The Urokinase-Streptokinase Pulmonary Embolism Trial (Phase II) Results

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In 1967 the National Heart and Lung Institute organized a multi-institutional controlled clinical trial to evaluate thrombolytic agents in the treatment of pulmonary embolism. The results of the first phase of that study (The Urokinase Pulmonary Embolism Trial) showed that 12 hours of urokinase compared to heparin and oral anticoagulants alone increased the resolution rate of pulmonary thromboemboli, especially massive emboli, as judged by arteriography, hemodynamics, and lung scanning, assessed within 24 hours of therapy. Serial lung scanning revealed that these differences in embolus resolution rates decreased when assessed at 14 days. A second phase (The Urokinase-Streptokinase Pulmonary Embolism Trial), recently completed and reported in more detail in the Journal of the American Medical Association, compares 12 hours of urokinase to 24 hours of urokinase and to 24 hours of streptokinase.

One hundred sixty-seven patients who satisfied the clinical criteria for embolism within five days of treatment and the specific angiographic criteria applied by an expert panel were randomized into the three treatment groups. One hundred seven of the patients had massive pulmonary embolism (significant filling defects or obstruction of at least two lobar arteries); twelve of these patients were clinically in shock. Sixty patients had submassive pulmonary embolism, as previously defined. The three treatment groups were found to be relatively well balanced on analysis of various clinical criteria. The end points of the study were changes in angiographic severity, lung scan perfusion defect, and hemodynamic variables between preinfusion and 24 hours after infusion was begun.

The changes in angiograms were nearly equivalent in the three groups (see table 1). The mean 24 hour change in hemodynamic variables showed no consistent differences favoring one therapy over another. Patients treated with 24 hours of streptokinase showed less improvement in pulmonary artery pressures, but a greater improvement in cardiac index than the two urokinase groups. The total pulmonary resistance changes after therapy, which take into account both pressures and flow, were not different among the three groups. The degree of resolution of lung scans favored 24 hours of urokinase compared with 24 hours of streptokinase, and this approached statistical significance. Twelve hours of urokinase was intermediate and not significantly different from either group. Lung scans performed at three and six months showed no differences.

In the massive embolism group, the differences in response favored both 12 and 24 hours of urokinase over streptokinase in lung scan and hemodynamics. In lung scans, the difference between 24 hours of urokinase and streptokinase was statistically significant. The hemodynamic changes, however, were inconsistent. Urokinase was superior in lowering pulmonary artery pressure; this was statistically significant for the comparison of 24 hours of urokinase with streptokinase. The improvement in cardiac index favored streptokinase. Total pulmonary resistance showed no significant differences among the groups.

Hemorrhagic complications were encountered with nearly equal frequency in the three treatment groups. Most of the bleeding was at incision sites for angiocatheter insertion. There was an increased incidence of mild temperature elevations as well as three allergic reactions (none fatal) in the streptokinase group.

In the two week post treatment period, 7% of the 12 hour urokinase group, 9% of the 24 hour urokinase group, and 9% of the 24 hour streptokinase group died. The total six month mortality was 10%, 15% and 15%, respectively. None of these differences was statistically significant.

It is noteworthy that in this second phase, which used a similar protocol to the first phase, the 12 hour urokinase treatment group had a nearly equivalent result to that in Phase I with the three end points; therefore, we feel that it is reasonable to conclude that all three of the Phase II dosage regimens are probably superior to heparin alone in accelerating the rate of resolution of acute pulmonary emboli.

The data in Phase II indicate that 24 hours of urokinase gives a small but insignificant added benefit compared to 12 hours of urokinase. The distinction between 24 hours of streptokinase and 24 hours of urokinase is less clear. The major significant difference is in lung scan perfusion defects, especially in the

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1070 Circulation, Volume 50, December 1974
Table 1
Change in Values from Preinfusion to 24 Hours After Therapy Begun*

<table>
<thead>
<tr>
<th></th>
<th>Massive and submassive embolism</th>
<th>Massive embolism only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 UK</td>
<td>24 UK</td>
</tr>
<tr>
<td>Number of patients</td>
<td>59</td>
<td>54</td>
</tr>
<tr>
<td>Angiograms - based on 4 pt extent of embolism</td>
<td>1.66</td>
<td>1.76</td>
</tr>
<tr>
<td>Lung scans - decrease in percent change in perfusion defect</td>
<td>8.98</td>
<td>11.61</td>
</tr>
<tr>
<td>Lung scans - decrease in percent change in perfusion defect</td>
<td>20.0</td>
<td>29.2</td>
</tr>
<tr>
<td>Pulmonary artery pressure (mm Hg)</td>
<td>-7.28</td>
<td>-7.53</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>+0.06</td>
<td>+0.30</td>
</tr>
<tr>
<td>Lung Total pulmonary resistance (dyne-sec-cm⁻²)</td>
<td>-0.33</td>
<td>-0.44</td>
</tr>
</tbody>
</table>

*All results are adjusted for levels of initial severity except for the lung scan decrease in severity based on percent change in perfusion defect.

massive emboli group where statistical significance is attained. The hemodynamic changes are inconsistent. In those patients in whom both pulmonary artery pressure and cardiac index were measured, there were no significant differences. Twenty-four hours of urokinase may be superior to 24 hours of streptokinase, but any difference appears small.

Throughout Phase I and Phase II, standardized dosage schedules of both urokinase and streptokinase were used. Although laboratory studies indicated successful activation of the endogenous plasminogen-fibrinolytic system in nearly 100% of the patients, different dosage schedules may produce different therapeutic results.

Contraindications to thrombolytic agents were observed as were restrictions on patients with recent streptococcal infections. Under these circumstances, the allergic, pyrogenic, and bleeding complications were controllable. About a third of the bleeding episodes occurred after the termination of the thrombolytic infusion but during therapy with standard anticoagulants.

Analysis of these trials shows no reduction in mortality with the use of thrombolytic agents. A trial designed with mortality as the main end point would require a prohibitively large patient sample. However, a major physiologic benefit, especially in patients with massive embolism, was observed. These agents have potential, therefore, in the severely ill patients with massive embolism and in patients with massive or submassive embolism who also have diminished cardiac reserve. When standard anticoagulation has been chosen as the initial treatment in a patient with pulmonary embolism, thrombolytic therapy should be considered if the clinical response is unsatisfactory. Both urokinase and streptokinase have promise as useful alternatives to heparin and oral anticoagulants and the hazardous procedure of embolectomy.

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Circulation. 1974;50:1070-1071
doi: 10.1161/01.CIR.50.6.1070

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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http://circ.ahajournals.org/content/50/6/1070.citation

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