ically makes them ideal for use in treating other smooth muscle disorders. Although the three available drugs all inhibit the entrance of calcium into cells, they are different compounds and vary in their clinical effect. Nifedipine is a stronger peripheral vasodilator, verapamil causes more myocardial depression and diltiazem and verapamil affect the sinoatrial and atrioventricular nodes. Consideration of these factors is important in choosing which drug will be used, either alone or combined with other drugs such as β-blockers or nitrates.

Several clinical trials have shown the effectiveness of these drugs in treating systemic hypertension, often used as monotherapy. Nifedipine has been extensively studied and may be more beneficial due to its more potent peripheral vasodilating property, and it is very effective in managing cases of hypertensive crisis. Verapamil and diltiazem are also effective in treating hypertension and it is felt by some that they may be more suitable for long-term treatment because nifedipine is more likely to lead to reflex activation of the sympathetic nervous system.

The use of calcium channel blocking drugs in the treatment of pulmonary hypertension is encouraging. All three drugs have reduced pulmonary artery pressure and pulmonary vascular resistance in patients with primary pulmonary hypertension and some types of secondary pulmonary hypertension. However, the response to calcium entry blocking agents in patients with precapillary pulmonary hypertension is unpredictable and the drugs may sometimes produce deleterious effects.

Active clinical investigation is continuing in the use of calcium channel blockers for other conditions, including congestive heart failure, hypertrophic cardiomyopathy, myocardial preservation, bronchial asthma, Raynaud's phenomenon, migraine headache, cerebrovascular spasm, cerebral ischemia, premature labor and disorders of esophageal motility. Calcium channel blockers will likely be increasingly used in smooth muscle disorders, especially as new drugs become available that are more specific for certain types of smooth muscle.

ROY V. JUTZY, MD
Loma Linda, California

REFERENCES

Bussey HI, Talbert RL: Promising uses of calcium-channel blocking agents. Pharmacotherapy 1984 May-Jun; 4:137-143

Klein WW: Treatment of hypertension with calcium channel blockers: European data. Am J Med 1984 Oct; 77:143-146

Middleton E Jr: New ER drugs in management—Calcium antagonists. Chest 1985 Jan; 87(suppl): 79S-81S

Schwartz ML, Rotmensch HH, Vlasses PH, et al: Calcium blockers in smooth-muscle disorders—Current status. Arch Intern Med 1984 Jul; 144:1425-1429

Weir B: Calcium antagonists, cerebral ischemia and vasospasm. Can J Neurol Sci 1984 May; 11:239-246

The Protein C Anticoagulant Pathway and Thrombosis

PROTEINS C AND S are recently discovered vitamin K-dependent proteins that unlike the other vitamin K-dependent clotting factors—II, VII, IX and X—act as physiologic anticoagulants rather than procoagulants. Activated protein C inhibits coagulation by destroying activated factors V and VIII; protein S is an essential cofactor in the expression of protein C's anticoagulant activity. Protein C circulates in an inactive zymogen form and is activated by thrombin bound to an endothelial-cell surface protein, thrombomodulin. Activated protein C may also have a stimulatory effect on fibrinolysis. The protein C anticoagulant pathway thus provides a mechanism whereby formation of thrombin is accompanied by generation of anticoagulant and profibrinolytic activity, limiting fibrin formation to areas of local vascular damage.

Hereditary deficiencies of the protein C anticoagulant mechanism are associated with venous thromboembolic disease. Heterozygous protein C-deficient persons have about half the normal amount of protein C. Many but not all manifest recurrent episodes of thrombophlebitis, pulmonary embolism or both, beginning after the first decade of life, often associated with a precipitating event such as trauma or an operation. Administering heparin or warfarin is effective. Warfarin therapy reduces the levels of all vitamin K-dependent proteins, but protein C levels fall faster than levels of factors II, IX and X. Therefore initiating warfarin therapy, especially with loading doses, may create a brief period of increased vulnerability to thrombosis, including the rare syndrome of dermal thrombosis with necrosis ("warfarin skin necrosis"). Such complications can be avoided by continuing a regimen of heparin for several days, until full oral anticoagulation has occurred.

Homozygous protein C deficiency has been described in several newborns, who have little or no detectable protein C and who show dramatic, life-threatening thrombotic complications, including purpura fulminans, a necrotic dermal thrombotic lesion closely resembling warfarin skin necrosis. Constant protein C repletion with prothrombin complex concentrate is the only effective therapy so far described; however, this therapy is associated with a risk of transmitting hepatitis. Acquired deficiency of protein C is seen in cases of disseminated intravascular coagulation, liver disease, vitamin K deficiency and warfarin therapy; the clinical consequences of such deficiency states are not well established.

A diagnosis of protein C deficiency is best made with one of the recently described functional assays, as normal levels of a functionally defective molecule will not be detected by antigenic assays. Its diagnosis in a patient receiving warfarin requires finding a disproportionately low protein C level when compared with that of another vitamin K-dependent protein, such as factor II, VII or X.

Partial or complete protein S deficiency causes a tendency to venous thromboembolic disease very similar to that of heterozygous protein C deficiency. The use of warfarin or heparin is effective treatment. Neither protein C nor protein S deficiency has been clearly shown to increase the risk of arterial thromboembolism. A search for other defects in the protein C anticoagulant pathway, such as quantitative or qualitative deficiencies of thrombomodulin, is under way in many laboratories and may further increase our understanding of the pathophysiology of thromboembolic disease.

ROBERT B. FRANCIS, MD
Los Angeles

REFERENCES

Comp PC, Esmon CT: Recurrent venous thromboembolism in patients with a partial deficiency of protein S. N Engl J Med 1984 Dec 13; 311:1525-1528

Comp PC, Nixon RR, Cooper MR, et al: Familial protein S deficiency is associated with recurrent thrombosis. J Clin Invest 1984 Dec; 74:2082-2088

Griffin JH: Clinical studies of protein C. Semin Thromb Hemost 1984 Apr; 10:162-166

Schwarz HP, Fischer M, Hopmeier P, et al: Plasma protein S deficiency in familial thrombotic disease. Blood 1984 Dec; 64:1297-1300

Antibody Testing for the AIDS Retrovirus—Implications for Clinicians

A NEW HUMAN RETROVIRUS (variously called LAV, HTLV-III or ARV) has been isolated from tissues of patients with acquired immunodeficiency syndrome (AIDS) and with lymphadenopathy in both Europe and the United States. Antibodies against this virus have been detected in a high percentage of AIDS patients, asymptomatic homosexual men and men with hemophilia. Investigations of blood donors implicated as the source of transfusion-acquired AIDS suggest that there may be a prolonged asymptomatic period of infectivity. Testing of all blood donors for antibody to the AIDS retrovirus (ARV) may soon be required. Enzyme-linked immunosorbent assays (ELISA) for ARV antibody will be used to screen blood units and those found to have the antibody will be discarded. This measure appears both practical and reasonable as a means of preventing future cases of transfusion-acquired AIDS.

The availability of this test will create several problems for practicing clinicians. First, positive tests will be found in persons not in any group known to be at risk for AIDS. Many of these ELISA results will be false-positive. Because confirmatory tests such as Western blotting or immunofluorescence are expensive, technically demanding, not widely available and of uncertain sensitivity, it will be difficult initially to determine which positive results reflect possible infectivity for others or an increased risk of AIDS developing. Despite this uncertainty, persons with repeatedly positive tests should be notified because they can take actions to reduce potential spread of the virus via sexual contact, child bearing or nonsexual transfer of body fluids.

The notification of a positive test result will have enormous emotional impact on most persons and requires that physicians be well informed about the limitations of the tests and implications of the results. Even if systems are developed to inform persons of their results through public agencies, many will seek reassurance and follow-up from their personal physicians.

The second problem for clinicians will be the skillful use of these tests for diagnosis. Because of the wide spectrum of clinical manifestations of AIDS-retrovirus infections and the high prevalence of the AIDS-retrovirus antibody in groups at high risk for AIDS, the diagnostic usefulness of finding the antibody in high-risk patients with unusual clinical syndromes will be limited. For example, should a gay man with idiopathic Bell's palsy or thrombocytopenia and a test positive for AIDS-retrovirus antibody be diagnosed as having an ARV-associated condition? While these tests will help to expand knowledge of the clinical spectrum of AIDS-retrovirus infections, they may also be confusing and misleading.

One possible solution to these problems is the development of tests to detect the AIDS virus directly in blood and tissues. This may be accomplished by growing retroviruses in cultures or detecting virus-specific antigens or nucleic acids. These techniques eventually may replace the soon-to-be released antibody assays. In the meantime, physicians will be faced with the difficult task of explaining and interpreting a test of uncertain significance to anxious patients.

J. ALLEN McCUTCHAN, MD
San Diego

REFERENCES

Goldsmith MF: HTLV-III testing of donor blood imminent; complex issues remain. JAMA 1985 Jan 11; 253:173-181

Provisional public health service inter-agency recommendations for screening donated blood and plasma for antibody to the virus causing acquired immunodeficiency syndrome. MMWR 1985 Jan 11; 34:1-5

Weiss SH, Goedert JJ, Sarngadharan MG, et al: Screening test for HTLV-III (AIDS agent) antibodies—Specificity, sensitivity, and applications. JAMA 1985 Jan 11; 253:221-225

New Antiarrhythmic Agents—Amiodarone, Mexiletine, Tocainide

UNTIL RECENTLY, antiarrhythmic drug therapy has been restricted to a few agents. Over the past decade, however, there has been a dramatic increase in the number of agents that have been or are soon to be released for clinical use. One drug, tocainide, has just been released for clinical use and two others—amiodarone and mexiletine—are subject to intensive clinical investigation.

Amiodarone

Amiodarone, an agent that prolongs myocardial refractoriness in almost all types of cardiac cells, is quite effective in the clinical management of supraventricular and ventricular arrhythmias and arrhythmias associated with the Wolff-Parkinson-White syndrome. In numerous clinical trials amiodarone effectively suppressed these arrhythmias in patients who did not respond to conventional antiarrhythmic drug therapy. There appears to be general agreement that it requires days, sometimes weeks or even, rarely, months for the full antiarrhythmic efficacy of oral administration of amiodarone to become manifest. There still exists some controversy regarding amiodarone's antiarrhythmic efficacy when given intravenously. The drug is most commonly given orally, usually with a loading dose of 800 to 1,800 mg a day during the first week, followed by a daily maintenance dose of 200 to 800 mg a day. Amiodarone seems to be well tolerated by most patients, but with the increasing use of this drug, several unwanted side effects have been recognized. A small percentage ($\leq 10\%$) of patients have to stop taking amiodarone because of more serious and even life-threatening side effects. These include refractory heart failure; pulmonary fibrosis; central nervous system side effects such as tremor, ataxia, paresthesia, headache and nightmare; sinus arrest, and exacerbation of ventricular tachycardia. Less alarming side effects include corneal microdeposits, with possible association of photophobia, thyroid dysfunction (hypothyroidism or hyperthyroidism), a peculiar bluish or slate-gray discoloration of the skin including the face and abnormalities on liver function tests. These complications may take several weeks or even months to disappear after the drug regimen is discontinued. Many investigators, therefore, have suggested that this drug