Thrombolytic Therapy

Sol Sherry* M. D.

No one would question that the ability to dissolve thrombi in vivo by drugs is a significant medical achievement and should have practical application as a therapeutic measure. However proving such value has become increasingly more difficult and the field of thrombolytic therapy is almost completely occupied at present, as it has been during the past seven years, with the clinical evaluation of current forms of therapy. While such an evaluation is a must in terms of providing a base for further developments, it is becoming increasingly clear that the patient observations are raising questions which will have to be investigated further, both in the laboratory and the clinic, if the full potential of this new form of therapy is to be properly exploited. Before commenting on these problems, and to provide a perspective for them, it is important that we review the present status of the clinical experience with the fibrinolytic agents in current use.

Streptokinase, a bacterial product, has been commercially available abroad since the mid-sixties where it has been widely used. It is still under evaluation in the United States and Canada, and may become available in 1973. Currently, a fixed dosage schedule is recommended; this consists of a loading dose followed by a sustaining infusion for periods of 24~96 hours depending upon the clinical situation and response. The regimen used contains sufficient

streptokinase to overcome the resistance of approximately 85-90% of the patient population and maintains free circulating levels of the agent sufficient to sustain an intense thrombolytic state.

The major hazard with streptokinase, as with other thrombolytic agents is bleeding. This bleeding is most often encountered at the site of invasive procedures and is usually readily controllable by local measures. On occasion, more serious bleeding may occur into areas of trauma, recent operative wounds or in unexpected locations. The contraindications for streptokinase therapy are the same as for the use of anticoagulants. Other undesirable effects attributable to streptokinase are an occasional severe pyrogenic reaction, rash and, in rare instances, an anaphylactoid-like syndrome.

Urokinase is derived from human urine; consequently it has the advantage of being non antigenic and, except for the bleeding problem, has been free of adverse reactions. However, its production is much more costly. It is used much like streptokinase, i. e. a fixed dosage schedule consisting of a standard loading dose followed by a sustaining infusion for periods of twelve to twenty-four hours.

I . Deep Vein Thrombophlebitis

For deep vein thrombophlebitis, thrombolytic therapy could minimize the two major complications of this disorder, i. e., embolization and the post phlebotic venous insufficiency synd-

* From the Department of Medicine and the Specialized Center for Thrombosis Research, Temple University, School of Medicine.

rome. Were it almost always successful and without hazard from bleeding or adverse reactions, it would be used initially, by choice, for all cases and, then, followed by anticoagulant therapy so as to prevent rethrombosis or further growth of a partially lysed clot. However considering that the therapy is not always successful, that there are hazards involved, and that the morbidity and mortality following appropriate anticoagulant therapy is usually low, current indications are limited to those situations where (1) the thrombus is extending rapidly in the major vessels of the deep venous system, particularly when the involvement extends above the popliteal vein, or (2) embolization is present; or (3) edema and other signs of obstruction of the ilio-femoral and femoral venous system are readily evident.

What has been the experience with thrombolytic therapy? Most of the information to be discussed relates to streptokinase or SK, since this agent has been more readily available.

An article by Biggs¹⁾ cites venographic observations by four different groups of investigators in controlled studies comparing the frequency of lysis of deep vein thrombi in patients treated either with anticoagulants or streptokinase. Note that of 33 patients treated with streptokinase, 45% showed complete resolution, 33% partial lysis and 22% no lysis of the thrombus; these results compare favorably with anticoagulant therapy where less than one-third of the patients showed any significant evidence of resolution.

As for the immediate clinical effects, the careful studies of Robertson²⁾ are illustrative of the experience of others. The results relate to his second and third coded series. The clinical effects were graded as **good**, **fair** or **poor** by a panel of physicians

who made their judgement before the code was broken. Venographic observations also were done to confirm the diagnosis and to follow the fate of the thrombus, but these observations were not available in judging the effect. A **good** result was defined as complete disappearance of swelling and total regression of the induration and/or tenderness of the affected limb. A **fair** result was persistence of partial swelling but regression of the induration and/or tenderness. **Poor** was recorded when swelling, tenderness and induration remained unaffected. Note that 59% of the SK treated patients had a good clinical effect whereas 67% of the heparin treated patients had a poor response.

Relative to the objectives of a decreased incidence of post-phlebotic insufficiency and pulmonary embolism, there is only suggestive, but not definitive, evidence to support these accomplishments. Concerning the post-phlebotic insufficiency syndrome, Kakkar and his associates³⁾ reported that 4 of 5 patients, whose clots had been lysed by SK, had normal valvular function by phlebography, 6~12 months after the completion of therapy. Robertson's results⁴⁾ were even more striking. He repeated venography in eight patients, 11 to 30 months after complete lysis of the deep vein thrombosis; in all, patent vessels and intact valves were still observed. However no conclusions could be drawn from these studies, encouraging though they may be, since the post-phlebotic insufficiency syndrome may appear late and its anticipated incidence has varied greatly among authors.

As for reducing the incidence of pulmonary emboli, the only available information about this point, comes from the Urokinase-Pulmonary Embolism Trial or UPET⁵⁾. In this trial all patients had to have a documented recent embolism; therefore presumably most had an

accompanying deep vein thrombosis. The incidence of recurrent embolism, based on serial lung scans and careful clinical observations, in patients treated with heparin was 19%, whereas for patients treated with urokinase, the incidence was only 13%. Unfortunately, the number of observations were too small to establish a significant difference.

To summarize, extensive dissolution of deep vein thrombi can be achieved by thrombolytic therapy in approximately half the cases and partial dissolution in another quarter. These effects are associated with a salutary clinical response in terms of edema, induration and tenderness. It is less clear whether the therapy diminishes the incidence of post-phlebitic venous insufficiency and/or pulmonary embolism, though there is reason to suspect that successful therapy will accomplish both. Thrombolytic therapy should be followed by anticoagulants so as to prevent recurrent thrombosis; they should not be given together because of a summation and possible augmentation of their respective bleeding complications. The bleeding problem with thrombolytic therapy, can on occasion produce complications which are worse than the illness under treatment; therefore, at present, thrombolytic therapy is being restricted to those patients who have a rapidly extending thrombosis in the major vessels of the deep venous system, evidences of embolization, or clinical signs of obstruction in the ileo-femoral and femoral venous system.

II. Acute Pulmonary Embolisms

The best studies on thrombolytic agents have been carried out in acute pulmonary embolism, since this clinical situation provides an excellent model for evaluating the effects of a thrombolytic agent.

UPET⁵⁾ evaluated the effects of a 12 hour infusion of urokinase, followed by heparin

therapy as compared to conventional heparin therapy alone. Good stratification was achieved among the various subgroups, with approximately half the patients in each group having massive embolism, defined here as occlusion of two or more lobar arteries or its equivalent, and half characterized as submassive.

The results of the trial may be summarized as follows:

1. Urokinase, followed by conventional heparin therapy, as compared to heparin alone, significantly accelerated the resolution of pulmonary emboli, increased pulmonary capillary perfusion and restored the hemodynamic abnormalities toward normal.

2. The mean twenty-four hour improvement in angiographic findings was 1.78 on a four point improvement scale for the urokinase patients as compared to 0.54 for heparin.

3. The mean twenty-four hour improvement in the lung scan defect among urokinase treated patients amounted to 24% as compared to 7.5% for those receiving heparin.

4. Hemodynamically, patients treated with urokinase as compared to heparin alone, showed significantly greater improvement at twenty-four hours in the following pressure measurements: PA mean, RV systolic, RA mean, RVED; and in the arterial pO_2 and total pulmonary resistance. No significant differences were observed in the cardiac index; not a surprising finding since most of these were normal before therapy.

5. Urokinase appeared to have its greatest effect when the embolism was massive.

6. The most frequent complication was bleeding; this occurred in 44% of the urokinase group and 27% of the heparin group. While, bleeding from the sites of invasive procedures was more frequent in those receiving urokinase, spontaneous bleeding, including unexpected hematocrit falls, was equally

distributed. The high frequency of bleeding from invasive sites was anticipated since the study required multiple procedures.

7. As for other complications, recurrent embolism occurred in 19% of the heparin treated patients and in 13% of the urokinase treated patients; the fewer episodes encountered in the urokinase group provides some reassurance that leg vein thrombi in the process of lysis are not likely to embolize more frequently. 12% of the heparin group underwent subsequent inferior vena caval interruption, while this procedure was deemed necessary in 4 % of the urokinase group. No patients in either group underwent subsequent pulmonary embolectomy, though 11 patients had appropriate indications (persistent shock and massive embolism) at the time they were entered into the trial.

8. The mortality in the urokinase group was 7.3% and for the heparin group, it was 9.0%.

A number of reports⁶⁾⁷⁾ indicate that twenty four hours of streptokinase therapy has produced an effect quite similar to that described for urokinase. Consequently, at the conclusion of UPET, the Urokinase-Streptokinase Pulmonary Embolism Trial or USPET was initiated. This trial was designed to compare the effects of 24 hours of streptokinase therapy to both 12 and 24 hours of urokinase. Otherwise the format of the protocol is essentially identical with the earlier trial. USPET has now been in progress for 30 months, and 151 patients have been studied. No report on the data has been issued as yet.

UPET did not establish any mortality benefits from urokinase therapy. Furthermore, logistical considerations make it unlikely that such information will be forthcoming; to establish mortality benefits probably would require observations on at least 4~5000 patients

with well documented acute pulmonary embolism, and this is beyond the scope of practicality.

Nevertheless the observations made so far have important therapeutic implications. First, there would appear to be little indication for the use of a thrombolytic agent, as currently employed, in submassive embolism, particularly for those patients with stable vital signs. Here the patient is destined to recover spontaneously in the absence of other complicating disease or recurrent pulmonary embolism, and the agent's effect is not very impressive.

On the other hand, these agents should prove useful in the management of acute massive embolism since the effects noted here have been much more striking than for submassive embolism, and the problem facing the patient with massive embolism is considerably greater, both in terms of acute and long terms effects as well as in mortality. In this respect, in UPET, approximately 40~50% of the embolic material in the massive embolism group was lysed during the therapy, and the restoration of pulmonary capillary perfusion was impressive, as was the reversal of the hemodynamic abnormalities; the latter, in selected observations, was observed to begin within an hour of the initiation of therapy.

Most likely, the best single indication for thrombolytic therapy in pulmonary embolism will be for the management of the patient with massive embolism and an unstable blood pressure. The results of surgical embolectomy have not been impressive; approximately 50%, and more in the older age group, still succumb with this procedure. This mortality rate compares poorly with the 18% mortality achieved in UPET for patients with indications for a surgical embolectomy but who were randomized into the trial instead. Such observations suggest that medical therapy may be superior

to surgical embolectomy for most patients with massive embolism and persistent hypotension. This point, however, remains to be established.

III. Peripheral Arterial Thromboembolism

In the area of peripheral arterial thromboembolism, no controlled trials comparing thrombolytic therapy with other forms of therapy, particularly surgical, have been undertaken. The experience may be summarized as follows:

In acute arterial thrombosis involving the lower extremities, satisfactory dissolution of thrombi occurs in approximately half the treated patients; in embolic disease, the incidence of success is higher, approximately 70%. Surgery is still preferred to fibrinolytic therapy for aorto-iliac occlusion since the clinical results following endarterectomy for this lesion are generally excellent and better than that achieved with fibrinolytic agents. However for the management of thrombo-embolic occlusions situated in the popliteal artery or more distally, fibrinolytic therapy yields better results than surgery. In femoral artery thrombo-embolism, comparable effects are obtained by surgery or fibrinolytic agents, and currently thrombolytic agents are being used first in a number of Centers unless there is evidence to suggest impending irreversible damage to the limb.

Opinions differ on the use of streptokinase for the management of chronic arterial occlusions of the lower extremity; most, however, believe the hazards outweigh the limited benefits which can be achieved.

IV. Acute Myocardial Infarction

The major thrust with thrombolytic agents at present is to determine their possible usefulness in the treatment of acute myocardial infarction.

Considering that the size of the infarct and the efficiency of the residual myocardium as

a pump have become the most important considerations determining initial survival and the extent of recovery, and that these factors are dependent on the degree and duration of interruption of blood flow, rapid restoration of flow through the use of thrombolytic agents could have a salutary effect. First, reperfusion of occluded vessels and/or the microcirculation could improve cardiac output by limiting the extension of the infarct, salvaging some of the injured but dying muscle and augmenting myocardial function in the areas of marginal ischemia. Additional benefits also could result from a diminution of the irritability of the heart arising from ischemic areas, and avoidance of some of the thrombo-embolic complications through lysis of mural endocardial and peripheral venous thrombi.

A number of studies have been carried out with streptokinase in acute myocardial infarction. Four major ones^{8~11)} have been conducted in general hospital beds. Three of these, two German trials^{8~9)} and the European Working Party¹⁰⁾ study evaluated a 24 hour course of therapy at a comparable dose level and yielded a significant difference in favor of SK, but a Finnish investigation¹¹⁾ claimed no effect. Unfortunately, the latter study differed both in dosage and design.

With the advent of Coronary Care Units, one can no longer compare mortality as influenced by a particular therapy in general hospital beds or even in Intensive Care Wards with that observed in these highly specialized units. Thus the 25~30% reduction in mortality achieved in most studies among patients treated with SK in general hospital beds may already have been accomplished by the care and procedures utilized in units which have reduced the death rate by approximately 60%.

At present there are three studies which

relate to SK therapy in Coronary Care Units. The Italian study¹²⁾, which has been completed and reported upon, shows no difference in mortality, but their trial only evaluated a twelve hour infusion of SK. Of the other studies, the Australian trial¹³⁾, after 600 patients, shows a 24% reduction but this is unlikely to reach significance unless they are prepared to study another 1400 patients. The most recent is a United Kingdom study¹⁴⁾ which is still in its early stages; at last report only 130 patients had been studied and the mortality so far has been 50% less in the SK group. However the magnitude of this difference is unlikely to be maintained because of the high death rate among the controls in the early phase of this trial.

As might be expected, these discordant observations have created considerable controversy as to whether SK therapy is beneficial or not. Since our National Heart and Lung Institute has the desire to determine whether thrombolytic therapy is beneficial in acute myocardial infarction, they have decided to sponsor SUMIT, i. e., the Streptokinase-Urokinase Myocardial Infarction Trial, with a protocol quite similar to that used in the studies reporting a positive result. The pragmatic logistical feasibility of conducting such a study and bringing it to a successful conclusion represents a considerable challenge and one which is not being underestimated. SUMIT is targeted to begin by the first of the year and hopefully will provide an answer as to whether thrombolytic therapy has a role to play in the management of acute myocardial infarction.

V. General Comments

While studies on clinical efficacy will undoubtedly continue for some time, it is becoming increasingly apparent that thrombolytic therapy is being evaluated more and more on

the basis of one fixed dosage schedule rather than on what might be accomplished if we understood better how to use these agents and could more effectively prevent their hazards. Time will not permit an extensive discussion of the questions raised by the patient observations but two are worthy of brief comment since their investigation is critical to the further development of thrombolytic therapy.

First, what determines the success of therapy? Shown are the correlation coefficients achieved in the Urokinase-Pulmonary Embolism Trial between the various assessments of the resolution of the pulmonary embolus (i. e. improvement in the angiographic findings, restoration of the pulmonary capillary perfusion and relief of hemodynamic abnormalities) and the observations made on circulating fibrinolytic activity, activation of plasma plasminogen and fall in the fibrinogen level. Note that the extent of the changes in these biochemical tests were of no value in predicting the success of therapy. This lack of correlation is disturbing for it indicates that our present tests are not telling us what we need to know, and that we urgently require an assay or procedure which quantifies the amount of preformed thrombus being dissolved *in vivo*. Until such a test is available, the development of new and more effective therapeutic regimens will be governed by a lengthy trial and error approach rather than through a much more rapid scientific assessment.

The other major concern relates to the bleeding problem. This is a real risk with thrombolytic therapy, and in many instances, this hazard outweighs the clinical benefits which can be achieved. In earlier work with streptokinase, the bleeding hazard was attributed to the brisk hyperplasminemia often seen in the early treatment phase; fibrinolysis was extensive and large quantities of

fibrinogen degradation products accumulated in the circulation and were said to be responsible for the hemorrhagic diathesis. Urokinase, in the dosage employed, activates plasma plasminogen at a significantly slower rate and less extensively than previously observed with streptokinase; consequently fibrinogenolysis is not as great, fibrinogen breakdown product concentrations are lower and the coagulation abnormalities milder. Yet the bleeding risk with urokinase is as great, if not greater, than that encountered with streptokinase. Accordingly, other and perhaps more important factors must be involved in the bleeding diathesis associated with thrombolytic therapy. Again, there is an urgent need to identify these so that it can be determined whether by one means or another, they can be controlled without sacrificing the lytic effects of the therapy.

Ⅶ. Conclusion

It should be emphasized that thrombolytic therapy is still in its infancy and that ample justification exists for its active encouragement and development. However the latter requires a resurgence of interest in basic investigation to complement the patient studies which currently dominate this field of endeavor.

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