Thrombolytic Therapy in Cerebrovascular Disease

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The possible value of fibrin-selective thrombolytic agents in acute stroke is the subject of significant current interest. In addition to their use in acute thrombotic and thromboembolic stroke, plasminogen activators have been used to achieve vascular recanalization in selected patients with superior sagittal sinus thrombosis and acute retinal vascular thrombosis.

Thrombosis and Cerebrovascular Ischemia

Thrombus Formation

Arterial thrombosis and thrombus extension involve the overlapping systems of endothelial cell reactivity, platelet function, and coagulation. Thrombotic cerebrovascular occlusions arise secondary to thromboembolism from more proximal sites, e.g., the heart and proximal internal carotid artery, or from in situ thrombosis.

Thrombosis generation and extension involve thrombin-mediated fibrin formation and platelet activation. The early stages of intrinsic coagulation that lead to thrombin formation require the presence of a platelet-dependent factor XI receptor, high-molecular-weight kininogen, and platelet phospholipid (mediating factor V/VIII activation of factor X to Xa). Thrombin-mediated fibrinogen cleavage is accelerated by factor Xa bound to its platelet receptor (Va), promoting fibrin network formation in the thrombus. Endothelial cell ischemia or disruption promotes platelet aggregation and thrombus formation by disturbance of endothelial antithrombotic mechanisms, exposure of the subendothelium, induction of contact activation of the coagulation system, and granulocyte adherence. These processes may be most important in microvascular thrombus formation and the blocking of reperfusion in ischemic microvascular beds.

Thrombus Dissolution

Agents with thrombolytic activity are classified as endogenous or exogenous in origin. Thrombus dissolution results from the local generation and release of plasmin by endogenous fibrin-bound plasminogen activator (t-PA) and by single-chain urokinase plasminogen activator (scu-PA), where it is protected from the circulating inhibitors α2-antiplasmin and α2-macroglobulin. In contrast to the exogenous fibrin(ogen)olytic agents (see below), t-PA and scu-PA do not cause inactivation of factors V and VIII so that an anticoagulant state is generally not achieved.

The combination of thrombus-associated fibrinolysis and other forces in the microenvironment of the thrombus produce fragmentation and downstream embolism. Once a thromboembolism has lodged, the processes of thrombus growth and dissolution continue at the new site. These are of particular relevance to brain infarction since distal thromboembolic occlusion may account for symptom progression and may reflect spontaneous clot lysis and recanalization.

Exogenous agents, such as urokinase, streptokinase, and acylated plasminogen streptokinase complex, mediate fibrinogen dissolution in processes that generate products of fibrinogen degradation and deplete factors V and VIII and fibrinogen. These products interfere with fibrin multimer formation, thrombus extension, and new thrombus formation at the site of vascular occlusion. The transient anticoagulant effect that results may limit thrombus extension. Despite its fibrin-nonselective activity, infusion of an exogenous agent just proximal to the thrombotic obstruction may produce successful thrombus lysis at lower dose rates than required by systemic infusion.

Vascular Recanalization

Endogenous (t-PA– and possibly scu-PA–mediated) fibrinolysis underlies spontaneous vascular recanalization. Both recombinant DNA-generated t-PA (rt-PA) and scu-PA have been used to achieve lysis of thrombi in arterial and venous disease by intravenous infusion. Pharmacological levels of rt-PA have been associated with dose-dependent hypofibrinogenemia. Clinical experience with scu-PA is quite limited.

Exogenous agents have been employed to achieve thrombus lysis in short-term, high-dose, direct intra-
arterial infusion and in long-term intravenous infusion regimens. Significant improvements in function have accompanied recanalization in acute coronary artery thrombosis, pulmonary embolism with hemodynamic compromise, and selective peripheral arterial occlusions. Hypofibrinogenemia and plasminogen depletion are common features of systemic fibrinogenolysis resulting from the use of exogenous agents.

Cerebral Ischemia

The molecular mechanisms of cerebral ischemic injury are complex and poorly understood. The contributions of cerebral vascular anatomy, focal versus global ischemia, and collateral flow are relevant to thrombolytic intervention in acute cerebral ischemia. Information about the importance of thrombus location and clinical outcome in untreated and treated acute carotid and acute vertebrobasilar territory stroke is being accumulated. Focal rather than global ischemia would seem a more appropriate setting for establishing arterial reflow because of the potential for salvage of perifocal ischemic tissue ("ischemic penumbra") following cerebral arterial occlusion. Salvage of tissue in the ischemic penumbra depends in part on nutrient support from collateral arterial channels recruited acutely or established during chronic arterial insufficiency. Functional end-arteriolar ischemia and thrombosis, e.g., lenticulostriate arterial thrombosis secondary to M1 middle cerebral artery occlusions, would seem less likely to undergo recanalization ("no-flow" phenomenon) than large-artery occlusions with adequate collaterals or distal runoff.

Consequences of Reperfusion

Arterial recanalization by thrombolytic agents in a region of cerebrovascular ischemia is accompanied by a risk of reperfusion injury and of hemorrhagic transformation.

Recent investigation of the phenomenon of reperfusion injury suggests that the region of potential tissue salvage may be reduced by the generation of oxygen free radicals in the ischemic zone following reperfusion. The significance of this phenomenon and the effect of free radical quenching agents on the extent of cerebral tissue injury are under rigorous study in model systems.

The risk of hemorrhage is characteristic of all thrombolytic agents. In the central nervous system, parenchymal hemorrhage probably occurs secondary to lysis of fibrin-stabilized hemostatic plugs and exposure of damaged vessels to increased perfusion pressure. It has been suggested that in cerebrovascular ischemia there may be little advantage to the use of fibrin-selective agents over fibrinogenolytic agents if thrombus lysis is achieved. The risk and severity of hemorrhage is undoubtedly increased by systemic fibrinogen depletion and the anticoagulant effect characteristic of exogenous agents. The concomitant use of agents with antiplatelet (acetylsalicylic acid, hemodialutitional agents) or anticoagulant properties (heparin) may contribute to the hemorrhagic risk.

Of relevance in acute stroke is the distinction between hemorrhagic transformation of an ischemic/infarcted zone without clinical change and intracerebral hemorrhage with clinical deterioration. The spontaneous hemorrhagic conversion rate in cerebral infarction has been reported to be between 0% and 43% and is related to variables such as infarct size and mechanism (embolic versus thrombotic). Fibrinogenolytic agents have been associated with a 0–1.3% risk of intracerebral hemorrhage in patients without known cerebrovascular disease. The risk of hemorrhage in carotid and vertebrobasilar territory ischemia following thrombolytic agents remains unknown. Even though hemorrhage into a nonrecoverable ischemic zone may have little clinical significance, measures to minimize the incidence of intracerebral hemorrhage with clinical deterioration must be an integral part of clinical studies with fibrinolytic agents.

Timing of Reperfusion

While models of global or hemispheric ischemia indicate that irreversible neuronal death occurs within 6–8 minutes, functional recovery may follow even 3–6 hours of focal ischemia. The maximum interval from symptom onset to successful vascular recanalization with significant tissue recovery is unknown. Coronary artery recanalization after 4 hours of ischemic symptoms is not associated with significant myocardial functional recovery.

Thrombolytic Therapy in Stroke

Various animal model systems have been used to demonstrate dissolution of cerebral arterial thrombi and thromboemboli following immediate intravenous or intra-arterial infusion of exogenous thrombolytic agents, while improved survival after immediate rt-PA infusion has been reported. Functional improvement and apparent reduction in infarct size accompanied delayed local intra-arterial infusion of urokinase in a primate model. Several reports suggest that at low doses of rt-PA, the incidence of infarction-related hemorrhage is not significantly different from control. However, species variability with regard to dose rate and plasminogen activation must be taken into account in assessing the above reports.

Intravenous Infusion: Completed Stroke

Eight clinical trials evaluating the effect of late intravenous infusion of thrombolytic agents in patients with completed stroke have been reported (Table 1). In an early study by Herndon and colleagues, clinical improvement occurred in 22 of 45 patients, while hemorrhagic complications (all extracerebral) occurred in 13. Meyer et al demonstrated angiographically that thrombi were dissolved more frequently in the group receiving intra-
venous streptokinase, but there was no clinical improvement over the control group. Fletcher et al. observed no benefit in 31 patients with completed stroke receiving urokinase, and intracerebral hemorrhage occurred in seven patients. This observation supported a general contraindication to the use of fibrinolytic agents in stroke patients.26

Intra-arterial Infusion: Acute Stroke

Recanalization has accompanied local intra-arterial infusion of streptokinase or urokinase in patients with angiographically demonstrable acute arterial thrombotic occlusions in the carotid and vertebrobasilar territories (Table 2).47-55 Case reports and limited series have suggested neurological recovery following lysis in middle cerebral artery territory thrombotic occlusions47-48 and documented vertebrobasilar artery occlusions.49

Two prospective studies have used intra-arterial exogenous agents in consecutive acute stroke patients. Twenty patients with angiographically defined carotid territory occlusions were treated by intra-arterial local infusion of streptokinase/urokinase within 6 hours of symptom onset in a pilot study.50-52 Complete recanalization was achieved in 15 patients, of whom 10 displayed partial or complete symptom resolution. No improvement was observed in the absence of reperfusion. Hemorrhagic transformation was witnessed by serial cerebral computed tomograms (CT scans) in four patients (20%) although none deteriorated clinically. Resolution of the hemorrhage occurred in all patients, and two patients improved clinically. All hemorrhagic infarctions were confined to the ipsilateral subcortical white matter.

Zeumer and colleagues53,54 have demonstrated recanalization in 19 of 43 (44.2%) consecutive patients with acute thrombotic occlusions in the vertebrobasilar artery territory by local intra-arterial streptokinase/urokinase within hours of symptom onset. A significant improvement in survival and favorable clinical status were apparent in patients undergoing recanalization compared with those not displaying recanalization or those in a group not receiving fibrinolytic agents. Hemorrhagic transformation occurred in four patients (9.3%) receiving fibrinolytic agents, two undergoing recanalization and two not displaying recanalization.53,54,56 Two patients died secondary to fibrinolysis-related hemorrhage.

The incidence of hemorrhage in the above pilot studies falls within the broad expected range published. Without exception, all patients who hemorrhaged received a hemodilutional agent and heparin in the postfibrinolytic period.

Present Studies: Intravenous Infusion of rt-PA

The fibrin-selective character of rt-PA, its efficacy in coronary artery recanalization in acute myocardial infarction, and the suggestion that early intervention may contribute to functional recovery have

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**Table 1. Intravenous Fibrinolytic Therapy in Stroke Patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Patients</th>
<th>Improved</th>
<th>Hemorrhage</th>
<th>Deaths</th>
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<tbody>
<tr>
<td>Clarke and Clifton40</td>
<td>F</td>
<td>7</td>
<td>5</td>
<td>(0)</td>
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<tr>
<td>Herndon et al41</td>
<td>F</td>
<td>29</td>
<td>15</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Meyer et al33</td>
<td>P</td>
<td>11</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Meyer et al42</td>
<td>S</td>
<td>37</td>
<td>16</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Fletcher et al43</td>
<td>C</td>
<td>36</td>
<td>21</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Matsuo et al44</td>
<td>U</td>
<td>31</td>
<td>0</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Abe et al45</td>
<td>—</td>
<td>52</td>
<td>36</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abe et al46</td>
<td>U</td>
<td>57</td>
<td>48</td>
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<td>0</td>
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<tr>
<td></td>
<td>—</td>
<td>58</td>
<td>48</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

F, fibrinolysin; P, plasmin/plasminogen; S, streptokinase; U, urokinase; C, control.

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**Table 2. Local Intra-arterial Thrombolytic Therapy in Acute Stroke**

<table>
<thead>
<tr>
<th>Territory</th>
<th>Patients</th>
<th>Recanalization</th>
<th>Recovery</th>
<th>Hemorrhage</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid territory</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Miyakawa48</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Zeumer, Del Zoppo1,2,55</td>
<td>20</td>
<td>18</td>
<td>12</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Vertebrobasilar territory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nenci et al49</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Zeumer, Hacke1,56</td>
<td>43</td>
<td>19</td>
<td>8 (6*)</td>
<td>2 (21)</td>
<td>29</td>
</tr>
</tbody>
</table>

*Partial recovery.
†Contributed to patient demise.
provided the basis for examining the safety and efficacy of t-PA in acute atherothrombotic stroke.

At least four preliminary studies of various designs have been proposed to evaluate rt-PA given early in patients presenting with acute stroke. In a multicenter CT scan/angiography-based dose range study of safety, within 8 hours of the onset of symptoms patients receive a 60-minute infusion of rt-PA after documentation of an arterial occlusion in the territory appropriate to the symptoms and in the absence of hemorrhage. The study design examines recanalization (efficacy) versus the absence of hemorrhagic transformation with clinical deterioration (safety) as parallel outcomes. Anticoagulants are not used in the initial 24 hours. This study is in progress.

A separate National Institutes of Health-sponsored contract study in progress examines the incidence of hemorrhage following rt-PA administered at several dose levels within 90 minutes of symptom onset. All patients are screened by CT scan to rule out intracerebral hemorrhage as a cause of the neurological deficits. Two additional studies, in the Netherlands and in Scandinavia, have been undertaken, the results of which are not yet available.

scu-PA has been used in limited preclinical studies in animal models and has been discussed as an alternative to rt-PA in acute stroke.

No data are available on intracerebral hemorrhagic risk versus dose rate of rt-PA, but these will be obtained from the preliminary studies. The concomitant use of anticoagulants may increase such risk.57-58

Concerns About Thrombolysis in Acute Stroke

The potential benefits of fibrin-selective agents in acute stroke should be weighed against the unknowns:

1. The dose rate of t-PA (scu-PA) necessary to lyse thrombotic occlusions in acute thrombotic stroke is unknown and cannot be inferred from animal models or acute myocardial infarction studies.

2. The risk of intracerebral hemorrhage with these agents in a given individual is unknown. Studies with urokinase and streptokinase suggest that attendant conditions, such as hypertension, microvascular disease, or diabetes mellitus, may increase the risk of hemorrhage.

3. The success of t-PA-mediated thrombolysis may be dependent on thrombus location (carotid versus vertebral, stem versus branch), the recruitment of collateral pathways, and thrombus size.

4. Functional outcome per se may be an inadequate measure of thrombus lysis. Because arterial recanalization and clinical improvement are theoretically interdependent, a favorable clinical outcome can be attributable to t-PA or scu-PA only if recanalization has been demonstrated.

5. There is insufficient clinical experience with scu-PA to allow specific recommendations in cerebrovascular disease.

These concerns suggest caution in future studies with t-PA (scu-PA) in acute stroke. Carefully designed prospective studies in two stages will be necessary: 1) a determination of the dose rate capable of achieving recanalization without hemorrhage, followed by 2) a larger blind study of clinical outcome and hemorrhagic risk with the use of fibrin-selective agents at preselected dose rates and competing therapy. It should be remembered that the clinical efficacy of rt-PA in stroke has not yet been demonstrated, and its use should be confined to the study setting.

Retinal Vascular Thrombosis

Exogenous fibrinolytic agents (urokinase, streptokinase) have been used with variable outcome in patients with acute and chronic retinal vascular occlusions. Limited experience has suggested that intervention in acute retinal artery thrombosis must take place immediately after symptom onset.59 Kwaan60 and colleagues61 have demonstrated that vision restoration in retinal artery thrombosis was not possible with exogenous thrombolytic therapy, whereas vision improvement occurred after even delayed thrombolytic intervention in central retinal vein thrombosis.

This limited experience suggests that the role of fibrin-selective agents in acute retinal vein thrombosis should receive careful study.

Superior Sagittal Sinus Thrombosis

Intra-arterial (internal carotid artery) administration of urokinase may have a role in certain comatose patients with documented sagittal sinus thrombosis with lateral sinus extension (H. Zeumer, personal communication). Zeumer1 has reported sinus recanalization and clinical improvement/survival in four patients so treated. Great care must be taken since cerebral hemorrhage frequently accompanies sinus thrombosis. No experience with fibrin-selective agents, such as rt-PA, has been reported. However, selected patients with sinus thrombosis may benefit from intravenous rt-PA. It is imperative that studies of the use of fibrinolytic agents in serious cases of this type be carried out under angiographic control.

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