Pharmacologic Agents in Stroke Prevention, Acute Stroke Therapy, and Interventional Procedures

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Pharmaceutical agents have moved far beyond just the aspirin and heparin that were the mainstays of stroke and interventional therapy as recently as 10 to 15 years ago. Our understanding of the mechanisms of thrombus formation and vascular response to damage as well as our armamentarium has tremendously improved in the past decade. Direct thrombin inhibitors, powerful antiplatelet agents, new fibrinolytic agents, and statins now allow far greater manipulation of the intraprocedural and postprocedural clot cascade and atherogenesis. It is mandatory that current-day interventionists understand the correct and appropriate use of these agents to achieve the desired outcomes of therapy.

THE CONCEPT OF THROMBUS

THROMBI that form under conditions of slow flow and low shear are comprised mainly of red cells and fibrin and can be thought of as blood sludge. Conversely, arterial thrombi that form under high shear conditions are made up of platelet aggregates stuck together by glycoprotein IIb/IIIa receptors and fibrin strands; these can be pictured as the primary mechanism for repairing holes in vessels and for preventing bleeding when cut. Venous thrombosis is often triggered by vascular injury at surgery or trauma or by mechanical damage secondary to indwelling central venous catheters and in typical slow flow conditions. These types of clot can also be found in venous stasis disease as well as atrial stasis (atrial fibrillation).

Most arterial thrombi are superimposed on active atherosclerotic plaques (1) or damaged endothelium in high flow situations and are largely composed of platelets. Injury to the endothelial lining of veins or arteries exposes subendothelial matrix proteins such as collagen and von Willebrand factor. Platelets adhere to these matrix proteins, at which point they become activated, release vasoactive and procoagulant substances, and subsequently aggregate. Simultaneous exposure of tissue factor initiates coagulation and leads to thrombin generation. Thrombin, a potent platelet stimulant, stimulates platelets to adhere to the site of vascular injury. Thrombin also converts fibrinogen to fibrin, which stabilizes these platelet aggregates (1). Platelets themselves are activated by adhesion factors (eg, collagen, von Willebrand factor), thrombin, epinephrine, adenosine diphosphate, and thromboxane A₂.

Heparin is a cornerstone of therapy for venous and arterial thrombosis. It is effective in the treatment of venous thrombosis, it has limitations in the setting of arterial thrombosis. It must be given parenterally and requires careful laboratory monitoring to ensure that the anticoagulant response is therapeutic (2–4). Optimal effectiveness is achieved when given prophylactically before clot formation; thus, for example, the current standard of care for deep venous thrombosis prevention requires administration before a surgical procedure. When used in patients with acute coronary syndromes, the addition of heparin to aspirin reduces the risk of cardiovascular death and recurrent myocardial ischemia; the primary benefit, however, is believed to be produced by the aspirin. Despite its widespread use, patients remain at risk for recurrent thrombotic events that can be fatal. This confirms that the process of thrombus formation is not completely attenuated by heparin or even heparin and aspirin.

Thrombin generation continues during and after heparin therapy. Results of recent studies have helped explain this phenomenon. Heparin functions by forming a heparin/anti-
Molecular-Weight Heparin

Unfractionated Heparin and Low-molecular-weight heparins; this includes an inhibition of thrombin as well as free thrombin and thrombin inhibitors adhere to bound heparin/antithrombin complex, direct only active when they form the bound molecular-weight heparin, which are bound thrombin (6–9). In contrast to both unfractionated heparin and low-molecular-weight heparin, which are only active when they form the bound heparin/antithrombin complex, direct thrombin inhibitors adhere to bound thrombin as well as free thrombin and block its interaction with its substrates; this includes an inhibition of platelet activation.

Unfractionated Heparin and Low-molecular-Weight Heparin

Unfractionated Heparin.—Heparin is not approved by the U.S. Food and Drug Administration (FDA) for either the prevention of stroke or the treatment of acute stroke. Heparin is a multifractionated glycosaminoglycan, and its major anticoagulant effect is caused by a pentasaccharide with a high affinity for antithrombin III. This binding results in greatly enhanced activity of antithrombin III, the operational agent that inactivates thrombin (factor IIa), factor IXa, and factor Xa (all of which are coagulation enzymes). The average weight of these heparin molecules is 15,000 d (daltons) but ranges from 2,000 d to more than 30,000 d. The larger molecules are bound by plasma proteins and are the ones that influence the activated clotting time and partial thromboplastin time. It is the binding by plasma proteins that clears the heparin from the circulation so quickly and gives heparin its short half-life, which is widely variable and on average about 1 hour. The variation in these “unfractionated” samples of heparin produces the variability of effect that necessitates repeated and precise measurement of anticoagulant activity to ensure that a therapeutic anticoagulant response is obtained (11).

Low-molecular-weight Heparin.—In contrast to unfractionated heparin, low-molecular-weight heparin produces a more predictable anticoagulant response (12). As a result, low-molecular-weight heparin rarely requires laboratory monitoring and is easier to use than unfractionated heparin. These low-molecular-weight heparins are simply the low-weight molecules contained in “unfractionated” heparin. The average molecular weight of these molecules in various commercial preparations is about 4,000 to 6,000 d. This range results in some variability in the ratio of anti-Xa to antithrombin activity in these commercial preparations. They are, however, remarkably predictable compared with unfractionated heparin.

The differences in action between low-molecular-weight and regular unfractionated heparins are subtle but real. The low-molecular-weight heparins have greater anti-Xa activity, are more resistant to PF4 (a thrombin activator on platelets), have more specific binding, and result in greater thrombin inhibition than does regular heparin. However, because the activated clotting time and partial thromboplastin time measure activity of the larger molecules of heparin more than the small low molecular weight heparins, the typical laboratory tests used by interventionists do not assess the activity of low-molecular-weight heparin. To measure their activity, a plasma anti-Xa assay is needed, and this is not readily available in most hospitals. Because there are no large molecules in low-molecular-weight heparin, plasma protein binding does not affect the serum clearance as much as it does with regular heparin, and, thus, the low molecular weight heparins have a longer half-life. These more predictable pharmacokinetics allow the dose to be based on a patient’s weight and essentially eliminate anticoagulant monitoring.

Although low-molecular-weight heparin overcomes the pharmacokinetic limitations of unfractionated heparin, both drugs share the same biophysical limitations. Once the heparin/antithrombin complex is formed, neither agent stops the formation of additional clot induced by thrombin that is already in the clot. Neither agent inhibits factor Xa bound to platelets within the coagulant complex, nor do they inhibit thrombin bound to fibrin. Therefore, even in the presence of heparin, platelet-associated factor Xa can trigger additional thrombin generation (13). Once bound to fibrin, thrombin itself is also protected from inactivation by the heparin/antithrombin complex and can continue to promote the growth of more thrombus (7,14).

The effects of all heparins—even the low-molecular-weight heparins—are reversible with protamine. Because it is so difficult to measure the activity of the low molecular weight heparins, however, the dose of protamine is empiric. The dose of protamine for heparin is about 10 mg per 1,000 units. For a typical interventional case, 3,000 to 5,000 units are given to achieve adequate heparinization. Reversal of “on-board” low-molecular-weight heparin can be achieved with about 30 to 50 mg of intravenous protamine (depending on the load of low-molecular-weight heparin), with clinical evaluation of clotting status and additional dosing if necessary.

Heparin has been used in stroke therapy for years and is still the most frequently used drug for stroke therapy by neurologists in the United States, although, as stated earlier, it is not approved by the FDA for any use related to stroke and has never been shown to be of clinical benefit. In the International Stroke Trial (15), heparin was conclusively proved to be of no benefit. Trials of low-molecular-weight heparin have also shown no benefit (16,17). The American Stroke Association and the American Academy of Neurology, after review-
Direct Thrombin Inhibitors

Hirudin, bivalirudin, and argatroban are the three parenteral direct thrombin inhibitors currently approved by FDA. Hirudin and argatroban are licensed for the treatment of patients with heparin-induced thrombocytopenia, whereas bivalirudin is approved as a heparin substitute in patients undergoing coronary angioplasty. Ximelagatran is an orally administered precursor drug that, once absorbed, is rapidly converted to melagatran; however, neither of these agents is approved by the FDA as yet.

Hirudin.—The original direct thrombin inhibitor, hirudin, comes from the salivary glands of the medicinal leech, Hirudo medicinalis. A polypeptide comprised of 65 or 66 amino acids, hirudin is a bivalent inhibitor of thrombin. Typically, hirudin-like drugs are cleared by the kidneys; therefore, there is accumulation in patients with renal insufficiency (19). Because no specific antidote is available to reverse the anticoagulant effect of these drugs, they should not be used in patients with impaired renal function. Accidental overdose of hirudin in patients with renal insufficiency can be managed with specialized dialysis.

Bivalirudin.—Bivalirudin is a 20-amino-acid polypeptide that is a synthetic version of hirudin (20). Like hirudin, bivalirudin also forms a 1:1 complex with thrombin. Bivalirudin has a half-life of about 25 minutes (21). Unlike hirudin, renal excretion is not the major route of bivalirudin clearance (only 20%) (22); it can be used (with caution) in patients with renal insufficiency. Bivalirudin has been shown to be more effective than heparin at reducing postintervention ischemic events in coronary intervention and appears to cause less retroperitoneal and major bleeding than does heparin (23).

Argatroban.—Argatroban, a synthetic small molecule, acts as a competitive inhibitor of thrombin. Argatroban is metabolized in the liver, a process that generates at least three active intermediates (24). Although the half-life of argatroban is 45 minutes, it is prolonged in patients with hepatic dysfunction (25).

Potential Advantages of Direct Thrombin Inhibitors over Heparin.—Direct thrombin inhibitors have potential advantages over heparin. Because they do not bind to plasma proteins, direct thrombin inhibitors produce a more predictable anticoagulant response than does heparin (they are not cleared by the plasma proteins). Unlike heparin, direct thrombin inhibitors do not interact with platelet factor 4 or von Willebrand factor. Therefore, direct thrombin inhibitors remain active in the vicinity of a platelet-rich thrombus. Further, thrombin bound to fibrin and/or fibrin degradation products can be inactivated by direct thrombin inhibitors as opposed to heparin (7,8).

Future Directions Concerning Thrombin Inhibitors.—On the basis of randomized trials, parenteral direct thrombin inhibitors are more effective than heparin in the treatment of arterial thrombosis. Thus, hirudin is superior to heparin in patients with unstable angina (26), and both hirudin and bivalirudin are more effective than heparin in patients undergoing coronary angioplasty (23,27,28). In patients with unstable angina, hirudin reduces the risk of recurrent ischemia to an extent similar to that produced by glycoprotein IIb/IIIa antagonists (27,28). Hirudin also is better than low-dose subcutaneous heparin or low-molecular-weight heparin for thromboprophylaxis in patients undergoing hip arthroplasty (29,30).

Currently, bivalirudin is the only direct thrombin inhibitor with an established indication in acute coronary syndromes. Bivalirudin is superior to heparin in the treatment of patients undergoing coronary angioplasty for postinfarction angina (23,28) and, on the basis of repeat analysis of the phase III data (23), may also be advantageous in lower-risk individuals. Although bivalirudin produced less bleeding than did heparin in patients undergoing coronary angioplasty (31), recent data from the Hirulog and Early Reperfusion or Occlusion (HERO)-2 Trial (32) suggest that, like hirudin, the dose of bivalirudin must be carefully titrated when the drug is given as an adjunct to thrombolytic therapy.

STROKE PREVENTION

Antiplatelet Therapy

Antiplatelet therapy has been shown to reduce the risk of subsequent vascular events in patients with recent ischemic stroke or transient ischemic attack (TIA). The Antiplatelet Trialists (33) found that antiplatelet agents reduce the odds of a composite outcome of stroke, myocardial infarction (MI), or vascular death in secondary prevention by about 27%. Specifically, the odds of a nonfatal stroke were reduced by 31%. Several oral antiplatelet agents have been shown to be effective in clinical trials of patients with ischemic stroke and/or TIA. All were effective in preventing recurrent vascular events in patients who have had an ischemic stroke. In general, in patients with ischemic stroke or TIA, antiplatelet therapy reduces the risk of subsequent stroke, MI, or vascular death by more than 20% (range, 22%–35%).

The available antiplatelet agents inhibit platelet aggregation in a variety of ways. Aspirin works by inhibiting the enzyme cyclooxygenase in the platelet, thereby inhibiting the production of thromboxane A2. The absence of thromboxane A2 leads to the inhibition of platelet aggregation. Ticlopi-
Aspirin.—The inhibition of the enzyme cyclooxygenase is irreversible in a platelet and, therefore, the effects of one aspirin last as long as the life span of a platelet (about 7–10 days). A severe weakness of aspirin, however, is that it has little effect on other pathways of platelet activation. Thus, it has no effect on activation by thrombin or collagen. In general, the oral administration of aspirin is effective within 1 hour and frequently in as little as 15 minutes.

Although aspirin administration is an extremely cost-effective method of stroke prevention for most patients, the optimal effective dose remains unclear. Results of earlier trials led to consensus recommendations for higher doses of aspirin (>900 mg); however, subsequent studies of lower doses (<325 mg) also established effectiveness. Few trials have directly compared high and low doses of aspirin. In 1998, the FDA provided a statement recommending doses of 50 to 325 mg to prevent recurrent stroke. Recent data, however, indicate that “coated” baby aspirin may result in subtherapeutic levels of aspirin activity, and, indeed, even adult coated aspirin has been shown to suffer this same fate (34). The recently reported “aspirin resistance” may, to some degree, be related to subtherapeutic dosing of aspirin. Therefore, the use of regular-strength, uncoated, “adult” aspirin (325 mg) is suitable for most of the population who can tolerate this regimen.

Many patients who take aspirin daily still have an ischemic stroke or TIA. These patients can be considered to have failed aspirin therapy. Appropriate steps in the prevention of recurrent stroke include risk factor modification and determination of the cause of the original ischemic event. For patients with atrial fibrillation and possibly those with other cardiac conditions, warfarin therapy is appropriate unless there are contraindications. Patients with symptomatic carotid stenosis should be considered for endarterectomy. Although the benefits of changing to another antiplatelet regimen have not been established, this seems reasonable. Of note, the substitution of warfarin for aspirin was not shown to be of benefit in the Warfarin versus Aspirin in Recurrent Stroke Study (WARSS) (35). To my knowledge, no specific studies have been performed of patients failing aspirin therapy to determine what the best antiplatelet regimen should be in this situation. Acceptable approaches include the use of combination therapy with extended release dipyridamole and aspirin or aspirin combined with clopidogrel. A study is ongoing to test the efficacy of these combination therapies in patients with prior ischemic stroke (Prevention Regimen for Effectively Avoiding Second Strokes).

Ticlopidine.—Ticlopidine inhibits the adenosine diphosphate–induced binding of fibrinogen to platelets, a necessary platelet-to-platelet binding step. The effect of this drug builds for the first few days. The thienopyridines also slightly inhibit the platelet response to collagen, thrombin, fibrinogen, and von Willebrand factor, thus possibly giving some increased efficacy compared with aspirin. In the Ticlopidine versus Aspirin Stroke Study (36), 3,069 patients were studied within 3 months of stroke or TIA. Half were treated with aspirin and half with ticlopidine. The ticlopidine group had a 9% relative risk reduction of stroke, MI, or vascular death at 3 years and a 21% relative risk reduction of stroke compared with the aspirin group.

Ticlopidine is associated with about 1% incidence of severe neutropenia resulting in thrombocytopenic purpura. This makes it necessary to check the platelet count every 2 weeks during the first 3 months of therapy and has resulted in the widespread decrease in the use of this agent. A recent (2003) study indicated that aspirin may be as effective as ticlopidine in the prevention of stroke (37).

Clopidogrel.—Clopidogrel is in the same family as ticlopidine and works the same way. Although it takes several hours to achieve the maximum effect with the oral dose, the platelet effect is irreversible for the life of the platelet (about 7–10 days). The Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events study (38) compared the outcomes for stroke, MI, and vascular death with clopidogrel versus aspirin. In that study, 19,185 patients were enrolled. The annual stroke rate was 5.32% for the clopidogrel group and 5.83% for the aspirin group, for a relative risk reduction of 8.7% in favor of clopidogrel and an absolute risk reduction of 0.5%. There were no differences in safety between aspirin and clopidogrel. Although the overall effects of clopidogrel appear to be comparable or, possibly, slightly less than those of ticlopidine, the differences might be statistically insignificant. Further, the results of pharmacokinetic and clinical trials indicate that clopidogrel in combination with aspirin has an additive effect (39). This is the justification and rationale for the fact that the combination of aspirin and clopidogrel is now the de facto standard of care for coronary intervention and for most peripheral and intracranial interventions.

Extended-release Dipyridamole Plus Aspirin (Aggrenox; Boehringer Ingelheim Pharmaceuticals).—The results of several trials have indicated that dipyridamole alone has no benefit for stroke prevention. However, extended-release dipyridamole and low-dose aspirin (Aggrenox) has been shown to be of great benefit. In the European Stroke Prevention Study 2 trial, patients with recent ischemic stroke or TIA were studied by using combination therapy with extended-release dipyridamole and low-dose aspirin (40). Extended-release dipyridamole plus aspirin reduced the risk of stroke by 37% compared to that with aspirin alone. The
absolute risk reduction was 3% at 2 years, which is larger than the reduction produced by clopidogrel or ticlopidine alone. Aggrenox, however, is associated with side effects (most frequently headache) that are disagreeable to many patients, thus inducing them to stop therapy. Starting therapy with a single daily dose and increasing to the standard twice-a-day dose after 2 weeks seems to improve this problem.

Cilostazol.—A unique antithrombotic quinoline derivative, cilostazol has platelet antiadhesion, vasodilator, antiangiogenic and cardiotoxic properties (41). It is a potent inhibitor of phosphodiesterase 3A. In addition, it inhibits adenosine uptake, resulting in changes in cyclic adenosine monophosphate levels. Cilostazol inhibits platelet aggregation and has considerable antithrombotic effects. It also relaxes smooth muscle and inhibits mitogenesis and migration of smooth muscle cells. In the heart, cilostazol causes positive inotropic and chronotropic effects but may cause adverse reactions when administered to patients with class III–IV congestive heart failure (41). Cilostazol decreases serum triglyceride levels and causes some increase in high-density lipoprotein cholesterol levels (42). It is metabolized in the liver and has a half-life of approximately 10 to 13 hours; thus, twice-a-day dosing results in twofold accumulation of the drug with chronic therapy. Although originally proposed and approved for claudication (43), it has been shown to promote cerebrovascular blood flow and prevent stroke (44). In the United States, it is not generally recognized for its antiplatelet properties, but rather for the vascular smooth muscle cell relaxation resulting in the beneficial effect on claudication. In Japan, it is a widely used drug for intracranial atherosclerosis (Asian obliterator cerebrovascular disease) and has been shown to increase cerebral blood flow in chronic cerebral hypoperfusion (45). The multiple actions of cilostazol render this drug uniquely beneficial for certain conditions.

Comparative Efficacy.—There is little difference in effectiveness among the antiplatelet agents listed earlier. They are all effective and there is minimal benefit over aspirin alone (see absolute benefits discussed above). Clopidogrel appears to have fewer side effects compared with ticlopidine and, for this reason, is the currently preferred agent for substitution for aspirin or addition to aspirin. Perhaps the most important use for clopidogrel is in combination with aspirin to achieve an additive effect. This is undergoing study. However, the unique vasodilatory effects of cilostazol render this agent useful for more than just its antiplatelet effect and, on the basis of its clinical pharmacology, it should be considered for a wide range of indications and, in particular, intracranial atherosclerotic stenosis.

Warfarin

Warfarin is not approved by the FDA for the treatment of any type of cerebrovascular disease (nor, specifically, intracranial atherosclerotic stenosis) or for arterial dissection, nor, to my knowledge, has any study proved benefit of warfarin for the treatment of any cerebrovascular condition. With the results of the recently completed WARSS (below) and Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) trial (see below), the use of warfarin for cerebrovascular disease should be at an end.

Warfarin is an orally administered anticoagulant that acts by inhibiting the synthesis of vitamin K–dependent clotting factors, which include factors II (thrombin), VII, IX, and X. These factors have their own half-lives, which causes a sequential depression in the overall anticoagulant effect of warfarin. Initial effects of warfarin administration occur within 24 hours, but peak effects may take 3 to 5 days. A single dose lasts for 2 to 5 days. Treatment of overdose is dependent on the degree of anticoagulation and the urgency. Parenteral vitamin K can be given in doses of 10 to 25 mg. More rapid reversal can be obtained with 200 to 500 mL of fresh frozen plasma. The administration of commercial factor IX for warfarin reversal is not recommended as it can result in thrombosis.

Warfarin has no place in the acute treatment of stroke. The therapeutic response is obviously too slow to be effective for this condition. Further, warfarin has essentially been of no use in the prevention of stroke except for one crucial exception: atrial fibrillation (46,47). Atrial fibrillation results in a 600% increase in the risk of stroke, with an average annual risk of 5% (48). Warfarin has been recognized as the treatment of choice for atrial fibrillation and has been shown to reduce the risk by 68% (48,49). Aspirin and/or aspirin with low-dose warfarin has been shown to be less effective than standard warfarin (International Normalized Ratio [INR], 2.0–3.0) (48). For patients with acute MI, high-intensity warfarin or medium-intensity warfarin with aspirin is better than aspirin alone (50). However, even the indication for atrial fibrillation is under study. Both aspirin and warfarin have shown benefit for atrial fibrillation, but warfarin superiority was proved in selected populations that underrepresent the elderly. The Protocol for the Birmingham Atrial Fibrillation Treatment of the Aged study will examine warfarin versus aspirin for stroke prevention in an elderly population (51). Cardioembolic sources were the primary cause of stroke in patients enrolled in the Prolyse in Acute Cerebral Thromboembolism (PROACT) trial (52) and remain the typical finding during acute intraarterial therapy for stroke (ie, the cervical carotid artery is clean in most patients with an M-1 occlusion).

Except in the case of cardioembolic stroke, the relative benefit of aspirin versus warfarin does not differ with stroke subtype. The WARSS showed that aspirin (325 mg) and warfarin (INR, 1.4–2.8) have equivalent effects in patients with ischemic stroke or TIA without a cardioembolic source (35); indeed, warfarin was slightly worse in all subsets. For example, patients with a patent foramen ovale, those with antiphospholipid antibodies, those with presumed aortic atherosclerosis, and those with presumed large-vessel atherosclerosis did not derive more benefit from warfarin than from aspirin. There has been some concern expressed regarding the lower range of INR values (1.5–2.8) used in the WARSS, however. Critics have argued that the design of the trial did not test the range most commonly used in contemporary practice (INR, 2.0–3.0). However, no relationship between INR value and the risk of recurrent stroke was found in the WARSS.
which suggests that the reason for the lack of benefit of warfarin was not due to the range of INR values chosen, but rather due to lack of efficacy. The WARSS showed that careful consideration of the underlying etiology is required when deciding whether to treat a patient with warfarin and essentially removes all indications for warfarin therapy for stroke prevention other than cardiogenic (mostly atrial fibrillation).

Specifically relating to intracranial atherosclerotic stenosis, warfarin has been “presumed” to be “best medical therapy” for years. In a trial of warfarin versus aspirin specifically for intracranial atherosclerosis (WASID) (53), investigators evaluated the possibility of an indication for warfarin for the prevention of stroke for this one stroke subtype. The failure of warfarin in WARSS to be superior to aspirin and particularly in the “large vessel” category raised serious doubts as to this belief, and only a strongly positive result from WASID could have changed this conclusion. Warfarin should not be considered the optimal pharmacologic therapy for intracranial stenosis for numerous reasons. First, in the WARSS, warfarin was shown to perform slightly worse than aspirin for prevention of recurrence of almost all types of stroke and specifically those presumed to have been caused by large-vessel atherosclerosis (although the difference was not statistically significant). Second, there is no other arterial bed in which warfarin has been shown to be superior to aspirin. Specifically for coronary artery and peripheral atherosclerotic disease, antiplatelets are the preferred therapeutic agent as described earlier in relation to the composition of high shear stress lesions. Third, there is clear pharmacokinetic rationale and clinical evidence that indicate that combination (“dual”) antiplatelet medication is better than the use of aspirin alone (39), thus further reducing the potential for warfarin superiority. Fourth, cilostazol has properties that could make it the optimal medication irrespective of the anticoagulant actions of simple antiplatelets and warfarin, thus making it the “best medical therapy.” WASID was prematurely terminated due to the futility of proving the benefit of warfarin over aspirin, the high endpoint results (stroke) with both agents, and the reconfirmed increased bleeding with warfarin. Even though the final results and complete data concerning WASID have not been released as of this writing, the premature termination of WASID removes consideration of warfarin for any indication relating to cerebrovascular pathology once and for all.

What, then, are the current indications for warfarin therapy? Essentially, warfarin is used only to prevent clot formation in static blood. This includes chronic deep venous thrombosis, pulmonary embolism prophylaxis, and atrial fibrillation. Furthermore, the possible advent of orally administered direct thrombin inhibitors could remove the major therapeutic target of warfarin: the thrombin cascade. Active investigation of these target conditions by pharmaceutical companies is now under way.

Statins

Statins were designed to control serum lipid and cholesterol levels. They do this far more effectively than does diet alone. As is known, dietary cholesterol is immediately digested and broken down and the liver manufactures essentially all serum cholesterol. Heredity is a primary determinant of how much cholesterol the liver makes in each individual person, and diet can only affect the serum level in a very limited fashion (typically, the overall effect is about 10%). Thus, statins are a mainstay in cholesterol and lipid management.

Recently, it has been found that statins have an independent positive effect on the progression of atherosclerosis and plaque (54). Statins not only limit atherosclerosis but also appear to have additional beneficial effects by promoting plaque stabilization, providing an anti-inflammatory effect (decreased C-reactive protein), and reducing the risk of thrombosis. Results of clinical trials have shown a decreased stroke risk in patients with coronary artery disease and a modest elevation in lipid levels. This is entirely separate from their effects on serum cholesterol levels (55). Indeed, the positive benefit of statins on vessel wall morphology—even in patients with normal or even low serum cholesterol levels—is still present (56). For this reason, the indications for statin use are broadening.

Although statins have been used in acute stroke therapy, no study has established the direct benefit of statin medication in patients with acute ischemic stroke. On the basis of the evidence of benefit in patients who are at risk for vascular events, statins should be considered for secondary prevention of stroke in all patients with ischemic stroke and/or TIA who have low-density lipoprotein levels greater than 130. Further, for younger patients with a strong family history of vascular disease, statin use may be considered prophylactically. To my knowledge, it has not yet been determined which statin is most effective in patients who have had an ischemic stroke or TIA. Results of an ongoing study (the Stroke Prevention by Aggressive Reduction of Cholesterol Levels Study) will help determine whether statins are useful for stroke prevention in patients with prior ischemic stroke or TIA but without cardioembolic cause; however, results of a previous study (57) strongly indicate that statins are useful in patients with coronary artery disease.

Angiotensin-Converting Enzyme (ACE) Inhibitors

Although angiotensin-converting enzyme inhibitors were designed to treat hypertension, they have many other beneficial effects. These effects include antiatherogenesis, endothelial cell multiplication, and platelet inhibition. Several studies have shown a substantial reduction in stroke risk. In the Heart Outcomes Prevention Evaluation trial (58), investigators studied the effects of ramipril in patients at high risk for ischemic events and found a beneficial effect. The combined endpoint of MI, stroke, or vascular death was significantly reduced. Furthermore, the endpoint of stroke was also reduced. In the Perindopril Protection against Recurrent Stroke Study (59), investigators tested the effects of combining perindopril with a diuretic, indapamide, in patients with ischemic stroke, TIA, or intracerebral hemorrhage and found that the combination therapy dramatically reduced the risk of recurrent stroke. No benefit for perindopril therapy alone was found, although the study was not designed to
test this. Both studies, however, showed benefit independent of hypertension. The results of these two studies suggest that patients with stroke or TIA should be considered for treatment with an angiotensin-converting enzyme inhibitor, especially if there are other vascular risk factors present. Combination therapy with a diuretic may be warranted to maintain long-term blood pressure control and maximize benefit. National consensus guidelines about the use of angiotensin-converting enzyme inhibitors after stroke are needed to incorporate the findings of these recently published clinical trials.

ACUTE STROKE THERAPY

Background

Emergent restoration of blood flow is the only form of acute stroke therapy that has been proved to be efficacious. Although other therapies aimed at protecting the brain from the effects of ischemia (neuroprotectant agents, hypothermia, hyperbaric oxygen, etc) are promising, none have been shown to be effective to date. More than 50 trials of neuroprotectants have been performed, all with uniform failure. Until recently, attention has been focused on fibrinolytic agents delivered with either intravenous or intraarterial methods. The National Institute of Neurological Disorders and Stroke (NINDS) Trial demonstrated that intraarterial administration of tissue-type plasminogen activator (tPA) within 3 hours of onset of stroke symptoms was associated with improved outcome at 3 months (60).

There are drawbacks to intravenous lytic therapy, however. The window for treatment is very short, and the rate of recanalization is too slow and/or ineffective in the presence of large-vessel occlusion (61). Direct local intraarterial infusion of the fibrinolytic agent addresses these concerns. PROACT I and II demonstrated the efficacy and safety of intraarterial thrombolysis in acute middle cerebral artery occlusion with an absolute benefit of 15% (25% of patients in the placebo group had modified Rankin scale scores of 0–2 at 3 mo vs. 40% of patients in the intraarterial therapy group) (52,62).

Fibrinolytic Agents

No FDA-approved fibrinolytic agent is approved for catheter-directed intraarterial delivery, even for MI. No currently available (ie, FDA approved) fibrinolytic agent directly dissolves clot. All currently available agents activate plasminogen to plasmin, and it is this plasmin that degrades fibrin. Fibrinolytic agents lyse preexisting clots either by potentiating the body’s own fibrinolytic pathways (eg, streptokinase) or by imitating the body’s own potentiator (eg, tPA). The original agents were not fibrin-specific (streptokinase and urokinase). Newer drugs have been designed to be more fibrin specific for the intended purpose of being intravenously administered and then traveling to the clot like a cruise missile. No intravenously administered lytic agent has been proved in a comparative trial to have a selective effectiveness for stroke as opposed to MI, and all fibrin-specific agents marketed for acute MI therapy have been shown to be very similar in efficacy for this clinical situation.

Streptokinase. Streptokinase (Streptase; AstraZeneca, Westborough, Mass) is a single-chain glycoprotein derived from hemolytic streptococci. The mechanism of action of streptokinase is indirect; it first binds to a single molecule of plasminogen, which then cleaves a second plasminogen molecule into plasmin, the active agent. Although it was the original agent used for thrombolysis, it is not widely used owing to perceived limited efficacy as well as its antigenicity. Its serum half-life is about 18 minutes.

Urokinase. Urokinase (Abbokinase; Abbott Laboratories, Chicago, Ill) is a double-chain protease derived from neonatal kidney cell cultures. Unlike streptokinase, urokinase is a direct plasminogen activator. Its half-life is about 15 minutes. Urokinase is the most reported lytic agent in case series of interventional therapy of acute stroke and is the lytic agent most similar to prourokinase.

Prourokinase. Prourokinase has proved efficacy for interventional stroke therapy utilizing intraarterial catheter-directed delivery in a double blinded, randomized controlled trial (52,62). However, due to the fact that the FDA typically requires two pivotal trials for approval of a new drug, prourokinase has not yet received FDA approval. The manufacturer of this agent (Abbott Laboratories) has determined that the costs of this second trial outweigh the potential financial gain from production. Unfortunately, the National Institutes of Health has not funded a second trial and this remains an orphan drug with no FDA approval even though the results of PROACT were the most positive of any stroke trial ever performed (15% absolute and 60% relative benefit) and the stroke victims treated were the most severe of any stroke trial ever performed (average NIH Stroke Scale score = 17) (62).

Alteplase. Alteplase (Activase; Genentech, San Francisco, Calif) is a naturally occurring enzyme found in human endothelial cells. Alteplase is the only pharmaceutical agent currently approved by the FDA for acute stroke therapy and is administered as a weight-based intravenous bolus followed by weight-based infusion. Activase is manufactured by using recombinant DNA methods. Contrary to urokinase, the activity of alteplase is limited in plasma, but increased about 1,000-fold in the presence of fibrin (and fibrin-bound plasminogen). With increasing doses of alteplase, however, substantial amounts of plasmin can be generated from circulating plasminogen and result in degradation of fibrinogen and influence the “systemic lytic state.”

Alfimeplase. Alfimeplase (Cerezyme, Genzyme, Cambridge, Mass) is a complex of streptokinase and para-anisoylated lys-plasminogen. This formulation conveys some fibrin specificity and increases the plasma half-life to about 100 minutes.

Alfimeplase. This agent is not approved by the FDA. Alfimeplase is a recombinantly produced fibrinolytic agent that is a truncated form of fibrinolysin, a known directly fibrinolytic metalloproteinase (65). Fibrolase was first isolated from the venom of the southern copperhead snake. Both fibrolase and alfimeplase have been shown to have direct proteolytic activity against the fibrinogen a chain. This results in the in vivo activity of these agents being up to six times faster than that of the plasminogen activators. Further, alfimeplase
can be bound and neutralized by serum α₂-macroglobulin. This can potentially result in less systemic bleeding complications. All of these factors suggest that this agent has great potential for acute stroke therapy if it ever becomes available in the United States. A pilot dose escalation trial has just been completed.

Tenecteplase.—Tenecteplase (TNKase; Genentech) is another altered form of tPA and was designed to have enhanced fibrin specificity as well as a longer plasma half-life. This alteration allows single-bolus dosing for acute coronary occlusion on the basis of patient weight. Further, an intended advantage is resistance to plasminogen activator inhibitors.

Reteplase.—Reteplase (Retavase; Centocor, Malvern, Pa) is a deletion mutation of tPA. The finger domain and epidermal and kringle-1 domains are removed, thus decreasing the fibrin specificity and the rapidity of clearance by the liver. This increases the half-life to about 15 minutes.

Desmoteplase.—The plasminogen activator from vampire bat (Desmodus rotundus) saliva (Desmodus rotundus salivary plasminogen activator) is an effective plasminogen activator but as opposed to alteplase, is nearly inert in the absence of a fibrin cofactor (66). Alteplase has been shown to promote neurodegeneration in the presence of N-methyl-d-aspartate in ischemic brain but desmoteplase does not (67,68). Desmoteplase is now undergoing trial in the United States as an intravenous therapeutic agent for acute stroke.

Considerations Regarding Stroke Therapy

The determination of the optimal fibrinolytic agent for stroke therapy has been problematic, both for intravenous and intraarterial use. Streptokinase was evaluated in several early trials, but its use was associated with an unacceptably high rate of intracranial hemorrhage. However, all trials involving streptokinase had a therapeutic window subsequently shown to be too long and ineffective even with the only agent later proved to be effective: alteplase. Alteplase was used in the successful NINDS acute stroke trial. Alteplase is the recombinant form of the naturally occurring tPA molecule and the first of the modern fibrin-specific agents, whereas reteplase and tenecteplase are genetically engineered fragments of native tPA. For emergency intravenous lytic therapy for any indication, alteplase is the most difficult to use of the modern agents simply because of the necessity of weight-based dosing and subsequent complexity of intravenous infusion. Alteplase is cleared during the “first pass” through the liver, and, thus, requires a precise bolus followed by a precise infusion to maintain the proper serum level. Further, it has been shown in studies of stroke therapy to induce posts ischemic direct neuronal death by its action on cellular waste products of ischemia (67,68).

Single- or double-bolus intravenous lytic administration has been shown in acute myocardial infarction trials to be a simpler and more error-free dosing regimen than is the complex weight-based administration of intravenous alteplase. Indeed, for essentially all emergency myocardial infarction lytic trials as well as acute stroke trials, the weight of the patient is simply estimated. Reteplase is a double-bolus, fixed-dose drug that is not based on weight and, thus automatically yields fewer dosing errors. Tenecteplase is given as a weight-based single bolus, but there are limited choices for the bolus dose, thus potentially resulting in fewer errors in dosing. A small trial of tenecteplase for stroke is under way (69). Also, an early trial of vampire bat salivary plasminogen activator (desmoteplase), a fibrinolytic enzyme that does not promote neurodegeneration, is also under way (66).

Intraarterial Lytic Infusion for Emergency Stroke Therapy

Most of the clinical experience in intraarterial thrombolysis in any vascular bed has been gained by using urokinase. Urokinase is an enzyme produced by the kidney. The PROACT trial for intraarterial stroke therapy did not use urokinase but rather employed recombinant prourokinase (52,62). Although PROACT did not receive new drug approval from the FDA with that one trial, the trial itself had positive results (P = .04), with a large margin of improvement (40% of patients who received prourokinase had a good outcome, compared to 25% of those who received placebo). Although no randomized trial has proved the safety and efficacy of urokinase (as opposed to prourokinase, which was used in PROACT), it is thought to be associated with an acceptable safety and efficacy profile and has been used predominantly in intraarterial stroke therapy worldwide. Several large series of intraarterial thrombolysis for acute stroke have shown positive results and have been recently published, with urokinase being the most frequently used lytic agent (70–73). A recent meta-analysis of interventional stroke therapy has been published (74), demonstrating favorable results for intraarterial therapy of stroke; again, urokinase was the most frequently used drug.

Reports of the intraarterial use of alteplase and reteplase for emergency stroke therapy have also been published (69,75,76). Alteplase has been the drug of choice for the Interventional Management of Stroke and Emergency Management of Stroke trials (77). After the initial intravenous dosing regimen, a 2-mg intraarterial bolus of alteplase was administered past the clot and 2 mg was administered in the clot, followed by an intraarterial infusion at a rate of 9 mg/hour. Although the intraarterial doses of alteplase used were efficacious, both of these trials used intraarterial doses of alteplase that were orders of magnitude more than the levels described below (73,77).

A potential drawback to the use of alteplase for intraarterial therapy is its stability in solution. Dilution beyond 0.2 mg/mL may result in precipitation because of dilution of the stabilizing agent, l-arginine (78). However, there appears to be a bimodal dilution curve, and further extreme dilution may result in re-solution: Many practitioners dilute alteplase to a degree commensurate with this solubility profile (76). Further, the solvent used with alteplase—arginine—may compete with binding for receptor sites for plasmin (described below).

The intraarterial use of alteplase and reteplase for both peripheral use and emergency stroke therapy has been reported. Although successful use is continuing for these indications, their use has been marked by inade-
quate scientific information and knowledge of dosing and administration parameters. Both of these agents are extremely powerful. A gross estimate of the lysing ability of alteplase is that 1 mg can dissolve 100 mg of fibrin. Bookstein and Bookstein (79) have performed more exacting studies that have indicated that 1 mg alteplase is capable of dissolving 4 g of clot (not pure fibrin), which is enough to essentially fill the entire femoral artery (20 cm clot in a 6-mm vessel). The equivalent amount of reteplase necessary in this setting would be about 1.6 U (80).

Moreover, Bookstein and others (79,80,81) have indicated that there is a bell-shaped curve of activity and that the presence of too much lytic agent (in too concentrated a fashion) can actually slow down lysis considerably. The hypothesis of “plasminogen steal” to explain this property of diminished speed of lysis with increasing dose has existed for years (82). The concept that more lytic agent actually slows lysis is counterintuitive. However, it has been demonstrated in multiple in vitro studies that this is the case. Both higher and lower concentrations produced markedly slower activity. Bookstein and Bookstein (79) determined that the fastest activity of lysis with alteplase occurred at a concentration of 0.01 mg/mL. Positive results with dilution of alteplase to a level of 0.002 mg/mL have been reported (76).

Although the counterproductive effects of highly concentrated lytic agents were originally blamed on plasminogen steal, there is direct laboratory evidence that another explanation is plausible. Both tPA and plasmin compete for the same receptors on fibrin. If all receptors are occupied by tPA molecules, plasmin cannot attach to these receptors, thus blocking its action. This would therefore slow the action of certain lytic agents if used in higher concentrations (81). These concentrations would automatically be produced in static-flow situations such as stroke therapy. This competitive binding for receptors on fibrin might be the root cause of decreased speed of lysis with increasing doses. The optimal serum concentration of alteplase for acute MI therapy has been shown to be on the order of magnitude of 1 μg/mL (77). MI trials (83,84) have demonstrated the bell-shaped curve of activity for certain fibrin-specific lytic agents and found that higher serum concentrations do indeed slow lysis. This bell-shaped curve of activity has been confirmed with alteplase and reteplase, but not with urokinase or tenecteplase; further trials may help clarify this question. Until definitive trials are performed, the speed of lysis with all of the currently available agents should be considered to be somewhat similar. Recognition of the fact that concentrations higher than a certain level can be counterproductive is recommended.

Correct concentrations and total doses of fibrinolytic agents when delivered intraarterially by means of a catheter-directed technique are still undefined. This is particularly true for pharmaceuticals designed and intended for systemic intravenous administration, as is currently the case with the newer fibrin-specific fibrinolytic agents. Intraarterial infusion parameters have been studied and evaluated in detail in the field of oncology, where correct dosing for tumor therapy is contingent on adequate serum concentrations and overdosing can be extremely hazardous. It has been determined that catheter-directed intraarterial delivery of medication results in serum concentrations that are 100 to 1,000 times as high as when given intravenously. This serum concentration is vastly amplified with a concentrated infusion into a static flow situation and the much lower dosing implied by this rationale is consistent with the observations and test results of Bookstein and Bookstein (79,80). If blood is flowing, serum concentrations can change drastically and the high concentrations would decrease to a lower level.

The duration of intraarterial infusion for stroke therapy and total dose of any lytic agent is still an issue. Only the general dose ranges for these agents are known. Alteplase appears to be effective in the range of 0.01 to 20 mg/hour, but, as stated earlier, the lower range is probably more effective as well as safer. Perhaps a useful amount might be a solution of 2 mg in 100 mL normal saline (0.02 mg/mL), the lowest dilution and close to that recommended by Bookstein (79,80) and infused at 50 mL/h. Reteplase is useful anywhere from 0.1–10 U/h; currently, a common dosing regimen for stroke is 1 U/h (2 U in 100 mL normal saline infused at 50 mL/h), resulting in 0.02 U/mL, as above. Urokinase appears to be optimally used at a rate of 250,000–1,000,000 U/h. A dosing regimen for stroke therapy would be 500,000 U urokinase in 100 mL normal saline infused at 50 mL/h, resulting in an infusion of 250,000 U/h.

Complications Associated with Lytic Therapy

The major risk associated with fibrinolytic therapy is intracranial hemorrhage; hemorrhagic complications elsewhere in the body are also of concern. These fears are the result of reports of intracranial hemorrhage from the acute MI trials as well as anecdotal reports from radiologists (85,86). Although the original postulate was that the fibrin specificity of the newer agents would decrease systemic bleeding complications, this has not proved to be the case. Rates of hemorrhagic stroke in acute coronary occlusion trials range from 0.7% to 2.0% (85,86). Additional minor and major bleeding rates vary, depending on total dose, bolus regimen, and total infusion time. Rates of intracranial hemorrhage can range from 0% to 9% (87). There is some indication that the risk of bleeding may be greater with alteplase than with reteplase (88), but at least some of this difficulty in the interventional radiology arena might be due to overdosing.

Heparin and Bleeding.—Heparin may be the cause of some of the bleeding complications in any form of lytic therapy, but particularly in stroke therapy. In the PROACT trial (62), two different doses were used initially: high and low. The high-dose regimen, however, was stopped due to excessive hemorrhage rates. PROACT II used a dose of 2,000 U bolus at institution of therapy followed by an infusion of 500 U per hour for 4 hours (62). The lytic infusion lasted only 2 hours.

Heparin metabolism is quite unpredictable. It is often difficult to maintain adequate anticoagulation; in studies of recombinant tPA for coronary intervention, it has been found that partial thromboplastin times were higher in patients who had bleeding episodes than in those who did not (85,89). There is no clear and convincing evidence that heparin is
necessary in thrombolysis cases, and the trend to lower and lower (or even subtherapeutic levels) is an indirect clinical indicator of this fact.

In summary, hemorrhagic complications with lytic therapy can be kept to a minimum with the lowest effective doses of lytic agent, careful patient selection, and avoidance of full anticoagulation during therapy (78).

Glycoprotein IIb/IIIa Inhibitors

Recently, there has been increased interest in the role of glycoprotein IIb/IIIa inhibitors in acute stroke therapy and thrombolysis in general (90–92). The class of antiplatelet agents used in acute thrombolysis is the glycoprotein IIb/IIIa receptor inhibitors. Three glycoprotein IIb/IIIa receptor inhibitors are currently available: abciximab, epifibatide, and tirofiban. Results of early studies indicate that intravenous abciximab may be beneficial and safe in the setting of acute stroke (92). In the Abciximab in Emergent Stroke Treatment Trial (AbESTT, which was approved by the FDA), 400 patients with acute stroke (0–6 h) were randomized to receive either placebo or abciximab (standard cardiac dose) (93). Although the mean National Institutes of Health Stroke Scale score was lower than that of other trials (average score was about 10 for AbESTT, about 14 for NINDS, and about 17 for PROACT), the symptomatic intracranial hemorrhage rate for the AbESTT was only 3.6%. This was despite the later time to treatment (average, 3 h). Further, the percentage of patients with a Rankin score of 0 at 3 months was 23.5% for the abciximab group and 13.5% for the placebo group. These positive results are cause for another definitive trial now being organized.

There are important differences between these agents. All three exhibit rapid binding to platelets (<1 min). Abciximab has a prolonged platelet-bound half-life, whereas the other two agents rapidly dissociate from platelets. Most of the initial abciximab bolus binds to platelets; the remainder is rapidly cleared. The platelet-bound portion is cleared as platelets are removed from the system. Conversely, the other two agents have short platelet-bound half-lives and longer plasma half-lives. Greater concentrations and longer infusions of these small-molecule agents are needed to maintain adequate platelet blockade. The binding characteristics of the three agents also differ. Abciximab binds to αIIbβ3 with affinity equal to that for the glycoprotein IIb/IIIa receptor; its affinity for Mac-1 receptors is less. The other agents bind only to glycoprotein IIb/IIIa receptors. Abciximab may have a greater effect in reducing thrombin generation as well as endothelial desensitization (94,95).

There is indication that prolonged platelet blockade may be important in interventional procedures. Immediately following vessel injury, the vessel surface is highly thrombogenic and platelet-reactive, leading to platelet aggregation, thrombosis, spasms, and possible restenosis. The vessel wall then undergoes passivation as it heals with subsequent loss of platelet activity and thrombogenicity. This can take up to 8 hours in normal vessels and several days in atherosclerotic vessels (96,97).

Although prolonged activity may be of value, reversibility is also an issue. Although abciximab in particular shows good results in prolonged platelet blockade, its effects can be reversed with platelet transfusion (98). The reversal of epifibatide and tirofiban depends on renal clearance; platelet function will normalize within a few hours of stopping infusion in patients with normal renal function. Platelet infusion is ineffective in reversing epifibatide and tirofiban.

Glycoprotein IIb/IIIa receptor inhibitors are less associated with the increased risk of intracranial bleeds (or bleeding in general), as seen with fibrinolytic agents (99). When there is vessel wall injury, a platelet monolayer forms at the injury site; this is the beginning of hemostasis. This binding is mediated by glycoprotein IIb/IIIa receptors and is not blocked by glycoprotein IIb/IIIa inhibitors. However, the complete explanation for the apparent reduced intracranial hemorrhage rate with glycoprotein IIb/IIIa inhibitors compared with lytic agents is not fully elucidated. There is a small risk of profound thrombocytopenia with use of glycoprotein IIb/IIIa inhibitors.

Direct experimental information as well as clinical experience also indicates that abciximab at least, but probably all glycoprotein IIb/IIIa inhibitors, are capable of "disaggregation" of thrombi (100). In other words, clots, presumably composed of various combinations of red cells, fibrin, and platelets, are to some degree broken down by these agents. Pure platelet clots (and typically the fresher ones) are broken down faster and more completely by these agents than by lytics. This activity is thought to occur because the glycoprotein IIb/IIIa receptor bond between platelets is dynamic and these agents can interrupt the connection between platelets formed by these receptors and thus cause platelet dissolution.

Glycoprotein IIb/IIIa Receptor Inhibitors in Interventional Cases.—For use in interventional cases, several points about glycoprotein IIb/IIIa receptor inhibitors must be made. The dosing for these agents was determined in trials analyzing their use in acute coronary syndromes (in which activated platelets underwent extreme and ongoing stimulation by angry endothelium and/or plaque) and interventional coronary procedures (which subsequently damages endothelium). Both of these conditions require high doses and continued inhibition while the repair process of the endothelium is underway and/or while the platelet cascade is still active. These conditions may or may not be present in interventional procedures. Specifically, when these agents are used for clot dissolution on coils, for instance, the action may not need to be as extreme or prolonged (therefore, a 12-h infusion may not be necessary) and the stimulus for platelet adhesion may not be as strong; therefore, the high initial doses necessary to stop platelet adhesion on a ruptured plaque are not necessary. For this reason, a reduced dose may give adequate response without unnecessarily increasing the bleeding risk. No trial has been performed to adequately define these parameters.

Further, as described earlier in the section about fibrinolytics, it is known that the concentration of pharmaceuticals when delivered intraarterially is between 100 and 1,000 times that of the same drug given systemically (depending on the size and speed of flow of the vessel). This implies that these agents can be de-
livered in a vastly reduced dose via catheter if the effect is purely intended to be local rather than systemic. Just as with lytic agents, however, the infusion should be slow and sufficient time allowed for the intended pharmacologic action, or else it just washes past the target. In other words, thrombus disaggregation can be achieved by infusing 10%-30% of the normal systemic dose in a dilute solution directly intraarterially over a period of several minutes. These parameters are not determined at present.

Combination Therapy for Acute Stroke

There are two types of combination therapy: intravenous lytic agent plus intraarterial lytic agent and intravenous and/or intraarterial lytic agent plus an antiplatelet agent. The use of a combination of intravenous and intraarterial fibrinolytic agents in the setting of acute stroke has been considered (Emergency Management of Stroke and Interventional Management of Stroke trials (77)). This makes fundamental intellectual sense because sooner is always better (achievable with intravenous administration), but intraarterial therapy gives more powerful results for large-vessel occlusion (61). Therapy can be begun by using intravenous pharmaceuticals while the angiography team is being mobilized, resulting in less delay in the actual initiation of therapy. Although there have been promising early results, no substantial benefit has been shown to date (77).

Inhibition of the final common pathway of platelet aggregation is the rationale for combination therapy with glycoprotein IIb/IIIa inhibitors. This rationale has arisen in recent years from two sources: basic clinical science and clinical observation. As noted at the beginning of this chapter, there are two types of thrombus that form at sites of vessel injury. “White” thrombus is rich in platelets but contains relatively little fibrin, whereas “red” thrombus contains abundant fibrin. White thrombus is typical of arterial and partially occlusive thrombus, and red thrombus is associated with venous clots and complete occlusion. Platelet accumulation is greatest at sites of plaque rupture. When platelets become activated, they express the glycoprotein IIb/IIIa receptor on their surface (101). Fibrinolytic therapy has a limited effect on white thrombus; indeed, platelets exhibit reaccumulation at the clot surface as fibrinolysis occurs and IIb/IIIa-mediated lytic therapy is procoagulant (102). Antiplatelet therapy, however, is effective for white thrombus. Both types of agents are effective against red thrombus. Thus, a combination of antiplatelet and fibrinolytic therapy may be the optimal approach for many varieties of thrombus (see comments below concerning intraprocedural stroke). Inhibition of platelet aggregation may result in increased fibrinolytic activity and a decreased rate of reocclusion (99).

Related to this basic understanding of clot composition is the clinical observation that heparin alone or in combination with lytic agents has appeared to be suboptimal and, in some cases, ineffectual. Combination therapies, such as aspirin and heparin plus lytic agents, have been used to balance the prothrombotic effect of thrombolytic agents (99,101). Glycoprotein IIb/IIIa inhibitors have been shown to be superior to heparin in this regard (96,103).

Glycoprotein IIb/IIIa receptor inhibitors have also been shown to speed up the entire process of fibrinolysis. This action has been demonstrated with all currently available lytic agents, including urokinase (100). The use of glycoprotein IIb/IIIa receptor inhibitors in conjunction with a reduced dose of fibrinolytic agent has yielded promising results in the coronary circulation (104,105). In the Thrombosis in Myocardial Infarction 14 Trial, fibrinolytic alone, abciximab alone, and combination therapy were compared. The fibrinolytic agents studied included alteplase, reteplase, and streptokinase. It was shown that combination lytic and antiplatelet therapy improved outcome. Not only is reperfusion accelerated and reocclusion minimized, the decreased dose of fibrinolytic agent required may reduce the risk of distant hemorrhage. The current standard of care is to use a reduced dose of fibrinolytic agent with glycoprotein IIb/IIIa inhibitor therapy. Clinical evidence also suggests that combination therapy can reduce microvascular obstruction, which may lead to an improvement in clinical outcomes.

The science of combination antiplatelet and lytic agent use specifically for stroke therapy is in its infancy. Previous studies of MI as well as the recent AbESTT trial have indicated that glycoprotein IIb/IIIa inhibitors are safer than lytic agents for use in patients with and patients without acute stroke (93). Anecdotal experience and the results of early work, however, have indicated that the more powerful the reperfusion therapy, the more likely the possibility of hemorrhage in all locations including the brain. A substantial amount of continuing study will be required to answer the question of the optimal method of therapy for acute stroke with this approach.

Combination Therapy for Intraprocedural Stroke

The ability of glycoprotein IIb/IIIa inhibitors to promote “disaggregation” may make these agents the first line therapy for intraprocedural stroke. At least a portion of these strokes is caused by fresh thrombus composed primarily of platelets. If this is the case, the initial target of therapy should be these platelet-platelet bonds and the glycoprotein IIb/IIIa inhibitors are the therapeutic agents of choice. A protocol might consist of a peripheral bolus of glycoprotein IIb/IIIa followed by slow low-dose intraprocedural glycoprotein IIb/IIIa inhibitor infusion alternating or combined with intraarterial lytic infusion. A possible regimen for this therapy would be administration of 10 mg abciximab as a peripheral intravenous bolus followed by intraarterial infusion of abciximab interspersed with low-dose lytic infusions (see above). Six milligrams of abciximab in 100 mL normal saline can be infused at 100 mL/hour for 10 minutes (resulting in 1 mg/min infusion) followed by low-dose lytic infusion and so on. Alternatively, a more robust intravenous glycoprotein IIb/IIIa dose (eg, 15 mg abciximab) could be given with only intraarterial lytic infusion.

A combination of lytic and antiplatelet agents will probably eventually be shown to be optimal for de novo stroke therapy; the Interventional Stroke Therapy Outcomes Reg-
istry (INSTOR) may help answer these questions.

INSTOR

INSTOR (www.strokeregistry.org) is intended to be the definitive evaluation for interventional stroke therapy, utilizing all means to optimally reverse the acute insult. INSTOR is collecting and analyzing observational outcomes data about hospitalized patients treated by interventional means, typically catheter-directed thrombolysis. Following statistical analysis of the data, comparative data reports will be provided to participating investigators. The goals of this registry are to improve patient outcomes by (a) assessing the effect of clinical decisions on patient outcomes; (b) evaluating the care delivery process, both individually and collectively; and (c) providing feedback for optimal critical pathways for treating patients with stroke. With the data provided by this registry, some of the unknowns concerning optimal pharmacotherapy for acute interventional stroke therapy will be answered.

Spasmolytic Agents

Verapamil.—Verapamil is a blocker of slow calcium channels. It produces relaxation of the arterial wall smooth muscle and, thereby, vasodilatation. It has been shown to inhibit vasospasm in the coronary circulation (106,107). The onset of activity is within 5 minutes after intravenous administration, and the effect lasts 1 to 6 hours. It is supplied in a concentration of 2.5 mg/mL. It can produce hypotension and cardiac rhythm disturbances and has been used to treat rapid atrial fibrillation. The optimal dose and delivery of verapamil for cerebral vasospasm has not been determined (108). Early experience ranges from infusion of a concentration of 1 mg/mL (for a total of 4–8 mg per vessel over 5 min) to infusion of a concentration of 0.1 mg/mL at a rate of 100 mL/hour for a total of 10 mg per vessel (maximum, 20 mg).

Nicardipine.—Nicardipine is also a calcium channel blocker. Its method of action is similar to that of verapamil. Nicardipine has been evaluated for the prevention of vasospasm associated with subarachnoid hemorrhage (109). It is supplied in a concentration of 1 mg/mL. Like verapamil, it can produce hypotension and cardiac rhythm disturbances. At present, it is diluted in saline to a concentration of 0.1 mg/mL and infused at a rate of 10 to 15 mg/hour (total, 5–10 mg per vessel; maximum, 20 mg). Early experience indicates a more sustained effect than that of papaverine.

Nitroglycerin.—Nitroglycerin produces relaxation of vascular smooth muscle; it affects venous, arteriolar, and arterial vessels. It acts by forming nitrous oxide, which leads to an increase in cyclic guanosine monophosphate and dephosphorylation of myosin light chains, which in turn leads to smooth muscle relaxation. It is supplied in various concentrations, from 0.5 to 5 mg/mL. Onset of action is in 1 to 3 minutes. A safe preparation is a solution of 50 μg/mL in normal saline, which is then infused as a slow intraarterial bolus, typically 2 to 5 mL. Systemic hypotension is an end point, and these effects should be noted. The use of topical and intravenous nitroglycerin in the setting of vasospasm has also been explored (110,111).

Papaverine.—Papaverine inhibits phosphodiesterase, producing increased cyclic adenosine monophosphate and smooth muscle relaxation. The vasodilatory effect is more transient than is desired. It is supplied in a concentration of 30 mg/mL. Typically, a mixture of 300 mg in 100 mL normal saline is prepared. This can then be infused over a period of 20 to 60 minutes. Its use can be associated with an increase in blood pressure and heart rate if given too quickly. It should be infused distal to the ophthalmic artery origin. Papaverine has been noted to form crystalline precipitates when mixed with human blood at 3.0% or 0.3% concentrations. In addition, when a 3.0% solution is mixed with a saline solution containing heparin, a precipitate can form. This instability is related to concentration density. The precipitate formed is spicules of 30 to 100 μm and can result in microemboli during administration. The concentration of papaverine in saline should not be increased to more than 300 mg per 100 mL (0.3%). Even this concentration may be too high and, in conditions of stagnant blood flow, perhaps should be decreased. Precipitate forms when the infusion volume equals the quantity of serum (a rarity). Although there is more experience with the use of papaverine for the treatment of vasospasm than with other agents, serious limitations to its use have been identified. In addition to hypertension and tachycardia, transient elevation in intracranial pressure, paradoxical worsening of vasospasm, seizures, and brain stem depression have been reported (112–114). In addition, repeat treatment is often necessary because of the transient nature of the vasodilatation (115).

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