Front-Loaded Accelerated Infusions of Tissue Plasminogen Activator: Putting a Better Foot Forward

DOUGLAS F. VAUGHAN, MD, FACC, EUGENE BRAUNWALD, MD, FACC
Boston, Massachusetts

Background. Two years ago in this Journal, Neuhaus et al. (1) first reported on the enhanced clinical efficacy of a "front-loaded," accelerated regimen of recombinant tissue-type plasminogen activator (rt-PA) in the treatment of patients with acute myocardial infarction. This regimen differs from the standard regimen of rt-PA in several aspects, as summarized in Table 1. In terms of clinical efficacy, defined as angiographic patency at 90 min, the accelerated regimen offers nearly a 20% improvement over the standard regimen (2). In the earlier report of Neuhaus et al. (1) and in the rt-PA-APSAC (anisoylated plasminogen activator complex) Patency Study (TAPS) trial reported in this issue (3), the accelerated regimen provided 90 min patency rates >80%, a value that would probably approximate the optimal expected rate of thrombolysis, given that thrombi are identified in 80% to 97% of patients with acute myocardial infarction (4). It is appropriate that the dosage, rate and profile of rt-PA dosing schedules and clinical experience, rather than prospectively designed trials, has contributed importantly to the development of the standard 3-h rt-PA regimen (5,6). In fact, the currently recommended dosing schedule (9) indicating that the hepatic rt-PA clearance mechanism or mechanisms have the capacity to deal with the elevated plasma levels that accompany the front-loaded regimen. Despite the increased plasma levels of rt-PA produced by the front-loaded regimen, the systemic effects of the enzyme, as measured by decrements in circulating levels of fibrinogen, plasminogen and alpha 2-antiplasmin, are similar to those obtained with the standard dosage regimen (14). This finding confirms that rt-PA is a fibrin-specific agent and a relatively inefficient activator of circulating plasminogen (17).

Implications. The present study (8), together with the earlier article (1) describing the improved efficacy of a front-loaded accelerated regimen of rt-PA, indicates that the pharmacokinetic properties of rt-PA can be expected to yield an agent with nearly optimal thrombolytic properties for both the achievement of maximal early patency rates and limited systemic plasminogen activation and fibrinogen breakdown. One can reasonably argue that the front-loaded accelerated regimen should supplant the standard regimen in patients who are designated to receive rt-PA. However, it remains to be seen if the accelerated regimen, which appears to exploit some of the most desirable properties of rt-PA on a theoretic basis (18), will have any additional impact on survival. The ongoing GUSTO and Thrombolysis in Myocardial Infarction (TIMI-4) trials, which are designed to...
Table 1. rt-PA Dose Regimens for Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Total Dose (mg)</th>
<th>Bolus Dose (mg)</th>
<th>Infusion Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>100</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Front-loaded, accelerated</td>
<td>100</td>
<td>15</td>
<td>1.5</td>
</tr>
</tbody>
</table>

- rt-PA = recombinant tissue plasminogen activator.

Thrombolytic therapy of acute myocardial infarction has now been under intensive investigation for a decade. Its immediate goal is to reestablish patency of the infarct-related artery as rapidly as possible and to maintain its patency without causing serious bleeding. Although the effectiveness of this mode of therapy in reducing mortality has been well demonstrated (19), there is no consensus regarding the optimal thrombolytic regimen. There is evidence that n-PA is a thrombolytic agent, much less the optimal dose or the established (19), there is no consensus regarding the optimal approach to this mode of therapy in reducing mortality has been well demonstrated (19), there is no consensus regarding the optimal thrombolytic regimen.

The future. An important goal in improving the care of patients with acute myocardial infarction during the next decade will be to optimize thrombolytic therapy. It is possible that a “one-two punch” consisting of a front-loaded accelerated regimen of rt-PA, such as that developed by Neuhans et al. (1) and studied by Tanswell et al. (8), followed by the infusion or injection of a more slowly acting, nonfibrott-specific agent to help sustain patency, is being tested in TIMI-4 with antistreptase and in GUSTO with streptokinase, will prove to be advantageous. The incidence of serious bleeding, the principal risk of thrombolytic therapy, appears to be dose dependent, at least insofar as rt-PA is concerned (3,6) and is related, albeit in a complex fashion, to baseline risk factors such as age, hypertension, gender and perhaps body size. The potential benefit of thrombolytic therapy varies even more widely than the risk and is a complex function of baseline left ventricular function, the size and location of the jeopardized myocardium and the time interval between the onset of symptoms and treatment.

Thrombolytic therapy will probably not be identical for all patients but will require a judicious balance between risk and benefit. Thus, the optimal dose of one or more thrombolytic agents is likely to be lower in a small (40 kg) 80-year-old woman with borderline hypertension and evidence of a modest-size inferior-wall infarct who is seen 4 h after the onset of chest pain (relatively high risk/low potential benefit) than in a younger (45 year old), 100-kg man without a history of hypertension who is seen 1 h after the onset of a large anterior wall infarct (relatively low risk/high potential benefit).

When the dust settles, there will probably not be a single standard thrombolytic regimen (such as 100 mg of rt-PA for 3 h, 1.5 mg of streptokinase for 1 h or a 30-mg bolus of anistreplase) for all patients with evolving myocardial infarction but rather a regimen that is tailored to the individual patient. Therefore, detailed pharmacokinetic studies, such as those presented by Tanswell et al. (8), may contribute importantly to optimizing thrombolytic therapy.

References


