Thrombolytic Therapy in Stroke: Possibilities and Hazards

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AGENTS WHICH MEDIATE THE dissolution of thrombi are receiving increasingly wide therapeutic application. Urokinase or streptokinase have been employed in the treatment of acute thrombosis of coronary123 and selected peripheral arteries,14-24 traumatic internal carotid artery occlusion,25 as well as of pulmonary embolism26-30 and peripheral deep venous thrombosis.21-23

The demonstration that acute stroke is typically an atherosclerotic or thromboembolic process6-7 provides a theoretical basis for the use of thrombolytic therapy in the treatment of acute stroke. However, because of the possibility that intracerebral hemorrhage may develop during thrombolytic therapy, use of such agents in stroke treatment has generally been contraindicated. Nevertheless, limited recent experience indicates that careful infusion of thrombolytic agents may lead to thrombus dissolution and clinical improvement in selected patients presenting with acute stroke.77-79

It is the purpose of this discussion to review the molecular basis for the thrombolytic state, clinical experience with systemic and local treatment of stroke patients with various thrombolytic agents, and to weigh the relative risk of intracerebral hemorrhage in patients treated with fibrinolitic agents for stroke and for other thrombotic disorders.

Mechanism of Thrombolysis

Arterial thrombosis and thrombus extension involve to varying degrees the processes of endothelial injury, platelet aggregation and release, and thrombin generation. Thrombin-mediated fibrinogen cleavage results in fibrin formation which is required for thrombus stabilization.80 Thrombin-mediated fibrin formation occurs in direct relation to platelet activation by several mechanisms. Platelets promote activation of the early stages of intrinsic coagulation by a process that involves a factor XI receptor and high molecular weight kininogen.81 Also, factors V and VIII interact with platelet membrane phospholipids to facilitate the activation of factor X to Xa and the conversion of prothrombin to thrombin.82 Platelet-bound thrombin-modified factor V (factor Va) serves as a high affinity platelet receptor for factor Xa.83 Consequently, the rate of thrombin generation is accelerated 100 fold, providing a potent positive feedback mechanism for initiation of thrombin formation on the platelet surface, fibrin network formation in the thrombus, and indirectly, fibrinolysis.

Thrombus dissolution is, in large part, mediated by fibrinolysis localized within the thrombus.84-86 Fibrin (and fibrinogen) degradation is catalyzed by plasmin, the product of plasminogen activation.87 In the consolidating thrombus plasminogen binds to fibrin and to platelets, allowing local release of plasmin within the thrombus. The circulating plasminogen activators, tissue plasminogen activator (tPA) and single chain urokinase plasminogen activator (scuPA), catalyze plas-
min formation, which may lead to de novo lysis of thrombi and thromboemboli.88-89

In reported clinical studies of arterial occlusion, urokinase, streptokinase, or preformed plasminogen-streptokinase complex have been used therapeutically as exogenous plasminogen activators. The conversion of plasminogen to plasmin in the circulation by these agents involves different mechanisms.84-86 Urokinase activates plasminogen directly by first order kinetics to produce plasmin. In contrast, streptokinase combines stoichiometrically with plasminogen to form a streptokinase-plasminogen complex, exposing an active site in the complexed plasminogen. The active streptokinase-plasminogen complex converts circulating uncomplexed plasminogen directly to plasmin, and itself eventually undergoes further intramolecular activation to form streptokinase-plasmin. Ultimately, free circulating plasmin degrades both fibrinogen and fibrin, and inactivates prothrombin, factor V, and factor VIII, thereby inhibiting the coagulant phase of thrombus formation.87 The systemic thrombolytic state is marked by a decrease or depletion of circulating plasminogen, fibrinogen, and factors V and VIII with reciprocal generation of fragments of fibrinogen and fibrin. The fragments interfere with subsequent fibrin multimerization contributing to the limitation of thrombus formation. In addition, the circulating fragments, hypofibrinogenemia, and factor depletion produce a transient anticoagulant state which may limit thrombus extension, as well as thrombus formation. Inactivation of plasmin outside the thrombus by the circulating plasmin inhibitors α2-antiplasmin and α2-macroglobulin may modulate thrombus formation and extension.89 The use of exogenous streptokinase-plasminogen complex (Fibrinolysin®, Thrombolysin®) to catalyze thrombus dissolution has no known practical advantages over streptokinase alone.

Tissue plasminogen activator (tPA)90 and single chain urokinase plasminogen activator (scuPA) are two endogenous plasminogen activators with relative fibrin specificity.91 tPA has been produced by recombinant DNA techniques in sufficient quantity for clinical study.92 tPA is considered to be fibrin-dependent because of its favorable binding constant with respect to fibrin90 and its consequent activation in association with fibrin. However, as demonstrated in the TIMI I trial, intravenous infusion of large doses of tPA may produce clinically measurable fibrinogenolysis and plasminogen destruction, although significant inactivation of factors V and VIII does not occur, and an anticoagulant state is generally not achieved.19,93 Since circulating scuPA is coupled to a protective inhibitor and becomes activated by plasmin on the surface of the thrombus, it also manifests thrombolytic properties similar to tPA. Its biochemical and in vivo kinetic characteristics are currently under investigation.91

Limitations to the use of thrombolytic agents derive from complications associated with thrombolysis. Specific immunologic side effects unique to streptokinase have been described in detail.84-86 However, it is the risk of hemorrhage, characteristic of all thrombolytic agents, that underlies the concern for their unrestricted use in thrombotic disease occurring in cerebral vessels.84 Hemorrhage probably occurs secondary to lysis of fibrin-stabilized hemostatic plugs protecting sites of vascular disruption.95,96 The anticoagulant effects of fibrinogenolytic products per se are probably less important to this process. However, hemorrhage at a site of injury is probably augmented by systemic depletion of fibrinogen and coagulation factors V and VIII, and the rising level of fibrin degradation products that interfere with fibrin multimer formation. These events limit thrombus extension and new thrombus formation at the site of vascular injury. Sites of recent or ongoing vascular disruption (e.g. mechanical, ischemic, inflammatory) are at some increased risk of hemorrhage independent of the presence of therapeutic fibrinolytic agents, although such agents undoubtedly augment this risk. Furthermore, there are no conclusive data to suggest that the age of the prior vascular injury and its protective thrombus, is important as a predictor of hemorrhagic risk.

In the case of de novo arterial thrombosis or thromboembolic occlusion, early therapy to effect immediate thrombolysis is theoretically desirable to a) limit vascular endothelial ischemia, consequent vascular necrosis, and the possibility of parenchymal hemorrhage, and b) maximize functional tissue recovery by limiting the duration of ischemic parenchymal injury. This general approach is illustrated by the current strategy of treating patients within six hours of the onset of myocardial ischemia secondary to coronary artery thrombosis.1-23

Thrombosis and Acute Stroke

Solis and coworkers,71 in a prospective angiographic study of 81 consecutive patients, demonstrated the presence of atherothrombotic stenoses and/or occlusion of an artery or arteries appropriate to the neurologic deficits in 80 to 90% of patients examined by angiography within 12 hours of the initial symptoms. This frequency was independent of the cerebral territory examined. When angiography was performed at later times from the onset of the acute neurologic deficit, the percentage of corresponding thrombotic occlusions was markedly decreased. This experience has been confirmed at other institutions72 as well as our own. Analogous observations have been made by De Wood and colleagues97 regarding the incidence of acute thrombotic occlusion of coronary arteries in individuals presenting with acute myocardial infarction. The utility of thrombolysis in acute myocardial infarction is now a matter of record.1-2 It is the association of atherothrombotic or thromboembolic cerebral arterial occlusions with acute neurological symptoms that has prompted the use of thrombolytic agents in stroke patients.

Clinical Experience with Thrombolytic Therapy in Acute Stroke

Early Studies: Intravenous Infusion

Experiments in animal models accompanying early clinical use of thrombolytic agents employed arterial
thrombi generated by intracarotid infusion of powdered pumice. Dissolution of pial arterial thrombi followed immediate intravenous infusion of plasmin preparations and thrombolytic agents in the animals.

Seven clinical trials evaluating the effect of late intravenous infusion of thrombolytic agents in patients with stroke have been reported (table 1). Herndon and colleagues, in a preliminary study of 45 patients with presumed cerebral arterial occlusion treated with either Fibrinolyxin® or plasmin, noted improvement in 22 patients. Hemorrhagic complications, all extracerebral, occurred in 13 individuals. No untreated control group was entered in this study. In an angiographic study, Meyer and colleagues demonstrated that thrombi were dissolved with greater frequency in the group receiving intravenous streptokinase, but no clinical improvement over the control group was evident.100 “Reperfusion” was associated with a “small but significant risk of cerebral hemorrhage.”

Fletcher et al observed no benefit in 31 patients receiving urokinase later than 24 hours from the onset of symptoms for completed stroke.101,102 Intracerebral hemorrhage occurred in 7 of the 31 patients. Four patients with carotid territory symptoms suffering intracerebral hemorrhage in the ischemic hemisphere were considered in detail.103 Of those patients two had histories of definite antecedent focal neurological deficits, two were hypertensive, one had a history of atrial fibrillation and congestive heart failure. At post-mortem or angiography 2 patients had internal carotid artery occlusion ipsilateral to the cerebral hemorrhage. In only one patient (case 4) was treatment clearly initiated less than 8 hours from symptom onset. Cases 1 and 3 awoke on the morning of admission with signal deficits, thereby making precise timing difficult. Where such data were available, two patients had fibrinogen levels greater than 200 mg dl⁻¹ at the time of the complication. It was felt that cases 3 and 4 might have had undiagnosed primary cerebral hemorrhages. One patient suffered a similar carotid territory hemorrhage while undergoing saline infusion.104

The lower incidence of hemorrhage observed by Abe, et al in two later studies is a reflection of the very low doses of urokinase employed. Fibrinogenolysis was not observed in those studies,103,104 and there was no apparent clinical benefit.

In general, those clinical studies have been interpreted to indicate that intravenous urokinase or streptokinase infusions are unsafe and provide little evidence of benefit for acute stroke patients. The validity of these conclusions is compromised by several observations: 1) because CT scanning equipment was unavailable, patients with intracerebral hemorrhage could not be excluded from any study at the outset; 2) cerebral angiographic documentation of thrombotic occlusion at the time of presentation was not performed in most studies; 3) the dose-rate of urokinase/streptokinase infusion was variable from patient to patient and was not apparently controlled; 4) when clearly documented, and with rate exception, patients were not treated early, e.g. within 6 hours of symptom onset. Furthermore, it was not possible to discriminate the patients who developed hemorrhage into a cerebral infarction secondary to a thrombolytic or anticoagulant state. These considerations suggest that a reexamination of questions of safety and efficacy of thrombolysis in the treatment of acute thrombotic stroke is in order.

Recent Studies: Local, Intraarterial Infusion

Functional neurological recovery without CT scan-detectable intracerebral hemorrhage has been demonstrated in an animal model of proximal middle cerebral artery (MCA) occlusion when urokinase was administered by ipsilateral intracarotid infusion within 5 hours of the onset of cerebral ischemia. Intracranial hemorrhage occurred in 13 individuals. No untreated control group was entered in this study. In an angiographic study, Meyer and colleagues demonstrated that thrombi were dissolved with greater frequency in the group receiving intravenous streptokinase, but no clinical improvement over the control group was evident.100 “Reperfusion” was associated with a “small but significant risk of cerebral hemorrhage.”

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The lower incidence of hemorrhage observed by

### TABLE 1 Intravenous Fibrinolytic Therapy in Stroke Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Patients</th>
<th>Improved Hemorrhage Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herndon (1961)</td>
<td>F</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td>Meyer (1961)</td>
<td>F</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Meyer (1965)</td>
<td>P</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Matsuo (1979)</td>
<td>S</td>
<td>37</td>
<td>16</td>
</tr>
<tr>
<td>Fletcher (1976)</td>
<td>C</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>Abe (1981)</td>
<td>U</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Abe (1981)</td>
<td>U</td>
<td>49</td>
<td>39</td>
</tr>
<tr>
<td>Abe (1981)</td>
<td>U</td>
<td>57</td>
<td>48</td>
</tr>
</tbody>
</table>

U = urokinase; S = streptokinase; P = plasmin/plasminogen; F = Fibrinolysin®; C = conventional therapy; — = placebo.
In a given individual this is related to the variability of collateral flow. The precise time limits for initiation of local thrombolytic therapy in acute stroke relative to the onset of symptoms have not yet been defined. Furthermore, the distinction between a parenchymatous hemorrhage with associated clinical deterioration and the more clinically benign, but CT scan evident, hemorrhagic infarction will be critical in safety assessments. Other important practical considerations include a) the necessity to demonstrate thrombotic occlusion of a cerebral arterial supply appropriate for the symptoms, b) the distinction between fluctuating or reversible neurological deficits and those which are fixed and stable, c) the respective natural histories of arterial occlusion in the carotid and vertebrobasilar territories and their individual subgroups, and d) the necessity to exclude alternative diagnoses in the early minutes to hours of the event. Finally, it is apparent that early intervention requires the mobilization and cooperation of individuals with neurological, neurophysiological, neuroradiological, and hematologic expertise. A prospective controlled study will be necessary to resolve the question of whether early thrombolytic therapy can salvage function without significant risk.

Spontaneous Thrombolysis in Acute Stroke

To assess the efficacy of thrombolytic therapy in acute stroke, the rate of spontaneous dissolution of arterial thrombotic or thromboembolic occlusions secondary to intrinsic fibrinolysis must be considered. The incidence of such events, particular in the setting of thromboembolic fragmentation is unknown; however, such events have been observed, and probably account for the lower incidence of angiographically demonstrated occlusions when patients are examined more than 12 hours after the signal stroke.

The recent clinical studies emphasize a number of poorly defined complex factors surrounding the issue of efficacy and safety. Although electrophysiological studies have suggested that ischemic injury to cerebral tissue may be tolerated for longer periods than previously thought, local thrombolytic therapy may only preserve tissue within the ischemic penumbra. Other. No improvement was observed in the absence of reperfusion. No intracerebral hemorrhage was observed in any of the four patients.

Zeumer and colleagues, at the Rheinische Westfälische Technische Hochschule (RWTH), Aachen, in the most extensive series reported to date (table 2), have demonstrated recanalization of acute thrombotic arterial occlusion in the carotid or vertebrobasilar territories in 19 of 29 consecutive patients treated within hours of symptom onset using local intraarterial urokinase infusion. Minor infarction-related hemorrhages without detectable neurological sequelae were found by CT scan in 5 patients (17%) in the postinfusion period. Three patients with proximal M1 segment MCA occlusions developed corpus striatal hemorrhages without clinical deterioration. Two patients with brainstem strokes treated later than 6 hours after symptom onset had hemorrhages confined to the area of infarction demonstrated by CT scan. In three of the 5 patients, hemorrhage occurred during the period of heparin anticoagulation after the completion of urokinase infusion. Patients with M1 segment MCA occlusion who did not show recanalization demonstrated either a severe neurologic deficit or died. In the combined experience of the RWTH and SCRF, 19 of the 20 patients demonstrating early recanalization of occluded arteries displayed either a moderate deficit or no deficit. Neuroelectrophysiological monitoring (somatosensory and brainstem evoked potentials) in a limited number of patients revealed that no deterioration due to intraarterial administration of urokinase occurred. Electrophysiological recovery of initial function was documented in some of the monitored cases. This uncontrolled prospective clinical experience suggests that early local infusion of thrombolytic agents in selected patients may be efficacious and safe.

The recent clinical studies emphasize a number of poorly defined complex factors surrounding the issue of efficacy and safety. Although electrophysiological studies have suggested that ischemic injury to cerebral tissue may be tolerated for longer periods than previously thought, local thrombolytic therapy may only preserve tissue within the ischemic penumbra.
techniques, such as Doppler-ultrasonography and transcranial Doppler-ultrasonography, in the context of prospective controlled studies of early thrombolytic therapy in acute stroke, should allow a more precise definition of the contribution of spontaneous thrombolysis, while reducing the need for multiple serial angiographic studies.

Hemorrhagic Risk in Acute Stroke

To assess the risk of intracerebral hemorrhage following infusion of thrombolytic agents, the incidence of parenchymatous hemorrhage and hemorrhagic infarction associated with untreated atherothrombotic stroke must be known. The distinction between a parenchymatous hemorrhage and hemorrhagic infarction is not merely academic. The term parenchymatous hemorrhage refers to a well localized clot of blood (hematoma), easily visualized on CT as a homogeneous density (high attenuation), often with mass effect. Clinically, the occurrence of hemorrhage is often associated with neurological worsening and easily recognized signs depending on its location. In contrast, hemorrhagic infarction may be the more natural state of brain tissue following recanalization of a previously occluded artery. In hemorrhagic infarction, the bleeding component refers to petechial hemorrhage, single or confluent, usually maximal in cerebral gray matter, but not a true clot of blood. On CT scan a hemorrhagic infarction may not be apparent or may appear less dense and homogeneous, patchy in configuration with mixed areas of low and high density. Many hemorrhagic infarctions probably are not visualized by CT, especially when performed with earlier-generation scanners. To our knowledge, no systematic clinical-CT-pathologic study has been carried out to elucidate the clinical important of hemorrhagic infarction. Serious efforts to assess the benefits and safety of thrombolytic treatment must take this distinction between hemorrhage and hemorrhagic infarction into account.

The frequency of embolic infarcts that are hemorrhagic has been estimated to be between 55 and 65 percent by neuropathology; however, the number that are clinically evident as hemorrhagic infarctions or parenchymatous hemorrhages (hematomata) is much lower. The incidence of clinically detectable intracerebral hemorrhage following cerebral embolism of cardiac origin and subsequent cerebral infarction in the absence of anticoagulation is low. In two retrospective non-case controlled studies no intracranial hemorrhages were noted among 53 patients and 92 patients not receiving anticoagulants. Similarly, in two consecutive series totalling 44 patients, no hemorrhagic events were noted. Baker, in a randomized prospective study of anticoagulation following cerebral embolic events, reported no central nervous system hemorrhages in the control group of 16 patients. In contrast, among 38 patients submitted to CT scan within 24 hours of the onset of nonseptic focal cerebral ischemia of cardiac origin, 3 (8%) presented with hemorrhagic infarction. This finding is tempered by a lower incidence (2%; 1 patient) of CT-detectable hemorrhagic infarction among 54 consecutive patients with acute nonseptic embolic cerebral infarction. In a multicenter randomized study of immediate versus delayed anticoagulation following nonseptic embolic cerebral infarction from a presumed cardiac source, among 63 patients entered, 53 patients (24 group A, 21 group B, 3 of 11 group C, 4 of 7 group D) were not receiving anticoagulants or antiplatelet agents prior to entry into the study. Two of the 53 patients (4%) presented with a hemorrhagic infarction demonstrable or initial CT scan.

Although the above analysis suffers from the paucity of prospective randomized studies and the restricted size of individual series, the incidence of intracerebral hemorrhage at presentation of or subsequent to cardiac embolism is probably less than 10% in any series. Because the definition of a cardiac source cerebral embolus in an acute situation is often difficult given the limitations of patient history and the diagnostic techniques presently available, the incidence of intracerebral hemorrhage secondary to thromboembolism from a cardiac source cannot be precisely determined.

The incidence of hemorrhagic cerebral infarction in acute embolic stroke from any source is also difficult to determine. At neuropathology 66 (18%) of 373 brains with vascular occlusion demonstrated “hemorrhagic infarctions,” of which 95% were associated with “embolic arterial occlusion.” Further clinical and histological data were not provided, so that questions of the definition of embolic occlusion, the incidence of hemorrhage at presentation, hemorrhagic transformation, and therapeutic intervention can not be resolved. However, data from the Harvard Cooperative Stroke Registry indicated that 17% of patients presenting with acute stroke had “intracranial hematoma” as a final diagnosis. The incidence of hematoma formation from this prospective study is somewhat greater than previously reported, but is confirmed in other series. Of interest is the observation that embolism accounted for 31% of acute stroke presentations. In the subgroup undergoing angiography (88 patients), 59% had arterial occlusions in the clinically affected territory presumed to be embolic in nature. Finally, of 214 patients presenting with the initial diagnosis of cerebral embolism in this study, 10 (5%) in fact developed intracranial hematoma. The frequency of intracranial hemorrhage in the patients with angiographically determined vascular occlusion (42 patients) was not described.

In summary, the incidence of intracerebral hemorrhage in patients carrying the diagnosis of acute stroke secondary to cerebral embolism of cardiac origin is less than 10%, and probably less than 5%. Among patients appearing with acute stroke from all etiologies, hematoma or intracranial hemorrhage account for approximately 17-18% of deficits as noted in one autopsy series, and retrospective and prospective analyses. It cannot be concluded from those data that intracerebral hemorrhage necessarily leads to equiv-
alent mortality. Interestingly, the high incidence of hemorrhage secondary to embolic infarction reported by Fisher and Adams is not apparent from clinical studies, or CT scan data.120, 121

Effects of Thrombolytic Therapy in Patients with Previously Unknown Cerebrovascular Disease

The risk of intracerebral bleeding in stroke patients treated with thrombolytic agents is partly addressed by considering the risk of intracranial bleeding found in patients receiving thrombolytic therapy for other thrombotic conditions in the absence of demonstrable cerebrovascular disease.

The incidence of spontaneous intracerebral hemorrhage during or following intravenous or intraarterial infusion of streptokinase or urokinase in patients unselected for intracranial disease is estimated to be less than 1%.15 The precise incidence, however, is not known. Published clinical series often do not provide sufficient description of central nervous system-related complications to offer insight regarding the risk of the therapy. Furthermore, the variables that determine the development of intracerebral hemorrhage are not easily defined. Nevertheless, a review of the incidence of intracerebral hemorrhage by disease-treatment category is of interest (tables 3–5). Such a review may not be entirely representative of reported experience and undoubtedly underestimates the actual risk.

Pulmonary Embolism

In the acute treatment of pulmonary embolism, among 82 patients receiving urokinase (Urokinase in Pulmonary Embolism Trial, UPET), one patient (who suffered a stroke one month prior to therapy), who succumbed after termination of the infusion was noted at autopsy to have multiple cerebral hemorrhagic infarcts.36 In contrast, among 169 patients with angiographically demonstrated pulmonary emboli entered in the Urokinase/Streptokinase in Pulmonary Embolism Trial (USPET), Phase 277, no episodes of intracranial hemorrhage were noted. Similarly, no CNS events were noted in 27 patients receiving streptokinase in two separate smaller studies comparing heparin and streptokinase.34, 39

Peripheral Arterial Occlusion

Limited published information is available regarding intracranial hemorrhagic complications following local infusion of thrombolytic agents for peripheral arterial thrombotic occlusions (Table 3). No central nervous system related-hemorrhagic complications were documented in three retrospective studies including 165 patients with peripheral arterial thrombosis treated with low dose (1-10 × 10^5 IU/hr) directed infusions of streptokinase (total 4-1695 × 10^5 IU).24-26 Only one patient suffered an intracerebral hemorrhage from a combined series of 113 individuals with peripheral arterial thrombosis treated with high dose (100 × 10^5 IU/hr) intravenous streptokinase or streptokinase and plasminogen.15, 28-29, 31-33 This individual had a previous transient hemiparesis remote from the arterial thrombosis and subsequent thrombolytic therapy. When a history of previous central nervous system disease was used as a contraindication to thrombolytic therapy, no episodes of intracranial hemorrhage would have occurred. Martin and Auel34 reported intracerebral hemorrhage as a complication of intravenous streptokinase infusion in 4 of 600 consecutive patients

<table>
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<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Agent</th>
<th>Dose (×10^5 IU hr^-1)</th>
<th>Antithromb</th>
<th>CNS*</th>
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<td></td>
<td></td>
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<tr>
<td>Dotter24</td>
<td>1974</td>
<td>17</td>
<td>S</td>
<td>1-10</td>
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<td>S</td>
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<td>Hess26</td>
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<td>S</td>
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<td>Verstraete27</td>
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<td>Reichle32</td>
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<td></td>
<td></td>
<td>6</td>
<td>H</td>
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<tr>
<td>Martin33</td>
<td>1978</td>
<td>26</td>
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<td>Martin34</td>
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<td>Aldrich35</td>
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<td>10</td>
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<td>100</td>
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S = streptokinase; P = plasmin/plasminogen; H = heparin; (0) = not reported.

*CNS = central nervous system hemorrhage (hemorrhagic infarction/hematoma).
†Represents peripheral arterial occlusions, thrombi, and emboli rather than patients.
‡Total dose per patient.
**Table 4** Intracranial Hemorrhage Associated with Thrombolytic Therapy for Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Author</th>
<th>Yr</th>
<th>N</th>
<th>Agent</th>
<th>Dose* (x 10^3 IU)</th>
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<tr>
<td>Rentrop†,‡</td>
<td>1981</td>
<td>29</td>
<td>S</td>
<td>128 ± 36</td>
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<td>Mathey³</td>
<td>1981</td>
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<td>20</td>
<td>(S + P)</td>
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<td>11</td>
<td>S</td>
<td>30–200</td>
<td>Heparin</td>
<td>0</td>
</tr>
<tr>
<td>Neuhaus⁶</td>
<td>1981</td>
<td>30</td>
<td>S</td>
<td>800–2600</td>
<td>(0)</td>
<td>0</td>
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<td>Rutsch⁷</td>
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<td>232</td>
<td>S</td>
<td>2–4 min⁻¹</td>
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<tr>
<td>Ganz⁸</td>
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<td>81</td>
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<td>250</td>
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<td>1982</td>
<td>89</td>
<td>S</td>
<td>2 min⁻¹</td>
<td>ASA/Dipyrid</td>
<td>0</td>
</tr>
<tr>
<td>Khaja¹¹</td>
<td>1983</td>
<td>20</td>
<td>S</td>
<td>250</td>
<td>ASA/Dipyrid</td>
<td>0</td>
</tr>
<tr>
<td>Anderson¹²</td>
<td>1983</td>
<td>24</td>
<td>S</td>
<td>100–390</td>
<td>ASA/Dipyrid</td>
<td>0</td>
</tr>
<tr>
<td>Kennedy¹³</td>
<td>1983</td>
<td>134</td>
<td>S</td>
<td>250–350</td>
<td>Heparin</td>
<td>0</td>
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<tr>
<td>Leiboff¹⁴</td>
<td>1984</td>
<td>22</td>
<td>S</td>
<td>240</td>
<td>Heparin</td>
<td>0</td>
</tr>
<tr>
<td>Aldrich¹⁵</td>
<td>1985</td>
<td>60</td>
<td></td>
<td>100</td>
<td>Heparin</td>
<td>1</td>
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2. Intravenous

<table>
<thead>
<tr>
<th>Author</th>
<th>Yr</th>
<th>N</th>
<th>Agent</th>
<th>Dose* (x 10^3 IU)</th>
<th>Antithromb</th>
<th>CNS†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuhaus⁶,¹⁶</td>
<td>1981</td>
<td>10</td>
<td>S</td>
<td>800–2600</td>
<td>(0)</td>
<td>0</td>
</tr>
<tr>
<td>Schroeder¹⁷</td>
<td>1983</td>
<td>93</td>
<td>S</td>
<td>500</td>
<td>Heparin</td>
<td>0</td>
</tr>
<tr>
<td>Spann¹⁸</td>
<td>1984</td>
<td>43</td>
<td>S</td>
<td>850–1500</td>
<td>Heparin</td>
<td>0</td>
</tr>
<tr>
<td>TIMI¹⁹</td>
<td>1985</td>
<td>122</td>
<td>S</td>
<td>1500</td>
<td>Heparin</td>
<td>0</td>
</tr>
<tr>
<td>Euro. Coop.²⁰</td>
<td>1979</td>
<td>156</td>
<td>S</td>
<td>1450</td>
<td>Coumarin</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>159</td>
<td>C</td>
<td></td>
<td>Coumarin</td>
<td>0</td>
</tr>
<tr>
<td>Amery²¹</td>
<td>1969</td>
<td>83</td>
<td>S</td>
<td>1250</td>
<td>Coumarin</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84</td>
<td>H</td>
<td></td>
<td>Coumarin</td>
<td>0</td>
</tr>
<tr>
<td>Heikinheim²²</td>
<td>1971</td>
<td>219</td>
<td>S</td>
<td>600–2350</td>
<td>Warfarin</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>207</td>
<td>H</td>
<td></td>
<td>Warfarin</td>
<td>2</td>
</tr>
<tr>
<td>Aber²³</td>
<td>1976</td>
<td>302</td>
<td>S</td>
<td>2500</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>293</td>
<td>C</td>
<td></td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

S = streptokinase; P = plasmin/plasminogen; H = heparin; C = conventional therapy; — = placebo; (0) = not reported.

*Total dose per patient, except where indicated.
†CNS = central nervous system hemorrhage (hemorrhagic infarction/hematoma).

(0.7%). No details regarding these patients have been presented, however.

The two series reporting the highest incidence of intracerebral hemorrhage involved patients treated with intravenous streptokinase for acute and chronic pelvic and peripheral arterial thromboses. Poliwoda noted 3 fatal intracerebral hemorrhages among 120 patients in a series of 132 individuals receiving systemic streptokinase at 125 x 10^3 IU/hr for 16 hours each of three consecutive days. Heparin (30 x 10^3 IU/hr for 24 hr) and an oral anticoagulant were given. Verstraete reported a nonrandomized multicentre retrospective series collected by Hess of streptokinase treatment at a dose-rate of 100 x 10^3 IU/hr following titrated initial dose. Among patients presenting a total of 458 peripheral arterial occlusions, thrombi, or emboli, 7 fatal intracerebral hemorrhages occurred. It was noted that "this study was not planned ahead but results of the [fifteen] centres were collected, assuming that the patient’s condition, the dosage scheme, and the criteria of evaluation were similar." Unfortunately, in both studies the pertinent antecedent clinical (neurological) history of the affected patients, the degree of control of the thrombolytic agent and subsequent anticoagulation, and the precautions taken to exclude high risk patients were not provided.

**Acute Myocardial Infarction**

Intracerebral hemorrhage has been a rare complication of intracoronary artery thrombolytic therapy for...
TABLE 5 Intracranial Hemorrhage Associated with Thrombolytic Therapy for Deep Venous Thrombosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Yr</th>
<th>N</th>
<th>Agent</th>
<th>Initial (×10^3 IU)</th>
<th>Maintenance (×10^3 IU/hr−1)</th>
<th>Duration</th>
<th>Antithromb*</th>
<th>CNS†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robertson</td>
<td>1967</td>
<td>12</td>
<td>S</td>
<td>TID 50</td>
<td></td>
<td>10.5 hr</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1968</td>
<td>8</td>
<td>H</td>
<td>6.0 1.9</td>
<td></td>
<td>10.5 hr</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Kakkar</td>
<td>1969</td>
<td>10</td>
<td>S</td>
<td>500 150</td>
<td>7 d Heparin/Anticoag</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mavor</td>
<td>1969</td>
<td>9</td>
<td>S</td>
<td>TID + 750 93</td>
<td>16–52 hr</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mavor</td>
<td>1973</td>
<td>40</td>
<td>S</td>
<td>TID + 750 93</td>
<td>7–83 hr</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsapogas</td>
<td>1973</td>
<td>19</td>
<td>S</td>
<td>TID 100</td>
<td>48–72 hr Heparin</td>
<td>(0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astedt</td>
<td>1974</td>
<td>41</td>
<td>S</td>
<td>250 100</td>
<td>72 hr Heparin</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chavatzas</td>
<td>1975</td>
<td>9</td>
<td>S</td>
<td>600 100</td>
<td>48–72 hr Heparin</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duckert</td>
<td>1975</td>
<td>93</td>
<td>S</td>
<td>TID 100</td>
<td>160 hr Heparin</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1975</td>
<td>15</td>
<td>H</td>
<td>7.0 1.5</td>
<td>48 hr Anticoag (oral)</td>
<td>(0)</td>
<td></td>
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</tr>
<tr>
<td>Kakkar</td>
<td>1975</td>
<td>12</td>
<td>S + P</td>
<td>600 25</td>
<td>5 d Heparin</td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>1975</td>
<td>5</td>
<td>S</td>
<td>600 25</td>
<td>5 d Heparin</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marder</td>
<td>1977</td>
<td>12</td>
<td>S</td>
<td>100 100</td>
<td>72 hr Heparin</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1977</td>
<td>12</td>
<td>H</td>
<td>150Ukg⁻¹</td>
<td>with adjustment Coumarin</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seaman</td>
<td>1976</td>
<td>24</td>
<td>S</td>
<td>250 100</td>
<td>72 hr Heparin</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1976</td>
<td>26</td>
<td>H</td>
<td>150Ukg⁻¹</td>
<td>with adjustment Warfarin</td>
<td>0</td>
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<tr>
<td>Bieger</td>
<td>1976</td>
<td>5</td>
<td>S</td>
<td>250 100</td>
<td>72 hr Heparin</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1976</td>
<td>5</td>
<td>H</td>
<td>15.0</td>
<td>with adjustment Phenprocoumon</td>
<td>0</td>
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<tr>
<td>Arnason</td>
<td>1978</td>
<td>21</td>
<td>S</td>
<td>250 100</td>
<td>72–90 hr Heparin</td>
<td>0</td>
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<tr>
<td></td>
<td>1978</td>
<td>21</td>
<td>H</td>
<td>15.0 1.25</td>
<td>72–90 hr Warfarin</td>
<td>0</td>
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<tr>
<td>Jarvinen</td>
<td>1978</td>
<td>44</td>
<td>S</td>
<td>600 100</td>
<td>72 hr Warfarin</td>
<td>0</td>
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<tr>
<td>Marbet</td>
<td>1982</td>
<td>114</td>
<td>S + P</td>
<td>10–20</td>
<td>5.3 d Heparin</td>
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<tr>
<td>Schulman</td>
<td>1984</td>
<td>39</td>
<td>S</td>
<td>250 100</td>
<td>7 d Heparin</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1984</td>
<td>41</td>
<td>S</td>
<td>50 8.3</td>
<td>12 hr Heparin</td>
<td>0</td>
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<tr>
<td>D'Angelo</td>
<td>1984</td>
<td>10</td>
<td>U</td>
<td>2.5Ukg⁻¹ 1.5µkg⁻¹</td>
<td>2 d Heparin</td>
<td>0</td>
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<tr>
<td></td>
<td>1984</td>
<td>11</td>
<td>U</td>
<td>3.5Ukg⁻¹ 2.5µkg⁻¹</td>
<td>3 d Heparin</td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>1984</td>
<td>10</td>
<td>U</td>
<td>5.0Ukg⁻¹ 2.5µkg⁻¹</td>
<td>7 d Heparin</td>
<td>0</td>
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<tr>
<td></td>
<td>1984</td>
<td>10</td>
<td>U</td>
<td>4.0Ukg⁻¹ 4.0µkg⁻¹</td>
<td>4 d Heparin</td>
<td>0</td>
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<tr>
<td>Trubestin</td>
<td>1984</td>
<td>148</td>
<td>S</td>
<td>250 100</td>
<td>3–6 d Heparin</td>
<td>2</td>
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<tr>
<td></td>
<td>1984</td>
<td>139</td>
<td>U</td>
<td>250–600 40–100</td>
<td>6–12d Heparin</td>
<td>0</td>
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<td></td>
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<tr>
<td>Serradimiggi</td>
<td>1978</td>
<td>58</td>
<td>S</td>
<td>250 100</td>
<td>18–80 hr Heparin</td>
<td>(0)</td>
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<tr>
<td>Aldrich</td>
<td>1985</td>
<td>18</td>
<td>S</td>
<td></td>
<td></td>
<td>(0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

U = urokinase; S = streptokinase; P = plasmin/plasminogen; H = heparin; (0) = not reported; TID = titrated initial dose.

Heparin infusions were most often followed by oral anticoagulant therapy.

CNS = central nervous system hemorrhage (hemorrhagic infarction/hematoma).

acute myocardial infarction. In general, local streptokinase infusions (30–294 × 10^3 IU/60 min) have been followed by heparin anticoagulation or antiplatelet (ASA/dipyridamole) therapy. A single patient (0.4%) suffered an intracranial hemorrhage following intracoronary artery streptokinase in a series of 232 consecutive patients reported by Rusch et al. In contrast, no cerebral events occurred in combined retrospective series of 183 patients, a case controlled series of 95 patients, or among 289 patients receiving intracoronary therapy in 5 prospective double blind studies (against placebo, anticoagulation, or standard therapy). More recently, Aldrich et al have described a single deep frontal intracerebral hemorrhage in a 69 year old female, three days after intracoronary artery streptokinase infusion for an acute MI. Of note, this patient displayed gross hematuria, hematemesis, and puncture site hemorrhage for two days following the procedure.

Intravenous thrombolytic therapy for acute MI has
generally required significantly higher doses (500–2600 × 10^3 IU) of streptokinase to achieve coronary artery reperfusion. Under these conditions a systemic fibrinogenolytic state is consistently produced. Two nonfatal intracerebral hemorrhages were reported among 156 patients (1.3%) receiving 1450 × 10^3 IU streptokinase in the European Cooperative Trial. Further studies and the details regarding the clinical outcome of the two patients were not reported. In four recent (prospective) series combining the outcome of 268 patients with acute MI, no episodes of central nervous system hemorrhage or dysfunction were observed. Among prospective randomized studies, Amery et al reported no intracranial events in either the thrombolytic group (n = 83) or the heparin group (n = 84), despite a history of cerebral vascular events antedating the acute MI in 1 patient and 6 patients, respectively. Heikinheimo et al reported two non-hemorrhagic central nervous system events (not specified) each in the group receiving streptokinase (n = 219) and in the group receiving heparin (n = 207) in a randomized prospective study. Similarly, in a randomized study comparing extended infusion of streptokinase (2500 × 10^3 IU over 24 hr) with conventional therapy in 595 patients with symptoms of myocardial ischemia of less than 24 hours duration, Aber et al reported 5 thromboembolic CNS events in each group. In the absence of statistical analysis it appears that thromboembolic or other cerebrovascular events are no more frequent in the groups of unselected patients receiving thrombolytic agents systemically, than in those receiving anticoagulation or conventional therapy for acute MI.

Current experience with tissue plasminogen activator is limited. In four series (two prospective, two prospective randomized) no central nervous system events were reported among patients with acute coronary artery thrombosis receiving tissue plasminogen activator at various dose rates. Although tPA is somewhat thrombus-selective in its action, it may not be presumed that this agent is less likely to be associated with intracerebral hemorrhage (see above). In addition, the use of anticoagulants following tPA infusion may augment the risk of such hemorrhage despite the lack of post-infusional anticoagulant phase associated with tPA.

Deep Venous Thrombosis

Systemic intravenous use of streptokinase or urokinase for the treatment of acute deep venous thrombosis (DVT) has been the subject of numerous small nonrandomized and randomized studies (Table 5). Among the nonrandomized groups, no central nervous system complications were reported in studies in which fibrinogenolysis was documented. Randomized studies have compared streptokinase with heparin. Marder et al reported a lethal cerebral hemorrhage in one patient who had a history of a completed ischemic stroke antedating the use of streptokinase. In a separate series reported by Trubestein et al, two patients who received streptokinase (n = 148) for treatment of DVT suffered intracerebral hemorrhages, one of which was fatal. Unfortunately, pertinent clinical details of the two patients were not supplied. Schulman and Lockner attempted local (retrograde) intravenous streptokinase infusion in 14 patients with acute DVT, none of whom demonstrated CNS complications. Serradimigni et al reported no intracranial complications among 58 patients treated for deep venous thrombosis, pulmonary embolism, or both.

In general, although the listing is not exhaustive, CNS hemorrhagic complications were not apparently more frequent in this group of disorders than in other thrombotic conditions treated with thrombolytic agents. Although no formal prospective intracerebral hemorrhage risk assessment studies have been performed in patients receiving local or systemic thrombolytic therapy for peripheral arterial or venous thrombosis, or coronary artery thrombosis, it is clear that such hemorrhagic complications do occur in a small number of patients. Detailed information regarding the historical and clinical aspects of such patients is insufficient to provide more than impressions regarding potential risk factors.

Patients with known previous recent neurological deficits of ischemic origin, whether single or multiple, may be at increased risk for intracerebral hemorrhage. This risk may be augmented by the presence of untreated hypertension. The risk of hemorrhage in patients with multiple lacunar infarctions, or multiple thromboembolic events of different or unknown age is not known. Furthermore, the duration and severity of fibrinogenolysis, the contribution of antiplatelet agents with or without anticoagulants, and the control of anticoagulant therapy in each of these series remain unknown but important variables. Particularly in the setting of acute myocardial infarction, the incidence of microscopic or macroscopic hemorrhage accompanying cerebral thromboembolism following thrombolytic therapy remains unknown. The question of which variables may be significant contributors to hemorrhagic risk can be answered only indirectly when functional or mortality outcome is measured in uncontrolled studies. A more direct answer to this question can only come from prospective randomized placebo or standard therapy controlled trials of the use of thrombolytic agents in the early treatment of acute stroke.

Conclusions

Early studies of thrombolytic agents given systemically for the treatment of stroke were interpreted to demonstrate that such therapy was not beneficial and might produce intracerebral hemorrhage. However, significant problems with study design, diagnostic specificity, and therapeutic application compromise this interpretation. Although the incidence of intracerebral hemorrhage as a cause of stroke is not precisely known, several studies suggest that it could be at most 17–18%. A number of small uncontrolled clinical studies utilizing CT scans suggest that the inci-
dence of intracerebral hemorrhages may be less than 10% in patients with a cardiac source cerebral embolism. The risk of cerebral hemorrhagic complications accompanying the use of fibrinolytic agents (which produce evidence of fibrinolysis) in patients not selected for cerebrovascular disease is low, probably 0–2%. However, the problems of such estimates are reflected in the small size and uncontrolled nature of series reporting a higher incidence \(^\text{15, 22}\) of hemorrhage. Therefore, evaluations of the incidence of intracerebral hemorrhagic complications following thrombolytic therapy for acute stroke should be made in the context of available data concerning hemorrhagic infarctions in untreated non-anticoagulated patients suffering cerebral atherothromboembolism and of intracerebral hemorrhage following thrombolytic therapy in patients without known cerebrovascular disease.

Despite the possibility of associated hemorrhagic complications, the theoretical advantages of thrombus dissolution in acute thrombotic stroke by local infusion of thrombolytic agents and the increasing experience with the agents in myocardial infarction make this approach attractive. Furthermore, recent careful attempts with interventional neuroradiological techniques to deliver thrombolytic agents in close proximity to a documented verteobasilar or carotid territory occlusion have demonstrated success without clinical deterioration. To date, the total published reports and unpublished experience (table 2) suggest an incidence of post-perfusion hemorrhage of 13% by intraarterial delivery. None of the reported hemorrhages have resulted in functional deterioration or demise. However, if intracerebral hemorrhage occurs secondary to lysis of thrombi protecting sites of cerebral arterial injury, the risk of hemorrhage from the use of fibrinolytic agents will remain unknown in a given patient. This unknown risk may presumably be reduced by early infusion of the thrombolytic agent and short-term infusions, directed at the occluding thrombus.

The need for careful patient selection and early intervention presently limit the widespread use of the local intraarterial approach. Selection criteria for experimental thrombolytic therapy in stroke patients require CT scan exclusion of hemorrhage and angiographic demonstration of arterial occlusion in the vascular territory corresponding to symptoms in patients presenting in less than 6 hours from symptom onset. Current protocols employ short term (1–2 hour) infusions of urokinase or streptokinase (100–250 × 10^4 IU) delivered by selective catheter in the immediate arterial supply of the thrombotic occlusion. Territorial infusion of thrombolytic agents may not in fact represent local delivery of drug because of the special anatomic considerations of the cerebral vasculature, e.g., proximal internal carotid infusions for M1 segment MCA occlusions. In these circumstances, interventional neuroradiological techniques using double lumen balloon or controlled leak balloon catheter systems (carotid territory) and guide wire directed catheters (vertebrobasilar territory) may be useful to deliver the agent locally proximal to the thrombus. The precise techniques are in evolution as more versatile catheter systems become available.

Because larger dose rates of streptokinase by intravenous infusion achieve a lower recanalization rate than local infusion in coronary artery thrombosis, \(^\text{1–22}\) it is unlikely that intravenous infusion of this agent will be used in cases of acute cerebrovascular thrombosis. However, with the advent of fibrin-specific thrombolytic agents such as tPA and scuPA, intravenous application of these agents may have certain advantages. The specific dose-rates and success of such an approach cannot be determined until careful systematic controlled studies with angiographic endpoints are undertaken.

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Thrombolytic therapy in stroke: possibilities and hazards.
G J Del Zoppo, H Zeumer and L A Harker

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