FEASIBILITY OF UROKINASE IN THE TREATMENT OF ACUTE MYOCARDIAL INFARCTION

ETSU HASHIDA, FUYUO MAEKAWA, YASUO MORI, KUNIO RIN,* AND TSUNEMICHI YAMADA**

Urokinase was administered daily to 15 patients with acute myocardial infarction in an early stage of this disease and found effective. Evaluation of the efficacy was made in terms of the modification by urokinase of serum enzyme changes as well as electrocardiographic changes which take a definite serial course in this disease. More rapid normalization of elevated ST segments and raised serum enzyme levels was attained than generally accepted. The two cases where death resulted were of complete atrioventricular block and congestive heart failure. The dosage and mode of administration have not yet been established for the fibrinolytic therapy of acute myocardial infarction with urokinase. In the form of drip-infusion a daily dose of 10,000 to 20,000 Ploug units of urokinase was administered for 3 to 14 days and was considered effective without any untoward side-effects.

Several attempts have been made previously to treat with thrombolytic agents patients with early acute myocardial infarction whose major etiologic factor is coronary artery thrombosis. Plasmin preparations such as plasmin alone and urokinase (UK)-or streptokinase (SK)-activated plasmin are not suitable for the lysis of thrombus because of the neutralization of plasmin by antiplasmin. Some reports on SK have described its efficacy, whereas it is pyrogenic, antigenic, and in addition, owing to previous manifest or latent streptococcal infection, the antibody titer increases with age. Accordingly, SK administered is partially or almost completely neutralized by the antibody, so that its dosage has to be decided depending upon the requirements of each subject. Furthermore, once SK is administered, anti-SK is produced, and it takes 3 to 6 months for anti-SK potency thus formed to reduce to the pre-administration level. When relapse takes place within several weeks following the first heart attack treated by the administration of SK, SK betrays the fault that it can never be administered repeatedly. Contrary to this, UK being a substance present in the normal human urine, though its origin even presently unknown, UK is neither antigenic nor pyrogenic, and in consequence its repeated administration in large doses is possible. It has come to be prescribed widely in the treatment of thrombosis of peripheral vessels and pulmonary artery but only in a few cases of acute myocardial infarction UK has been administered. The reasons why UK are not widely utilized in the treatment of acute myocardial infarction are probably that in a few cases acute myocardial infarction is caused by narrowing of the coronary arteries due to subintimal hemorrhage, particularly in the senile patients severe degree of mere atherosclerosis results in infarction of the coronary arteries without implication of thrombus, standard dosage and method of administration remain unsettled, conceivable side-effects of hemorrhage and so forth could be expected, difficulty in obtaining matched paris for double blind study of this drug could not be overcome because of

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the versatile nature of this disease, and lastly the major problem of the treatment has been directed recently toward the control and/or alleviation of chest pain, shock, congestive heart failure and, especially, various arrhythmias which have come to be treated satisfactorily due to recent rapid progress of CCU, and so on.

UK is a plasminogen activator, permeates into blood clots when given intravenously, and converts plasminogen abundantly present in the clot into plasmin. Plasmin is a proteolytic enzyme, digests fibrin and dissolves thrombus rich in fibrin, and thus produces thrombolysis. Since only a small quantity of antiplasmin is present in thrombus, plasmin produced by the administration of UK is able to dissolve it without undergoing neutralization by antiplasmin present in the circulating blood.

**Materials and Methods**

As shown in Table 1, the materials were 13 cases of in-patients at Health Insurance Hospital of Shiga and 2 at Mikami-kai-Yasu Hospital. Of these, however, Nos. 7 and 8, 9 and 10, and 11 and 12 were the same patients, respectively, with relapse and there were 12 patients in substance. The table indicates the site of infarction and mortality. UK was drip-infused intravenously in 5% glucose solution or normal saline in a dose of 10,000 to 20,000 Ploug units per day. Table I summarizes time interval from the onset of infarction (i.e., occurrences of the persisting chest pain and characteristic changes in the electrocardiogram) to the administration of UK, daily doses and number of days administered. Hemorrhage as a side-effect has not been observed since both daily and total doses were by far less than those in Europe and North America. Evaluation of effectiveness was made in regard to the serial changes of the electrocardiogram and serum enzymes. Since the present study was not double blind one, observation was made for modification by UK of the serial changes of serum enzymes as well as electrocardiogram which are admitted to take a definite serial change in the course of this disease. The serial changes of the electrocardiogram have generally been accepted as follows: i.e., it was the understanding in the late 1940s and early 1950s that ST segments elevated within a few hours immediately after the onset of the infarction followed by the appearance of abnormal Q waves within 24 hours, that gradual reduction of the ST segment elevation ensued with inversion of the terminal part of the T waves, and that finally ST segments returned to the base line to form coronary T waves. Recently, however, the electrocardiogram is known to undergo such a definite serial change in the course of time as described above, whereas mention seems to be made not so much as before with concrete figures concerning days after infarction. Likewise, serum enzymes have been found to exhibit a definite serial change in activity in the course of time. Therefore, daily measurements of GOT, GPT, LDH and CPK were performed to observe the serial changes in addition to those of the electrocardiogram. Therefore the efficacy of UK was assessed with the following parameters: shortening of the number of days required for the regression of raised ST segments, formation of coronary T waves and normalization of infarction curve characteristic of QRS complexes, and that required for the raised serum enzyme levels to return to the normal. Not heparin was combined but dicumarol derivatives were administered simultaneously with the onset of the infarction in certain cases and, in general, the day or two days before termination of continuous UK infusion anticoagulant therapy was initiated.

**Results**

Of the 15 cases studied, complication of complete atrioventricular block and congestive heart failure resulted in death in 2 cases at 6 (No. 14) and 3 (No. 15) days after the onset of attack. No artificial pacing was conducted. In the other cases, none of severe arrhythmias, congestive heart failure and pulmonary edema were observed though slight shock accompanied in some cases. The other 13 cases improved and were discharged in the states of Class I or II according to the functional classification of heart disease recommended by the New York Heart Association. Number of days required for raised ST segments to return to the base line and for serum enzymes, GOT and LDH, to normalize are shown in Table I. In general ST segments elevated slightly in almost all the cases and returned to the base line in 3 to 4 days after the onset in the majority of cases as seen in this table. Days required for the normalization of GOT and LDH were shorter and the results as follows:

- **GOT**: 2 to 3 days compared with 4 to 5 days
- **LDH**: about 7 days compared with 10 to 14 days

With regard to QRS complexes, R waves which

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<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr) &amp; sex</th>
<th>Site of infarct</th>
<th>Mortality</th>
<th>Time interval from the onset of acute myocardial infarction (hours)</th>
<th>Dosage of Urokinase (x 1,000u)</th>
<th>No. of days treated with UK</th>
<th>No. of days required for the normalization of the parameters used</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Initial dose</td>
<td>For first 4 days</td>
<td>Total dose</td>
<td></td>
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<tr>
<td>1</td>
<td>71 M</td>
<td>Anterior</td>
<td>Survived</td>
<td>13</td>
<td>20</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
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<td>Inferior</td>
<td>Survived</td>
<td>15</td>
<td>10</td>
<td>40</td>
<td>170</td>
</tr>
<tr>
<td>3</td>
<td>58 M</td>
<td>Antero septal</td>
<td>Survived</td>
<td>5</td>
<td>10</td>
<td>40</td>
<td>200</td>
</tr>
<tr>
<td>4</td>
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<td>Inferior</td>
<td>Survived</td>
<td>25</td>
<td>10</td>
<td>40</td>
<td>130</td>
</tr>
<tr>
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<td>Anterior</td>
<td>Survived</td>
<td>22</td>
<td>20</td>
<td>80</td>
<td>200</td>
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<tr>
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<td>Survived</td>
<td>10</td>
<td>10</td>
<td>40</td>
<td>120</td>
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<tr>
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<td>Survived</td>
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<td>10</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
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<td>Survived</td>
<td>24</td>
<td>10</td>
<td>40</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>55 M</td>
<td>Inferior &amp; Antero septal</td>
<td>Survived</td>
<td>24</td>
<td>20</td>
<td>80</td>
<td>140</td>
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<tr>
<td>10</td>
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<td>Inferior &amp; Antero septal</td>
<td>Survived</td>
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<td>20</td>
<td>80</td>
<td>160</td>
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<tr>
<td>11</td>
<td>51 M</td>
<td>Anterior</td>
<td>Survived</td>
<td>30</td>
<td>10</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td>51 M</td>
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<td>Survived</td>
<td>2</td>
<td>20</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
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<td>13</td>
<td>20</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>14</td>
<td>73 M</td>
<td>Inferior</td>
<td>Died</td>
<td>48</td>
<td>10</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>15</td>
<td>59 M</td>
<td>Inferior &amp; Lateral</td>
<td>Died</td>
<td>18</td>
<td>10</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

* No abnormal values were found or persistent elevation was present probably due to anticoagulants.
Case No. 8 is the recurrence of No. 7. Likewise case Nos. 9 and 10, and case Nos. 11 and 12 are examples of recurrence respectively.
were once lost appeared again in some cases.

**Discussion and Conclusion**

It is reasonable and effectiveness can be expected from it to attempt at as early as possible administration of thrombolytic agents after the onset of acute myocardial infarction insofar as its major etiologic cause is coronary artery thrombosis. To the 15 patients with acute myocardial infarction, UK was administered in an early stage (average 18 hours) after the onset and effectiveness of this agent was elucidated in terms of modification of serial changes of the serum enzyme levels as well as those of the electrocardiogram which are understood to exhibit a definite serial change in the course of time. In the recent report by Litman et al. where UK was administered to 17 patients with acute myocardial infarction, treatment was initiated within 14 hours of the onset of precordial pain by means of a continuous infusion pump at a priming dose of 1,650 CTA units/lb of body weight over 10 minutes, followed by a sustaining infusion of 1,650 CTA units/lb of body weight/hour for 8 hours. Although this dose is by far larger than our daily dose of 10,000 to 20,000 Ploug units, the administration is limited within the first 8 hours. Contrary to this, the mode of administration employed by us was drip-infusion with the above-mentioned dose over 2 to 3 hours daily for 3 to 14 days. Although differences in the mode of administration and dosage of this drug do not allow direct comparison between the two, both have revealed the effectiveness and safety of UK. As shown in Table I our total doses were much the same in some cases as those given by Litman et al. It remains undecided which is better, one shot of a large dose or the authors', i.e., the total dose being divided into about 10 infusions and given daily. In the report of Lippschutz et al. where double blind study was carried out with UK-activated plasmin, no difference was found as compared with the control group. This might be due to the inactivation of plasmin by antiplasmin. Efficacy of SK was clarified and no objection will be raised. However, problems have yet to be settled concerning the kind, dosage and method of administration of thrombolytic agents to be employed. That UK is superior to SK and plasmin alone or SK- and UK-activated plasmin is not preferable was pointed out by Friedberg. With regard to the time interval after the onset of acute myocardial infarction to the initiation of the thrombolytic therapy, there is no definite criterion except that Cliffton suggested administration within 6 hours after the onset. The treatment has to be done as early as possible and is of no value, as a matter of course, after the thrombus has been covered up with endothelial cells and subsequently organized. Only one conceivable side-effect with UK is hemorrhage and it matters little even with such a large dose as utilized by Litman et al. The thrombolytic effect rapidly disappears after discontinuation of UK and thus it could be administered without any side-effect. Feasibility of UK treatment was discussed on the basis of our experiences in the treatment of acute myocardial infarction with UK with reference to the reports so far presented in which thrombolytic agents including UK were utilized.

**References**

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