The Role of Recombinant Human Tissue-Type Plasminogen Activator in the Treatment of Acute Pulmonary Thromboembolism

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The effect of intravenous recombinant human tissue-type plasminogen activator (tPA) on arterial blood gases was compared with the effect of heparin treatment in acute pulmonary thromboembolism. Fifteen patients received heparin alone (group A), 5 cases were treated with \(7.7 \times 10^6\) I.U. of tPA (group B) and 10 cases with \(15 \times 10^6\) I.U. of tPA (group C) combined with heparin treatment. Arterial oxygen tension before treatment was not significantly different among the three groups. PaO\(_2\) was dramatically improved on the 1st day in group C. By the 7th day, PaO\(_2\) of group B had improved to the level of group C. However, the PaO\(_2\) of group A on the 7th day was not significantly different compared to the pre-treatment value. In group C, post-treatment perfusion lung scintigrams were improved compared to the pre-treatment images, but this was not the case in group B. Treatment with tPA is more effective for acute pulmonary thromboembolism than heparin alone and a high dose of tPA (\(15 \times 10^6\) I.U.) leads to rapid improvement in arterial blood gases and lung perfusion images.

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**Introduction**

The number of patients with acute pulmonary thromboembolism (acute PTE) has recently been increasing in Japan (1). Heparin and urokinase have been used for the treatment of acute PTE (2). However, serious bleeding complications and fibrinogenolysis have been reported with the use of urokinase (2, 3). Recently, a newer means of thrombolytic therapy with recombinant human tissue-type plasminogen activator (tPA), which is a relatively clot-specific fibrinolytic agent, has been introduced in Japan. It is expected to be useful not only for the treatment of acute myocardial infarction (4) but also for that of acute PTE. We report here our experiences with peripheral intravenous infusion of tPA (TD-2061, Dai-ichi Pharmaceutical Co., Tokyo) in patients with acute PTE. TD-2061 is one of the recombinant human tissue-type plasminogen activators, synthesized employing recent DNA technology. Urokinase has only one kringle but tPA carries two kringles in its molecules. It is thought that the second kringle of tPA can combine with fibrin.

We undertook a study to investigate, first, whether tPA improves arterial oxygen tension (PaO\(_2\)) and perfusion lung scintigrams, whether improvement depends on the dose of tPA, and finally, whether tPA can be administered without serious fibrinogenolysis in peripheral blood.

**Methods**

The study subjects consisted of 30 patients who were within five days of the onset of symptoms or signs of acute PTE. We established the diagnoses of acute PTE on the basis of clinical signs, blood gas measurements, electrocardiographic findings, chest X ray findings, ultrasound cardiographic findings and perfusion lung scintigrams. Up to the autumn of 1986 we used heparin alone and then we were allowed to add tPA to our treatment for acute PTE. Fifteen cases (group A) were treated with heparin alone. These fifteen cases were patients during the period from spring of 1981 until autumn of
Immediately after patients were diagnosed as acute PTE, five thousand units of heparin were injected intravenously and then continuous intravenous heparin injection was started. The dosage of heparin was set for an activated partial thromboplastin time (APTT) about twice as long as the control value, and required from 12,000 units to 24,000 units of heparin in 24 hours. Five cases (group B) were treated with $7.7 \times 10^6$ I.U. of tPA and heparin, and the other 10 cases (group C) were treated with $15.0 \times 10^6$ I.U. of tPA and heparin. Heparin infusion was also combined both in group B and in group C and APTT was set twice as long as the control value. The dosage and method were similar to group A. Pulmonary angiography was performed before treatment in 4 cases of group A, in 3 cases of group B and in 6 cases of group C. One case in group B and 2 cases in group C had lobar artery embolization. The other 10 cases had segmental artery embolization. TD-2061 was dissolved in 100 ml of saline and was infused continuously over one hour in the initial three consecutive days. One case in group C had only one day of tPA treatment because of tPA-induced hypofibrinogenemia. Informed consent for the tPA administration was obtained from the subjects and/or their families. The exclusion criteria for tPA administration were: 1) major internal bleeding, 2) surgery within the previous five days, 3) severe impairment of hepatic or renal function, 4) hypofibrinogenemia, 5) intracranial bleeding within the previous three months, 6) past history of allergic reaction to vaccination, and 7) pregnancy or lactation.

After measurement of arterial blood gases collected while breathing room air, perfusion lung scintigraphy and blood samplings for plasma fibrinogen and serum fibrin and fibrinogen degradation products (FDP), therapy for acute PTE was initiated immediately after establishing the diagnosis. Supplemental oxygen therapy was initiated if necessary. Blood gases were measured on days 1, 3 and 7 after the initiation of treatment under room air breathing. Heparin had been infused intravenously for the observation period. Perfusion lung scintigrams were repeated on day 7 in group B and in group C. Plasma fibrinogen and serum FDP were measured in group C one hour after tPA administration and on day 1.

We calculated alveolar-arterial oxygen tension difference (AaDO$_2$), assuming a gas exchange ratio of 0.83, using the alveolar equation.

Pre- and post-treatment perfusion lung scintigrams were evaluated with regard to impaired perfusion lung area. We adopted a segmental method (5). Six pictures were obtained from each patient before and after treatment. Specifically, scintigrams were taken in one anterior projection, one posterior projection, two lateral projections and two oblique projections. We scored the images according to the number of segments with impaired perfusion and the degree of impairment. The scoring points were as follows: marked perfusion defect, 3 points; moderate defect, 2 points; slight defect, 1 point; and no defect, 0 point.

The data were entered into an NEC PC-9801VX and were analyzed with the Students' t-test. Values of $p < 0.05$ were accepted as statistically significant.

**Results**

**Changes in PaO$_2$ and AaDO$_2$**

Blood gas measurements were performed repeatedly in all thirty cases (Fig. 1). PaO$_2$ values obtained before treatment were not statistically different among the three groups. PaO$_2$ of group A did not improve during
The Role of tPA in Acute PTE

the 7-day observation period. In group B PaO₂ did not change on day 1, but a significant improvement in PaO₂ was observable by day 7. The most rapid improvement in PaO₂ was observed in group C. In this group, PaO₂ increased significantly on day 1, and improvement continued over the course of the observation period. PaO₂ values on days 3 and 7 in group C were significantly higher than those of group A.

As with PaO₂, AaDO₂ before treatment was not statistically different among the three groups (Fig. 2). It did not change during the observation period in group A. However, it did improve by day 7 in group B and by day 3 in group C.

![Fig. 5. Serum fibrin and fibrinogen degradation products (FDP) levels before and after tissue-type plasminogen activator (tPA) treatment in group C.](image)

FDP increased to more than 10,000 ng/ml in 2 cases one hour after the treatment. FDP levels were higher on Day 1 than the values before treatment.

**Perfusion lung scintigraphic scores**

Both pre- and post-treatment perfusion lung scintigrams were obtained in all 5 cases in group B and in 5 cases in group C (Fig. 3). One case in group B had a worse scintigraphic score after treatment, but the scores of the other 9 cases showed moderate to marked improvement. One case in group C had a normal scintigram after treatment. The scintigraphic scores of pre-treatment images were not significantly different between groups B and C. Pre- and post-treatment scintigraphic scores in group B were essentially the same, but in group C significant improvement was observed after treatment.

**Plasma fibrinogen and serum FDP**

Plasma fibrinogen levels were measured in nine cases in group C (Fig. 4). All nine had a normal plasma fibrinogen level (more than 200 mg/dl) before tPA administration. One hour after tPA administration, plasma fibrinogen levels were measured in five cases. One case showed a critically low fibrinogen level (87 mg/dl), but the other 4 cases had normal levels and 3 actually had higher levels than before treatment. Eight cases had normal fibrinogen levels on day 1 and one case, whose fibrinogen level was very low in 1 hour after treatment, remained below the normal range.

Serum FDP was measured in 8 cases before tPA treatment (Fig. 5). Two cases had a normal level (less than 100 ng/ml). In 4 cases FDP was measured 1 hour after tPA administration. FDP increased up to more than 1,000 ng/ml in two cases, and more than 10,000 ng/ml in two other cases. In all eight cases, FDP levels were
higher on day 1 than before treatment.

Discussion

Since Bounameaux et al (6) reported successful results of tPA treatment in a patient with acute massive PTE, several reports on intravenous administration of tPA in the treatment of acute PTE have appeared. Goldhaber et al (7) used 50 mg of tPA in 36 patients with angiographically documented acute PTE. After 6 hours, 34 of the 36 patients had angiographic evidence of clot lysis. Plasma fibrinogen concentration decreased by 30% from baseline at 2 hours and 38% from baseline at 6 hours. Further, Goldhaber et al (8) compared the effects of tPA and urokinase in 45 patients with acute PTE. After 2 hours, 82% of tPA-treated patients showed clot lysis, compared with 48% of urokinase-treated patients. Verstraete et al (9) reported that intrapulmonary infusion of tPA does not offer a significant benefit over the intravenous route and that a prolonged infusion of tPA (100 mg) over a 7-hour period is superior to a single infusion of 50 mg over 2 hours. These studies strongly support that tPA is very effective in the treatment of acute PTE. We used 7.7 x 10^6 I.U. or 15.0 x 10^6 I.U. of tPA, as 1 mg of tPA was 600 x 10^3 I.U., our dose was half that of used in previous studies.

To our knowledge changes in blood gases after tPA treatment have not yet been reported. We repeatedly analyzed arterial PaO2 in the recumbent position while the patients were breathing room air. We observed that tPA produced rapid improvements in PaO2. Patients treated with 15.0 x 10^6 I.U. of tPA showed significant improvement on day 1 as compared to pre-treatment values. This improvement might have been caused by clot lysis, which occurred within 24 hours. This possibility was supported by changes in FDP and fibrinogen. Serum FDP levels were 10 to 100 times greater than baseline levels one hour after tPA treatment, but plasma fibrinogen levels remained unchanged or only slightly higher than baseline levels. FDP is composed of material degraded from both fibrin and fibrinogen. If tPA degrades plasma fibrinogen, plasma fibrinogen levels would be expected to decrease and FDP levels would be expected to increase. In the present study, while plasma fibrinogen levels did not change, FDP levels did increase. Therefore it might be reasonable to state that tPA degrades fibrin clots which occlude pulmonary arteries.

Improvement of AaDO2 followed improvement of arterial oxygen tension in group C. Increased AaDO2 is caused by an intrapulmonary shunt, uneven distribution of the ventilation-perfusion ratio (VA/Q) and/or diffusion impairment. VA/Q distributions obtained by the multiple inert gas elimination technique revealed the existence of small amounts of shunt and low VA/Q areas in patients with acute PTE (10, 11). These abnormalities might be caused not only by the clot itself but also by vasoospasm in the vicinity of the embolized area. Platelets in clots release vasoactive materials, such as prostaglandins, platelet activating factors, serotonin, bradykinin, etc. These substances induce vessel constriction in and around embolic sites. As clot lysis proceeds, the degree of vasoconstriction decreases and the uneven distribution of VA/Q improves.

Arterial oxygen tension and perfusion lung scintigrams improved rapidly in group C. These findings suggest that high dose therapy of tPA is suitable for the treatment of acute PTE.

We did not observe fibrinogenolysis in peripheral blood either one hour or one day after tPA treatment in group C except in one subject. Goldhaber et al (8) reported that 50 mg of tPA causes a 30% decrease in fibrinogen at 2 hours and a 38% decrease at 6 hours compared with the baseline level. The difference between our data and theirs might be due to the difference in the tPA dose; the dose used in the present study was half of theirs. This difference aside, our data suggest that tPA exerts an action preferentially on fibrin in clots rather than on fibrinogen in peripheral blood. The administration of 15.0 x 10^6 I.U. of tPA can be recommended for patients with acute PTE. This agent can rapidly, and for the most part safely, lyse clots in pulmonary arteries.

References


888