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UROKINASE THERAPY IN THE EARLY STAGE OF ACUTE MYOCARDIAL INFARCTION*)

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ABSTRACT

Urokinase therapy in the treatment of myocardial infarction has been clinically tested with the intent of using its thrombolytic properties to dissolive the embolism and thus prevent any necrotizing effects on the heart muscle. Howeve, during these clinical trials both proper dosage and application method have remained controversial, especially since the therapeutic results have fallen short of expectations. Another point that must be kept in mind is the time factor. If urokinase therapy is not initiated within 5 to 6 hours after the heart attack, since the heart muscle will begin to necrotize, therapy after that point becomes meaningless. A final vital point to keep in mind during urokinase thrapy is medication selection. Urokinase comes in two forms: high molecular (molecular weight 54, 000) and low molecular types. If we exclude manufacturers of other protein-containing medications from consideration, in Japan there are only two urokinase manufacturers, namely, Kowa Shinyayu Co. Ltd. and Fujisawa Yukuhin Co. Ltd. More than 75% of the urokinase produced by Kowa Shinyaku is of the high molecular type. When the effectiveness of urokinase therapy becomes a matter of debate, this particular drug displays its therapeutic effectiveness quite convincingly. In our report, we also tested the product of Fujisawa Yakuhin on some cases but Kowa Shinyaku Co. Ltd's medication proved clearly to be superior in its results. Since the fall of 1977, we have administered urokinase therapy to 12 patients who suffered acute myocardial infarction. During the observation period, 4 cases experienced reinfarcts and one patient died. Exitus occurred in case 8 who had been transfarred from another physician on the occasion of her second attack. The 11 remaining cases have recovered and are leading normal lives as of November 9, 1980.

INTRODUCTION

In acute myocardial infarction both electrical and pump failure can be fatal. As for electrical failue, number of cases can be saved by recent progress in cardiac electrophysiology. If we have a therapy that can inhibit thrombosis formation in the coronary arteries, facilitate the restoration of blood flow, salvages ischemic myocardium and does not cause myocardial necrosis, it can also prevent pump failure and death due to electrical failure. For the past

*) 大前清甫，佐藤幸男：急性心筋硬塞の発症初期におけるウロキナーゼ療法

fifteen years, thormbolytic clinical trials[1-3] using urokinase, one of the thrombolytic agents, have been made for acute myocardial infarction. Simon and associates[4,5], however, reported in their review that urokinase did not have the effect expected because it contained clot-promoting components. The aim of this paper is to show one special quality and usage of the urokinase preparations which we had used successfully to save the patient with acute myocardial infarction in its early stage.

METHODS AND MATERIALS

Selection of commerial preparations.

The urokinse preparations used were made by Kowa Shinyaku Co., Ltd. and Fujisawa Yakuhin Co., Ltd. Figure 1 is an analysis of the various companies' products in Japan that Kowa Shinyaku Co., Ltd. made using SDS polyacrylamide electrophoresis.

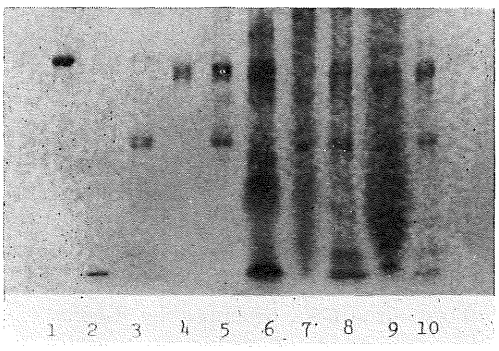

Fig. 1. Results of SDS polyacrylamide electrophoresis
1. Human albumin 5 μg/well molecular weight 70×10^3
2. Lysozyme 5 μg/well 14.7×10^3
3. Low molecular urokinase 300 unit/well 33×10^3
4. High molecular urokinase 300 unit/well 54×10^3
5. Commercial preparation of Kowa Shinyaku Co. Ltd. (1978)
6. Commercial preparation of green cross Co. Ltd. (1978)
7—10. Other commerical preparations

It is known that high molecular urokinase has a stronger thrombolytic activity, and that when dissolved and left at 37°C for 24 hours, high molecular weight urokinase decomposes into low molecular weight urokinase and polypeptide with 21×10^3 molecular weight and the fibrinolytic activity decreases[6]. The products from Kowa Shinyaku Co., Ltd. contain a rich 75% high molecular urokinase and can be expected to have the greatest, thrombolytic activity if given immediately after dissolution. On the other hand, regarding the amount of lysozyme hydrochloried, which is well-known as a clotpromoting or an anti-heparin substance, Kowa Shinyaku's preparation contained below 0.1 μg per 6×10^3 unit urokinase vial and A Co., Ltd. preparation more than 100 μg per 6×10^3 unit urokinase vial. Band 6 preparation also contained many unknow proteins, while the preparations from Kowa Shinyaku and Fujisawa Yakuhin contain no proteins other than urokinase.

Case Material:

On selecting the subjects for study, differentiation between attacks resulting from acute myocardial infarction, from unstable angina at rest, and variant forms of angina pectoris must be made. The criteria used for case selection were as follows: 1) classic history of acute myocardial infarction[7]; 2) diagnostic electrocardiographic criteria for myocardial infarction, including Q waves and S-T segment elevation or T wave inversion, or both[8]; 3) ability to initiate urokinase treatment within 18 hours from the onset of chest pains. In regard to the five cases with angina pectoris, pallor and coldness of the face and extremities as well as complaints of intractable pain in the breast and back, different from the usual ones were considered to be important points in differentiation.

As for ECG finding, urokinase can stop the appearance of Q waves. The subjects treated were the 12 cases shown in Table 1; ranging from 45 years to 82 in age, 9 males and 3 femals. The diseases under treatment when the attack occurred were angina pectoris (5), ischemic heart disease (2), essentialy hypertension (5)–the five cases with essential hypertension included two cases one having the complication of hypertensive heart disease and the other, diabetes mellitus.

Dosage and Method:

If the patient complains of pains in the breast on account of the myocardial infarction, the amount of time which has elapsed since the symptoms appeared should be noted. Opiumatropine is given to dispel the pains, and immediately a urokinase 24×10^3 unit, dissolved in 20 m*l* of 20% glucose, is given intravenously over 90–120 seconds. It is qute usual for the

patient's face and extremities, which were pale and cold to return to normal 20–30 minutes later, and for subcutaneous veins to dilate and get warm. If the extremities remain pale and cold even after 30 minutes has elapsed, an equal amount of urokinase is administered intravenously over 90–120 seconds. If a second of third attack occures opiumatropine and one shot of an intravenous infusion of urokinase is made to promote the restoration of temperature and color of the skin and the extremities. Because the object of urokinase administration is to make no Q wave on ECG, the therapy should commenced at least at a state of endocardial necrosis. Thus, the aim is to keep persistent ST depression as much as possible or, if failed that to remain in the same state only with a decreased amplitude of R wave remained on the ECG. Urokinase therapy, therefore, has little meaning for a patient after more than 24 hours has elapsed since his attack. This is because the condition of the disease has already progressed to transmural necrosis and an irreversible change has occurred ot the myocardium.

RESULTS

We have studyed consecutive 12 cases with acute myocardial infarction satisfying the above mentioned conditions up to this March, 1980, since we began this method in the fall of 1977. As shown in Table 1, the time from the onset of an attack to the initial administration of urokinase ranged from 20 minutes to less than 17.5 hours. But for most of the patients the time was less than 5.0 hours. The CPK values began to increase 3–6 hours after an attack and reached their peaks after 24 hours and then returned to normal within three days. The Cases whose CPK values could be measured over 24-hour were Case 5 and Case 12. Case 6 had 48-hour values. The CPK of Case 10 was got on the 5th day after the attack with 718 units of LDH. The CPK of Case 11 was a 48-hour value, 127, with 425 units of HED and 631 units of LDH. The other patients' CPK values, except for Case 1's which were not measured, were obtained within 5.0 hours after the attack because their blood was taken for examination immediately before urokinase administration. Tow cases show the early effects of urokinase therapy on the ECG.

Table 1. Patients Studied

Case No.	Name	Sex	Age	Diseases	Time from onset	CPK	site of MI on ECG	Period of observation	Mortality
1	Honda	F	48	Angina pectoris	20 min	—	Anteroseptal	27M	alive
2	Sakamoto	M	72	Ischemic H. D	1 hour	161	Antero lateral	25M	alive
3	Mukai	M	53	Ischemic H. D	2 hrs.	39	Anterior	26M	alive
4	Ikuta	M	48	Hypertensive H. D	2.5 hrs.	171	Anterior	18M	alive
5	Yumitori	F	77	Hypertension	3.5 hrs.	451	Posterior	30M	alive
6	Okimoto	M	65	Angina Pectoris	3.5 hrs.	304	(1) Anteroseptal (2) Inferior	17M	alive
7	Hikiji	M	82	Angina Pectoris	4.0 hrs.	41	main coronary	22M	alive
8	Tanaka	F	80	Angina Pectoris	4.0 hrs.	78 (HBD380)	(1) Inferior (2) ?	1W	died
9	Kodama	M	52	Hypertension	5.0 hrs.	40	main coronary	22M	alive
10	Noda	M	68	Hypertension	8.0 hrs.	64	(1) Antero lateral (2) Anterior	12M	alive
11	Katoh	M	45	Angina Pectoris	13.0 hrs.	127	(1) Infero lateral (2) Inferior	14M	alive
12	Kunichika	M	62	Kypertension Diabetes Mellitus	17.5 hrs.	479	Antero lateral	14M	alive

The cases whose CPK values could be measured over 24-hour were case 5and 12.

Case No. 6 went into ICU and was dript urokinase from the second administration.

Case No. 8 had consulted another doctor when her second attack occured and died 1 week later.

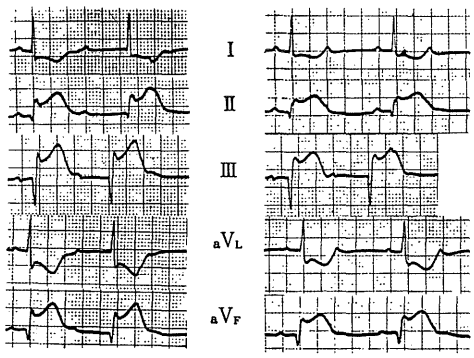

Fig. 2-1 2-2

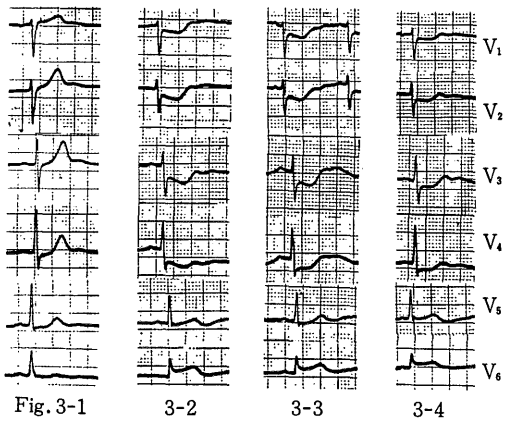

Fig. 3-1 3-2 3-3 3-4

Fig. 2—1. ECG findings before urokinase infusion of Case 8.

2—2. ECG findings show recovering ST changes 60 minutes after urokinase infusion.

Fig. 3—1. ECG findings of on the first attack day of angina pectoris of Case 6.

3—2. ECG findings on the next day of Case 6 show MI attack.

3—3. Nitrate treatment shows no remarkable ST changes 15 minutes after.

3—4. ECG findings 60 minutes after urokinase infusion show recovery of the ST changes.

In Case 8 (Fig 2), deepening of the Q wave stopped 60 minutes after urokinase administration, the ST, which had elevated, and the reciprocal ST depression improved. Case 6 (Fig 3), had effort angina with light exercise the day before and had recovered with Nitrate. The next day at 8 : 30 in the morning, he was orthopnea on account of congestive heart failure. There was no appearance of Q wave on ECG 60 minutes after urokinase was given. Face and extremities of this case had been pale and cold when he came to the hospital, his subcutaneous veins subsequently dilated and his face and extremities got warm and returned to normal. Further, 10 cases, the color and temperatuse of their skin showed the effectiveness of urokinase therapy. The ECG of these 10 cases, however, was not used. Case 6 went into ICU, and was dript urokinase from the second administration on.

Subsequently, he had a second attack, which left Q wave at a site of inferior wall. Case 8, having the second attack before dawn the next day, consulted another doctor, and was given temporary pacing without urokinase therapy and diet a week later. All the other 11 cases are still alive. Case 10 had the second attack of myocardial infarction on the 5th day after urokinase therapy began 24,000 units/day of urokinase dosage was continued for twenty days. The amplitude of R V_5 was 3.4 mV at the first attack, and 0.4 mV on the 5th day. After the second attack, it was below 0.1 mV on the next days after. The Q wave at that time was not deeper than that five days before the first attack. Case 11 had reinfaction at the inferior wall eight days after the first attack. The R wave amplitudes of aV_F and V_6 were 0.8 mV and 1.0 mV at the first attack and decreased to 0.3 mV and 0.8 mV respectively on the fourth day. On the fourth day after the second attack, aV_F became 0.1 mV of qRs type and V_6 0.6 mV. III and aV_F showed typical coronary inverted T waves after the second attack. III changed to the QS type on the fifth day from the second attack.

DISCUSSION

The aim of urokinase therapy is to activate thrombolysis of to prevent thrombosis formation in coronary arteries before myocardial necrosis. This is because it has no realistic value after transmural necrosis occurred. For this reason, urokinase therapy seems to reach its limits about 17-20 hours after the onset of an attack. Dewar, et al.[9] reported that the ST segment elevation, 24 hours laster, had decreased significantly in the streptkinase group. Streptkinase was given withn 12 hours from the onset of an attack.

Around 1963, streptkinase was not satisfacto-

rily purified, containing a lot of clot-promoting components. In addition to this, the use of a great dose of streptkinase became one of the important reasons that the therapy resulted in failure. In urokinase therapy, elevated ST on the ECG begins to decrease as early as 60 minutes after urokinase administration, as shown in Figure 2 & 3. Evaluation on clinical effectiveness of the drug can be possible from the fact that the patient's face and extremities, with had been pale and cold, became warm again and returned to a normal color with the dilatation of subcutaneous veins. The reason why the administration of urokinase causes dilatation of the peripheral arteries and veins, is that the result of increased plasma kallidin direct effect to vascular muscles by urokinase activated kallikrein-kinin enzyme system. We have used these physical findings whether urokinase therapy is effective or not.

Nearby ten kinds of urokinase preparations are sold in Japan. But the Lysozyme rich preparation by A Co., Ltd. shown in No. 6 in Figure I is the most widly used in thrombolytic therapy, and it is natural that Sakuragawa, et al.[10] found that urokinase therapy was not effective, because they used this preparation in their clinical and experimental study at that time. For it is clear from electrophoresis of No. 6 that it contains a considerable amount of lysozyme of 2. Of the many urokinase preparations, the two containing no other protein components than high and low molecular urokinase were, one by Kowa Shinyaku Co., Ltd. shown in 5 in Figure 1, and one by Fujisawa Yakuhin Co., Ltd., which was investigated later.

In urokinase therapy, very large units of the drug are generally used. Prentice[2] used 3,600 units/kg body weight/hour, Dubbler[11] 5,000 units/kg body weight/hour drip infusion for 18 hours, Fletcher[12] 4,000 units/kg/hour drip infusion for 12 hours, and Libman, et al.[13], who used the least amount, 1950 CAT units/lb body weight-at the conversion rate of 453 g to one pound, 747 CAT units/kg body weight/hour $\times$ 8 hours, total 5,976 CAT units/kg/day. Even this does exceeds by ten times the does that we give Japanese. Recently we have been administering 24,000 units/day in all cases. Supposing Japanese average body weight to be approximatery 60 kg, that figure correstonds to one shot administration of 400 units/kg/day. It seems that this is a satisfactory amount to save patients. But, if a second or third attack occurs, 24,000 units should always be added. We think it necessary that the drug be given for several days consecutively because a patient with myocardial infarction is in a platelet hyperaggregative state[15,16].

Continuous drip infusion has been conducted in most of urokinase treatment. This method has some weakpoints. One of them is that to use a greater amount of the drug containing lysozyme means injecting a large amount of lysozyme directly into the blood stream. We dissolved the drug in 20 m*l* of glucose solution and administered it in one shout over 90–120 seconds. Supposing the average Japanese men's weight to be 60 kilograms and Westernors to be one and a half times as heavy (90 kilograms) 400×90 $(=36 \times 10^3)$ units, or 50×10^3 units/day in one shot administration should bring about a corresponding effect. We belive, based on our study, that this dose and dosage of urokinase preparetion may cause a change in the prognosis of patients with acute myocardial infarction. Further study may still be needed regarding the dosage. This is because the cases we treated here were all Japanese.

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