversion of both soluble and surface-bound plasminogen to plasmin. Thrombolysis occurs when plasminogen is converted to plasmin, which subsequently digests fibrin and dissolves the clot. Although timely administration of thrombolytic therapy can decrease the extent of myocardial damage, unresolved concerns regarding therapy in AMI include:

- lack of sufficient thrombolysis in approximately 25% of patients;
- reocclusion in 6% to 16% of patients;
- intracranial hemorrhage in about 0.5% of patients.

Therefore, it is valuable to understand the clinical pharmacology of the commonly used thrombolytic agents.

Streptokinase

Streptokinase (Kabikinase), a protein elaborated by B-hemolytic *streptococci*, forms a complex with plasminogen that acts to convert additional circulating plasminogen to plasmin. Activation is rapid, and plasmin formation occurs promptly after streptokinase administration. Additional beneficial effects of streptokinase include reductions in plasma viscosity and systemic vascular resistance.

IV streptokinase is administered at a dose of 1.5 million units (MU) over 30 to 60 minutes. After streptokinase, patients receive full-dose IV heparin for 24 to 72 hours. Hydrocortisone 100 mg and diphenhydramine 25 mg may be given intravenously before treatment, although no data prove that these agents decrease the risk of allergic reactions to streptokinase.

Anisoylated plasminogen streptokinase activator complex

Anisoylated plasminogen streptokinase activator complex (APSAC, Eminase) is a direct plasminogen activator complex formed between streptokinase and human plasminogen that is acylated with a p-anisoyl derivative at its enzyme center. This renders the activator inactive, but the acylation of the catalytic site of the plasminogen molecule is reversible over time.

The streptokinase-plasminogen complex of APSAC dissociates at a slower rate than the deacylation rate, ensuring that plasminogen controls

the fibrinolytic activity of streptokinase. The deacylation half-life is about 105 minutes in human plasma or whole blood in vitro, and the plasma clearance half-life of fibrinolytic activity is 90 to 112 minutes in patients with AMI. The extended half-life of APSAC allows it to be administered as a single IV injection over four to five minutes.

The main advantage of APSAC over alternative thrombolytic drugs is in ease of IV administration in patients with AMI. The recommended dose is 30 units (U) injected IV over four to five minutes in patients with AMI of less than six hours' duration. Like streptokinase, APSAC reduces plasma velocity and systemic vascular resistance.

Recombinant tissue-type plasminogen activator

Recombinant tissue-type plasminogen activator (t-PA, Activase) produces clot-sensitive thrombolysis by activating fibrin-bound plasminogen; t-PA's activity is dose-dependent.

Although t-PA is generally well-tolerated, hematoma and prolonged bleeding at the injection site are the most commonly reported adverse effects; their frequency as well as the incidence of stroke is similar to that observed with streptokinase. Unlike streptokinase and APSAC, t-PA is not antigenic. However, t-PA is 10- to 20-fold more expensive than streptokinase.

The dose of t-PA for patients over 65 kg is 100 mg over three hours. A 6 to 10 mg bolus is given over two minutes; the remainder of the 60 mg initial dose is infused over 58 minutes. The remaining 40 mg of the 100 mg total dose is administered at a rate of 20 mg / hour. For patients weighing less than 65 kg, the dose of t-PA is 85 mg. The initial 10 mg bolus is followed by 40 mg infused over 58 minutes; then 20 mg is given over hour two and 15 mg is given over hour three. Heparin in a 5,000 U bolus is administered concurrently with the initiation of thrombolytic therapy, and then 1,000 U / hour are administered to maintain the activated partial thromboplastin time at two times above the control value for at least 24 hours.

Various dosing regimens for t-PA have been explored to increase patency and reduce the risk of bleeding. Recent studies suggest that an accelerated (front-loaded) 90-minute infusion of t-PA produces more rapid reperfusion without any change in safety.

Two hundred eighty-one patients with AMI were randomized to receive 100 mg of t-PA over three hours (i.e., a 10 mg bolus followed by 50 mg for one hour, then 20 mg / hour for two hours) or 100 mg of t-PA over 90 minutes (a 15 mg bolus followed by 50 mg over 30 minutes, then 35 mg over 60 minutes). The 60-minute patency rate was significantly higher ($p < 0.03$) with front-loaded t-PA. Both groups had similar rates of recurrent ischemia, reinfarction, angiographic reocclusion, stroke, major bleeding complications, and death. These findings suggest the speed of reperfusion is linked to the rate of administration of t-PA.

Reteplase

Reteplase (r-PA Retevase) is a nonglycosylated deletion mutant of t-PA that is produced by expression of an appropriately constructed plasmid in *E. coli*. The fully functional, nonglycosylated protein becomes available after an in vitro refolding process.

Reteplase consists of the kringle-2 domain and protease domain of t-PA, but it lacks the kringle-1 domain, the finger domain, and the epidermal growth factor (EGF) domain. The absence of attached carbohydrate moieties on reteplase decreases its clearance time at a rate of 250 to 450 mL / min and extends its half-life (13 to 16 minutes vs. five to six minutes for t-PA). The absence of the fibrin-specific finger region and the EGF domain on reteplase affects renal blood flow and fibrin specificity and affinity. In summary, these structural modifications result in less high-affinity fibrin binding, a longer half-life, and greater in-vivo thrombolytic potency compared with t-PA.

Reteplase is metabolized in the kidneys, liver, and blood; t-PA is primarily cleared by the liver. The effects of renal failure on the pharmacokinetic properties of reteplase in rats demonstrated a significant ($p < 0.001$) linear correlation ($r = 0.713$) between the decrease in insulin clearance and the decrease in reteplase clearance. It has been determined that reteplase clearance was impaired in renal dysfunction.

Reteplase offers potential advantages over t-PA. Reteplase produces more rapid and more complete reperfusion than t-PA. The long half-life of reteplase compared with t-PA permits the use of dual-bolus administration without a continuous infusion. The recommended dose of reteplase is two 10 U IV boluses given 30 minutes apart. This convenient regimen allows for ease of administration compared with the more complex bolus followed by infusion regimens of t-PA, especially in a busy emergency department or a hectic pre-hospital setting.

Streptokinase and APSAC are nonfibrin-selective thrombolytic agents; t-PA and reteplase are fibrin-selective agents. All these agents activate

Table 1

Comparison of Thrombolytic Agents

Agent	*Half-life (minutes)*	*Dose*	*Systemic Lytic State*	*Reperfusion Rate (%)*	*Reocclusion Rate (%)*	*Advantages*	*Disadvantages*
APSAC	90	30 U	yes	60-70	10	Long-acting	Antigenicity; expensive
SK	23	1.5 MU	yes	50-60	15	Inexpensive	Antigenicity
Reteplase	13-16	10 U + 10 U	minimal	63-85	6	Rapid lysis; clot-selective; bolus administration	Expensive; heparin needed
t-PA	6-9	100 mg	minimal	65-85	20	Clot-selective; rapid lysis	Expensive; heparin needed

Table 2

Results of the GUSTO-1 Trial

	SK with SC Heparin (%)	*SK with IV Heparin (%)*	*t-PA with IV Heparin (%)*	*SK with t-PA with IV Heparin (%)*
24-hour mortality	2.8	2.9	2.3	2.8
30-day mortality	7.2	7.4	6.3	7.0
or nonfatal stroke	7.9	8.2	7.2	7.9
or nonfatal hemorrhagic stroke	7.4	7.6	6.6	7.4
or nonfatal disabling stroke	7.7	7.9	6.9	7.6
Severe bleeding	0.3	0.5	0.4	0.6
Angiographic patency at 90 minutes				
TIMI grade 2-3	54	60	81	73
TIMI grade 3	29	32	54	38

plasma plasminogen. Fibrin selectivity is relatively dose-dependent, and all agents activate circulating plasminogen to different degrees (streptokinase > APSAC > reteplase = tPA).

The activation of circulating plasminogen generates a systemic lytic response, characterized by the conversion of fibrin to fibrin degradation products (FDPs), thereby dissolving the thrombus. The generation of FDPs is of clinical significance because of their inherent anticoagulant properties, which prevent subacute vessel reclosure. Table 1 **(above)** compares the half-lives, doses, systemic lytic effects, reperfusion and reocclusion rates, advantages, and disadvantages of these agents.

Efficacy and safety of thrombolytic agents

No discussion of AMI and thrombolytic therapy is complete without comparing the efficacy and safety of the available agents. The four endpoints currently used to evaluate efficacy are:

- reperfusion rate;
- patency rate;
- left ventricular function;
- survival.

Because pre-thrombolytic and post-thrombolytic angiographic studies are needed to assess reperfusion rates, this endpoint is not clinically feasible. The assessment of patency rates requires only a post-treatment angiogram.

Although 20% of patients will have spontaneous reperfusion, patency rates allow efficacy between thrombolytic regimens to be compared. The GUSTO trial, using front-loaded t-PA regimens, demonstrated an improved patency rate of 81%.

Clinical trials show that treatment with streptokinase, APSAC, or t-PA improves left ventricular function compared with placebo. Studies also show that thrombolytic therapy reduces AMI-related mortality compared with placebo. Streptokinase reduces in-hospital mortality by 3.7% to 10% and one-year mortality by 13.9%. APSAC reduces one-year mortality by 11.1%; t-PA produces a 3% to 7.2% reduction in prehospital mortality and a 5.9% to 7.3% reduction in one-year mortality.

(Continued on page 142)

Table 3

Generally Accepted Eligibility/Exclusion Criteria: Thrombolytic Therapy for AMI

1. Eligibility Criteria

Clinical

Chest pain or chest pain-equivalent syndrome consistent with AMI <12 hours from symptom onset with:

ECG

1. > 1 mm ST-segment elevation in > 2 contiguous limb leads
2. > 2 mm ST-segment elevation in > 2 contiguous precordial leads
3. New bundle branch block

Cardiogenic Shock

Emergency catheterization and revascularization if possible; consider thrombolysis if catheterization is not immediately available

2. Contraindications

Absolute Contraindications

Require consideration of other reperfusion strategy, such as PTCA or CABG:

1. Altered consciousness
2. Active internal bleeding
3. Known spinal cord or cerebral arteriovenous malformation or tumor
4. Recent head trauma
5. Known previous hemorrhagic cerebrovascular accident
6. Intracranial or intraspinal surgery within 2 months
7. Trauma or surgery within 2 weeks, which could result in bleeding into a closed space
8. Persistent blood pressure > 200/120 mm Hg
9. Known bleeding disorder
10. Pregnancy
11. Suspected aortic dissection
12. Previous allergy to streptokinase (these patients should not be treated with APSAC but may be treated with t-PA or reteplase)

Relative Contraindications

1. Active peptic ulcer disease
2. History of ischemic or embolic CVA
3. Current use of anticoagulants
4. Major trauma or surgery > 2 weeks and < 2 months
5. History of chronic uncontrolled hypertension (diastolic > 100 mm Hg), treated or untreated
6. Subclavian or internal jugular venous cannulation

Table 4

Critical Time Variables for Different Thrombolytic Regimens

Regimen	*No. of Study Cases*	*ECG Time**	*Decide Time**	*Process Time**	*Door-to-Needle Time*
100 mg t-PA	180	6 (4-15)	20 (7-41)	20 (13-29)	50 (38-79)
85 mg t-PA	4	7 (1-14)	6 (5-64)	36 (21-52)	50 (36-119)
Other dose t-PA	15	7 (3-10)	12 (3-38)	25 (14-33)	49 (35-67)
1-1.5 MU SK	5	10 (5-12)	35 (33-39)	25 (15-35)	55 (55-83)
30 units APSAC	6	4 (2-10)	26 (7-28)	9 (5-10)†	39 (18-45)†

* In minutes, median (25th percentile to 75th percentile)

† $p < .05$ when compared with all other regimens

The International Joint Efficacy Comparison of Thrombolytics (INJECT) trial compared the 35-day mortality rates after treatment with reteplase (10 U + 10 U in a bolus regimen) or streptokinase (1.5 MU over 60 minutes) in AMI patients. This study was undertaken to demonstrate that the mortality rate for patients given reteplase was at least equivalent to that for patients given streptokinase. The mortality rates did not differ significantly between the reteplase group (9.02%) and the streptokinase group (9.53%).

The GUSTO trial was designed to determine the importance of IV and subcutaneous heparin after administration of streptokinase and of t-PA. More than 40,000 patients were randomized to one of four treatment groups:

- streptokinase plus IV heparin;
- streptokinase plus SC heparin;
- t-PA plus streptokinase;
- front-loaded t-PA with IV heparin.

The 30-day mortality rates for the four treatment groups **(see Table 2, p. 140)** translate to the survival of one additional AMI patient following treatment with t-PA when compared with treatment with streptokinase for every 100 AMI patients treated with thrombolytics.

A review of available clinical evidence suggests that certain patients appear to benefit most from t-PA. In patients with anterior wall myocardial infarction, t-PA yielded a lower mortality rate (8.6%) when compared with streptokinase (10.5%). This is a difference of two lives saved per 100. Likewise, patients younger than 75 may receive more benefit from t-PA than from streptokinase. The mortality rates for t-PA vs. streptokinase inpatients under 75 were 4.4% and 5.5%, respectively.

In contrast, neither age $\geq$ 75 years nor the presence of inferior wall myocardial infarction affected the relative efficacy of the thrombolytics. Finally, in patients treated within two to four hours after the onset of symptoms, mortality rates appear to be lower with t-PA (5.5%) when compared with streptokinase (6.7%).

Safety and cost considerations often are used to differentiate between streptokinase and t-PA. Since thrombolytic agents cannot distinguish between pathologic clots (i.e., those that cause necrosis) and benign clots (i.e., those that are essential for hemostasis, there is always the risk of bleeding following either an overdose of thrombolytics or a drug interaction.

Finally, because the cost per dose of t-PA is substantially higher than for streptokinase, a disease management approach may provide a reasonable way to permit patients to receive whichever thrombolytic agent is most favorable for them, based on their age, elapsed time from symptom onset, location of AMI, or risk factor for stroke.

It is also important to look beyond the cost of the specific thrombolytic agent when assessing the real cost of treating the AMI patient. A subanalysis of the MITI project compared in-hospital mortality, long-term mortality, and resource utilization among 3,145 patients; 1,050 patients were treated with acute angioplasty, and 2,095 received thrombolytic therapy.

After a three-year follow-up period, the study showed no differences in acute mortality or long-term mortality rates between treatment groups. However, after three years, the mean total cumulative inpatient costs were more than $3,000 higher for patients treated with angioplasty than those initially treated with thrombolytic therapy. As expected, the primary cost drivers were repeat angiograms and repeat angioplastics, leading to the summation that thrombolytic therapy may produce better short-term benefits when compared with angioplasty in AMI patients.

Delays in thrombolytic therapy

Not all patients suspected of having AMI receive thrombolytic therapy. This is unfortunate because mortality is substantially higher among those patients who do not (18%) compared with those who do (2.5%). However, more patients are receiving thrombolytic therapy.

In 1988, estimates from community-based hospitals showed that only 5% of patients with AMI received thrombolytic therapy. In 1990, it was estimated that 10% of patients with AMI were being treated with thrombolytic therapy, and by 1993, the number grew to 39%. Clinical trials show a 30% to 40% reduction rate in acute mortality in patients with AMI who meet criteria and have no contraindications to thrombolytic therapy.

Although patients may be excluded from treatment because of contraindications to therapy, for an equivocal electrocardiogram (ECG), or for other reasons **(see Table 3, p. 141)**, the primary reason for not receiving the therapy is too long a delay between symptom onset and arrival at a treatment facility. Factors responsible for delay in the care of AMI patients can be grouped into three categories:

- patient bystander factors;
- pre-hospital factors;
- hospital factors.

Patient bystander factors

The patient component of total delay is two-thirds of the total time from symptom onset to initiation of reperfusion therapy. Patients typically delay seeking treatment a median of four hours from the time of symptom onset because these reasons:

- They don't know the risk factors for heart disease.
- They attribute their symptoms to other causes.
- They do not perceive the severity of their symptoms.
- They are elderly.
- They are women, who may not realize they're at risk because the disease affects men more often.

In general, younger patients, those with hypotension or cardiogenic shock, and those with no previous cardiac history are more likely to seek medical assistance in the first hour after an AMI. Unfortunately, it is difficult to convince patients to seek care more quickly. Prospective studies that evaluated whether patient response was affected by public education campaigns on the symptoms of AMI produced conflicting results.

Pre-hospital factors

Despite the widespread availability of emergency medical services (EMS) systems in most communities, only 50% of patients with AMI activate the EMS system. Patients who transport themselves to hospitals come at least two hours later than those who call 911. The door-to-treatment time tends to be longer for patients who do not arrive by ambulance. The use of pre-hospital ECGs can reduce the door-to-treatment time once the patient arrives in the emergency department (ED).

Hospital-related factors

The ED is a major focal point for influencing the timing of thrombolytic therapy because it is the hospital entry point for AMI patients who are candidates for thrombolytic therapy. However, long and avoidable delays after a patient reaches the hospital appear common.

A study to identify and measure four process points through which the AMI patient passes until thrombolytic treatment is administered found a mean interval of time from symptom onset to administration of the thrombolytic of 177 minutes. The in-hospital component of nearly one hour consisted of:

- ECG time — time from arrival in the ED to recording the 12-lead ECG (six minutes);
- decide time — the time from the initial 12-lead ECG to the decision to administer thrombolytic therapy (20 minutes);
- process time — time from the decision to actual administration (20 minutes);
- door-to-needle time — time from arrival to infusion of the agent (50 minutes).

Shorter in-hospital delays correlated with the following factors:

- treatment in an urban hospital;
- treatment in an academic medical center;
- high caseloads (i.e. > 16 cases / six months);
- stocking the agents in the ED;
- treatment by ED physicians;
- selecting an agent administered by bolus injection to avoid continuous infusion.

Table 4 **(see p. 141)** compares the four time variables across thrombolytic regimens, linking process times and overall door-to-needle times to the use of a simple bolus delivery compared with a complex bolus plus infusion regimen. Multiple barriers and impediments to timely care can occur in the ED during each interval. Identifying the causes for delays in evaluation and treatment and adopting interventions to minimize these delays will improve overall care of AMI patients.

Expediting thrombolytic therapy

Studies show that pharmacy department participation in thrombolytic therapy can be both negative and positive. Thrombolytic agents should be stocked in the ED and the coronary care unit to avoid considerable delays in administration. Pharmacists should help develop critical pathways and treatment guidelines for thrombolytic therapy in AMI.

Once these disease management initiatives are in place, pharmacists can conduct drug use evaluations to facilitate the availability of thrombolytic agents and appropriate adjunct therapies to meet individual patient needs. Pharmacists also can collect patient outcome data and prescriber compliance information that can be used to make formulary decisions. Information obtained from these evaluations also can be used to implement procedural changes and educational efforts that can significantly reduce hospital delays.

Summary

Thrombolytic treatment initiated within 60 to 90 minutes of symptom onset can reduce both the size and extent of myocardial infarction and mortality. As clinical trials continue to assess the best therapeutic approach for AMI, the pharmacist can

play a key role as a health care team member by seeking ways to ensure that door-to-needle time is reduced from the current 45 to 75 minutes to less than 30 minutes. Implementation of critical pathways for chest pain management and drug use evaluation provide significant opportunities to highlight the value of pharmaceutical care in the selection and administration of thrombolytic therapy for AMI.

[For more information about this therapy or the cited trials, contact Edgar R.Gonzalez, PharmD, FASHP, FASCP, Medical College of Virginia, P.O. Box 980533, Richmond, VA 23298. Telephone: (804) 828-8331.] ■

New FDA Approvals

These drugs and/or new indications have received final approval from the U.S. Food and Drug Administration:

✔ **New formulation of protease inhibitor Norvir (ritonavir) by Abbott Labs.** Twice-daily HIV drug for combination therapy approved as soft-gel capsule as an alternative to its liquid formulation, which was approved last year to replace its original capsule formulation. Also been approved for use in children between ages 2 and 16, drug is recommended with food and at dispensing storage at or below 77 degrees Fahrenheit if taken within 30 days of its original storage temperature of 36 to 46 degrees.

✔ **New indication for Doxil (doxorubicin HCl liposome injection) by Alza Corp.** New indication is for treatment of refractory ovarian cancer specific to front-line paclitaxel- and platinum-based chemotherapy, in which disease progresses during treatment or within six months after treatment completion. Approval follows Phase III trials, in which 13.8% of patients reached response rate goal of tumor size reduction of 50% or more. Common side effects: neutropenia, anemia, stomatitis, mild hair loss, rash, fatigue, diarrhea, constipation. Contraindicated for patients sensitive to aminothiol compounds, drug was approved in 1995 for treatment of Kaposi's sarcoma, where disease progression was determined during front-line treatment.

✔ **Xerostomia treatment Ethyol (amifostine) by U.S. Bioscience.** Approved for treatment of dry mouth caused by radiation treatment in post-operative head and neck cancer patients experiencing damage to salivary glands. Approval follows Phase III randomized trials of 300 patients resulting in incidences of xerostomia in 51% of patients taking the drug vs. 78% receiving radiation alone. At nine to 12 months after radiation therapy, 34% treated with amifostine continued to experience moderate to severe dry mouth vs. 57% who did not receive the drug, according to trial documents. Common side effects: nausea, hypotension, fever, skin rash, fatigue.

✔ **Urinary tract infection treatment cefadroxil (500 mg) capsules by Barr Laboratories.** Approved as generic equivalent to Bristol-Myers Squibb's Duricef.

✔ **Antihypertensive diuretic adjunct triamterene hydrochlorothiazide (37.5 mg/25 mg capsules) by Duramed Pharmaceuticals.** Approved as generic equivalent to SmithKline Beecham's Dyazide.

✔ **Antifungal ketoconazole tablets USP (200mg) by Taro Pharmaceuticals.** Approved as generic equivalent to Janssen's Nizoral for treatment of topical and systemic fungal infections. ■

IN THE PIPELINE

The following drug is still in clinical trials:

✔ **New indication for cancer treatment Taxol (paclitaxel) by Bristol-Myers Squibb.** A supplemental New Drug Application (sNDA) has been submitted seeking approval to combine paclitaxel injection with Genentech's Herceptin (trastuzumab) as first-line therapy for metastatic breast cancer treatment in cases of over-expression of HER2 protein, the condition Herceptin is indicated for. The sNDA was submitted after a randomized trial of 469 patients receiving either paclitaxel or a paclitaxel-Herceptin combination. Submitted results showed 38% response rate in those receiving combination vs. a 15% response to paclitaxel alone. Paclitaxel is currently indicated with cisplatin for first-line ovarian cancer; for breast cancer treatment after chemotherapy failure or relapse; for first-line combination treatment for non-small cell lung cancer; and for second-line Kaposi's sarcoma. ■

Lustman says affects a patient's cortisol levels, may then worsen insulin resistance to increase the atherogenic affects of diabetes, he notes. He also points out that depression tends to recur in diabetes patients, which calls for ongoing treatment by a physician and psychotherapist.

"In contrast to the association of depression seen in other diseases like heart attack and cancer, only in diabetes has it been shown that specific depression treatment can make a difference in the outcome of the underlying disease," he says.

[For more on the 59th Scientific Sessions of the American Diabetes Association or on specific papers submitted to the conference, contact the ADA at 1660 Duke St., Alexandria, VA 22314. Telephone: (703) 549-1500. Web: www.diabetes.org.] ■

Exterminating Y2K bugs: Contingency plan a must

Surveys find optimism, concern of stockpiling

A full 94% of 282 pharmacy managers surveyed by the American Society of Health-System Pharmacists (ASHP) say their computer systems have been "tested or certified" as Y2K compliant. The survey also found that 70% of the pharmacy managers feel confident that drug suppliers have compliant systems, meaning they believe the flow of order and delivery would not be disrupted by a system's misreading of the calendar year.

The main concern from the survey was a relatively low 48% positive response rate as to whether hospital pharmacies have established contingency plans in case a drug shortage occurs. But much of that fear has been calmed by manufacturers and distributors themselves in a series of meetings with national pharmacy organizations.

Still, about half of the 282 pharmacy managers surveyed said they are planning to increase drug and product inventories in areas such as IV sets as 1999 nears an end.

That response has furthered the issue of where the fine line is between having an adequate stock on hand and outright stockpiling or hoarding, which the health care industry as a whole is discouraging. But in a related survey done by drug supplier Novation in Irving, TX, which includes the VHA chain and University Health System Consortium among its clients, about one-fourth of the supply managers surveyed said they have been asked by senior management to stockpile supplies.

"If people believe there will be a disruption of the drug supply, then there will be a disruption," says **Gary Loeb** of HBOC / McKesson Corp., a drug wholesaler in San Francisco. "Perception is going to drive the events leading up to the year 2000."

Public perception has led to pending legislation in California and New Jersey, where bills have been filed that would require pharmacists to refill 60-day prescriptions if patients request them and the pharmacists believe patient harm or medication disruption could occur. The bills are contingency legislation that would be in effect from Dec. 1, 1999, to Feb. 1, 2000, if passed.

Representatives from the Pharmaceutical Research and Manufacturers of America (PhRMA) and the National Wholesale Druggists Association met this spring with the Joint Commission of Pharmacy Practitioners (JCCP) to report on computer system readiness and drug supply plans. Suppliers normally decrease their inventory at the end of every year for accounting purposes by estimating monthly needs and trying to match them as closely as possible. That practice has led to year-end shortages in the past. The JCCP urged the two organizations not to try to pinpoint supply and demand this year because it could be thwarted by hoarding or could cause shortage misperceptions leading to stockpiling.

At the meeting, PhRMA shared survey results of its members, which are available on-line at www.phrma.org / news / y2k.html. PhRMA's representatives say computer system compliance is on schedule, but they fear that "hoarding and stockpiling by patients could create a greater threat to the supply of medicines than any computer glitch."

The organizations also are cautioning that they are unsure how to gauge the readiness of overseas suppliers, which account for the majority of generic drugs used in the United States.

Meanwhile, a Department of Health and Human Services audit survey by its Office of the Inspector General states that billing and medical record systems should be fully compliant by year's end. It was conducted between December 1998 and February 1999. The audit covered hospitals, nursing homes, medical equipment suppliers, and physicians, among other areas. The report is available at www.dhhs.gov / progorg / oei.

The American Hospital Association (AHA) says its survey of 583 hospitals found that 85% expected to have fully capable systems by year's

Y2K resources on the Web

The following Web sites offer resources for dealing with year 2000 problems:

- ❏ The Food and Drug Administration's Year 2000 Impact on Biomedical Equipment Report: **www.fda.gov/cdrh/yr2000/year2000.html**
- ❏ The American Hospital Association's Year 2000 Resource Center: **www.aha.org/y2k/default.html**
- ❏ The American Medical Association's Preparing for the Year 2000 Program: **www.ama-assn.org/not-mo/y2k/index.htm**
- ❏ The National Wholesale Druggists Association Year 2000 Resources and Solutions site: **www.nwda.org/year2000/year2000.htm**

end or have systems not expected to be affected. The full report, which is broken down by hospital system categories, is available at www.aha.org/y2k/default.html.

As with drug suppliers, pharmacy organizations also have been involved in the White House Pharmaceutical Roundtable, which is part of the President's Council on Year 2000 Conversion. The roundtable reported in March that 93% of "mission-critical" federal government systems were compliant at that time, specifying that Medicare claims systems should not be hindered after the new year.

The council has used information from groups like AHA and the Department of Health and Human Services to compile its information. The council's summer 1999 quarterly report on Y2K compliance can be found on-line at www.y2k.gov/new/FINAL3.htm.

Among the pharmacy organizations involved in the roundtable is the Academy of Managed Care Pharmacy (AMCP), which is predicting computer problems extending even beyond Jan. 1, 2000. In a statement released after meetings with the pharmaceutical roundtable, AMCP notes, "Pharmacy relies more on computers than any other facet of healthcare. . . . Most embedded chip Y2K problems will not be easily tested or resolved before Jan. 1, 2000. Therefore, pharmacies should not relax just because they are operating normally on Jan. 1, 2000. Every pharmacist should be on the alert of any potential miscalculation when the output of the computer is not consistent with the current date through 2000 and 2001."

Sounding an even more contradictory tone on computer compliance, the Center for Y2K and Society in Washington, DC, which also had a representative on the White House Pharmaceutical Roundtable, cautions that too many people assume that systems will not fail and advocates certain levels of patient drug stockpiling.

"We're recommending that the government, the pharmaceutical industry, insurers, health care providers, distributors, and patients share the responsibility for ensuring that everyone who is dependent on medications for survival have a 30-day supply by January 1," says **Margaret Anderson**, Center for Y2K and Society policy director and roundtable member. "I am encouraged to see the industry working cooperatively to address Y2K issues, but it is both naive and dangerous to recommend that caregivers and consumers conduct business as usual in their purchases of critical medications."

Anderson says she is basing the center's stance in part on the simple interconnectedness of the drug delivery system. "The pharmaceutical industry does not have control over the purchasing decisions of health care institutions and patients, or over the nation's distribution and transportation systems and telecommunications," she says.

Specifically, Anderson says patient hoarding, if not institutional hoarding, will happen and will affect the drug supply. She cites a recent recommendation by *Consumer Reports* that patients should have a 30- to 60-day supply on hand at the end of the year. That's advice she says patients will take. She also believes that health care institutions will stockpile, a strategy alluded to in the Novation survey cited above. With statements coming from organizations like PhRMA, it's unclear how dependent overseas suppliers will be.

Legal issues also a concern

While the course of liability claims and court interpretations relating to millennial system failures that may affect patient care is largely guesswork, pharmacy managers are wise to protect their departments as part of Y2K preparation, say pharmacy organizations.

The consensus among them is that two main areas of liability protection should be pursued: the creation of a contingency plan in case of system failures and detailed documentation of all aspects of Y2K preparation.

After that, pharmacy managers should review vendor contracts to see where the initiative lies for system upgrades or replacement, and they should

review insurance policies to determine whether liability claims would be covered. But, cautions **Fern Zappala**, general counsel for ASHP, "Insurance coverage may not be available with these types of claims because the insurance company may argue that the Y2K problem was foreseeable."

And that, she says, heightens the need for contingency and documentation. "What you are doing to minimize or avoid malfunctions in order to protect patients from injury may be very helpful in limiting future liability claims," she says.

Pharmacy managers should inventory all systems that use microprocessors to calculate dates, which could include dispensing systems, labeling devices, electronic medical records, drug interaction or adverse reaction software, third-party claims, order entry systems, IV pumps, refill records, and patient profiles, for example.

Zappalo also says managers should be aware of the Year 2000 Information and Readiness Disclosure Act passed by Congress last year. The act grants limited liability protection for Y2K statements and disclosures through July 14, 2001, to allow competing vendors, manufacturers or health care institutions to compare notes on Y2K problems or solutions. ■

New protease inhibitor granted FDA approval

The Food and Drug Administration has approved a liquid formulation of the HIV-1 protease inhibitor Agenerase (amprenivar) by Vertex Pharmaceuticals / Glaxo Wellcome. The approval is aimed at expanding the use of the drug for pediatric patients by promoting easier administration of combination therapies.

The drug originally was approved in a solid form in April of this year. The new approval comes with recommended pediatric doses of 22.5 mg / kg twice daily or 17 mg / kg three times daily (for patients 4 to 12 years old or up to 16 if weighing less than 50 kg). The capsule and oral formulations are not interchangeable on a milligram-per-milligram basis.

The drug is available in grape, bubblegum, and peppermint flavors in 240 ml bottles (15 mg / ml) at a wholesale price of $25.20.

[For more information, contact Glaxo Wellcome at (919) 483-8580.] ■

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