Evaluation of a Standard Dosage Schedule with Streptokinase

By J. HIRSH, E. F. O’SULLIVAN and M. MARTIN

THE FEASIBILITY of producing dissolution of thrombi by enzymatic means has been demonstrated in experimental thrombi and pulmonary emboli in animals,1-3 in experimental venous thrombi in man4 and in patients with acute venous and arterial thromboembolic disease.5-18

Of the enzymes investigated, only the two plasminogen activators, streptokinase and urokinase, have proved acceptable as thrombolytic agents for clinical use.19 Streptokinase is now available in a highly purified form but has the disadvantage of being antigenic to man. Pyrogenicity, formerly a major difficulty with the earlier preparations,19,20 is no longer a serious problem if prophylactic corticosteroids are used. Streptokinase has the advantage of being considerably less expensive than urokinase and is more readily available; however, urokinase has the advantage of being nonantigenic.

The problems associated with the antigenicity of streptokinase are manifest in two ways. The first is due to the fact that streptococcal antibodies cross-react with streptokinase. These antibodies, the result of previous streptococcal infections, are present in most patients and must be neutralized before thrombolysis can be produced.21 The streptococcal antibodies combine with, and inactivate streptokinase, and the streptokinase–antibody complex thus formed is then rapidly cleared from the bloodstream.22 The neutralizing dose of streptokinase cannot be predicted with any certainty because the concentration of streptococcal antibodies varies over a wide range from patient to patient.21 For this reason a streptokinase resistance test is usually performed on every patient before commencing treatment. The second problem arising from the antigenicity of streptokinase is that treatment causes a marked increase in the level of streptokinase antibodies, and this precludes further therapy should this be necessary in the next one to six months.21,23

The principles of thrombolytic therapy with streptokinase, and more recently, urokinase, have been established by the important fundamental and clinical investigations of Fletcher, Sherry and Alkjaersig.21-25 Streptokinase produces its
proteolytic effect by converting plasminogen, a proenzyme, to plasmin, a proteolytic enzyme. Plasmin not only digests fibrin but also digests fibrinogen and other plasma-clotting factors. The aim of thrombolytic therapy with streptokinase is to digest the fibrin in the thrombus without producing a marked and sustained plasma proteolytic state. This aim can be achieved by using an initial high *inducing dose* of streptokinase which both neutralizes the antibodies and rapidly activates the circulating plasminogen. The plasmin so formed produces a plasma proteolytic state with some degree of fibrinogenolysis, but this is transient and usually asymptomatic, provided that the circulating plasminogen is maintained at low levels by an adequate *sustaining* dose of streptokinase. The streptokinase which is subsequently administered in the sustaining infusion then activates the plasminogen in the thrombus, producing fibrinolysis of the thrombus with only minimal plasma proteolysis.

In recent years various standard dosage schedules have been used in an attempt to overcome the need to perform a resistance test on each patient before commencing treatment with streptokinase. With this approach it is inevitable that some patients will receive an inducing dose in excess of minimum requirements, and others a dose which fails to neutralize the streptokinase antibodies. High inducing doses which exceed the patients' streptokinase resistance appear to be safe and effective, presumably because they produce rapid depletion of the circulating plasminogen; their only real disadvantage is that treatment in some patients becomes unnecessarily expensive. On the other hand, inducing doses which fail to neutralize the circulating antibodies are pharmacologically ineffective. The optimal standard inducing dose will vary according to the range and distribution of streptokinase resistance in the community. However, the dose required to maintain the circulating plasminogen at low concentrations appears to be less dependent on the results of the resistance test and can be achieved by a standard sustaining dose of 70,000-100,000 units per hour.

In a recent report, Verstraete and associates demonstrated that an inducing dose of 1,250,000 units, followed by a sustaining dose of 100,000 units per hour, rapidly produced and maintained plasminogen depletion and was relatively free of hemorrhagic and other complications. But, as they pointed out, their regimen is far from ideal because of its expense. Furthermore, Browse and associates, when using this large inducing dose, did note the occasional occurrence of pyrexia, rigors, loin pain and mild bronchospasm, in spite of the administration of prophylactic corticosteroids. Other investigators, when using a standard dosage regimen, have used lower inducing doses; however, the fibrinolytic effects of these lower standard inducing dosage schedules have not yet been systemically evaluated. A standard dosage regimen with an inducing dose considerably lower than that used by Verstraete and associates is currently being recommended by one of the manufacturers of streptokinase, and this regimen and other similar standard dosage regimens are being used in a number of centers. It therefore seemed important to evaluate this lower inducing dose from the point of view both of its safety and effectiveness.
EVALUATION OF A STANDARD DOSAGE SCHEDULE

METHODS

Streptokinase resistance tests were performed on 80 patients with thromboembolic disease by the serial dilution method of Fletcher and associates\textsuperscript{21} as modified by Deutsch and Fischer.\textsuperscript{29} Fifty of these patients were then treated with 250,000 units of streptokinase infused over one-half of an hour, followed by 100,000 units per hour, irrespective of their streptokinase resistance. The infusion was usually continued for 24 hours but sometimes for 48 hours. The other 30 patients were treated with an inducing dose based on their streptokinase resistance. In the patients initially treated, corticosteroids were used only if the patient developed a febrile reaction, but later prednisolone 30 mg. orally was administered to all patients before commencing the streptokinase infusion. The diagnosis in the patients treated with the standard dosage schedule was myocardial infarction\textsuperscript{*} in 17, retinal vein or retinal artery thrombosis in 16, major pulmonary embolism in 13 and acute deep vein thrombosis in four.

Tests of Fibrinolytic Activity

The following tests were performed by methods previously described by Fletcher and associates\textsuperscript{21,22}; thrombin clotting time, euglobulin lysis time, fibrin plate assay, plasma plasminogen assay and plasma fibrinogen assay.

\textsuperscript{*}These patients were treated as part of a pilot study for a controlled trial of streptokinase in myocardial infarction.

\begin{figure}
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\caption{Distribution of streptokinase resistance in 80 patients with thromboembolic disease. Median resistance 100,000 units; mean resistance 120,000 units.}
\end{figure}
Fig. 2.—Results of fibrinolytic and coagulation tests in 46 patients whose streptokinase resistance was 250,000 units or less. Continuous line represents mean; broken lines range for each test. T.C.T. = thrombin clotting time in seconds; EUG. LYSIS = euglobulin lysis time in minutes; FIB. PLATE = fibrin plate assay in sq. mm.; PLASMINOGEN in casein units per ml.; FIBRINOGEN in mg. per 100 ml.
RESULTS

Streptokinase Resistance

The distribution of streptokinase resistance in the 80 patients with thromboembolic disease is shown in Fig. 1. Eighty-eight per cent of the patients had a resistance test of 250,000 units per ml. or lower, 94 per cent had a resistance of 400,000 units or lower and 98 per cent of 600,000 units or lower. The median resistance was 100,000 units and the mean was 120,000 units. Of the 50 patients treated with a standard dose, 92 per cent had a resistance of 250,000 units or lower.

Fibrinolytic and Coagulation Tests

The results of fibrinolytic and coagulation tests in the 46 patients with a streptokinase resistance of 250,000 units or less is shown in Fig. 2. It can be seen that a brisk thrombolytic state with plasminogen depletion was rapidly obtained in all patients. One patient developed a severe hypofibrinogenemia, and one a moderate hypofibrinogenemia after infusion of the inducing dose. Four patients with a streptokinase resistance greater than 250,000 units were treated with the standard dose regimen; in all four there was a delay before an adequate thrombolytic state was attained, but once produced, an active thrombolytic state was maintained with plasminogen depletion and without a severe coagulation effect (Fig. 3).

DISCUSSION

The levels of streptokinase resistance in our patients were considerably lower than reported by a number of European and American investigators (Verstraete and associates), but similar to the levels reported by others. Presumably these differences in resistance are a reflection of the incidence of streptococcal infection in the various communities. Forty-six of the 50 patients treated with the standard dosage schedule had streptokinase resistance values of 250,000 units or lower and the mean value was only 100,000 units. All of these patients developed a very active thrombolytic state and rapid plasminogen depletion during the induction phase of treatment, and this was maintained with a sustaining dose of 100,000 units per hour. These findings therefore substantiate the reports of other workers on the safety of using an inducing dose of streptokinase in excess of the patient’s resistance and of continuing therapy with a standard dose which maintains plasminogen depletion.

It has been suggested on sound theoretical grounds that doses of streptokinase which fail to maintain plasminogen at low concentrations may be more dangerous than high doses, the reasoning being that slow plasminogen activation by relatively low concentrations of streptokinase could produce a sustained hyperplasminemia with a consequent marked hemostatic defect. It could therefore be expected that patients with a resistance in excess of the inducing dose might develop a severe coagulation defect. However, this was not so; thus, although the four patients with resistance tests in excess of 250,000 units showed a delayed fibrinolytic response, once obtained, the fibrinolytic effects were similar to those found in the other 46 patients. Presumably, the maintenance
dose was sufficiently large to produce plasminogen depletion after the streptokinase antibodies had been neutralized.

The standard dosage regimen used in our patients may not be optimal for other populations because it is likely that the range and distribution of streptokinase resistance will differ in other communities. However, the results clearly show that a high inducing dose is safe and effective, and that a suboptimal in-

Fig. 3.—Results of fibrinolytic and coagulation tests in four patients whose streptokinase resistance greater than 250,000 units. Streptokinase resistance (Res) indicated in upper portion of figures. T.C.T. thrombin clotting time in seconds; F.P. = fibrin plate in fibrinogen in mg. per sq. mm.; PLAS. = plasminogen in casein units per ml.; FIB. = 100 ml.
duc ing dose does not necessarily produce a serious hemostatic defect if it is followed by a maintenance dose of 100,000 units per hour.

The main complication of streptokinase therapy was bleeding. Analysis of the fibrinolytic state, the coagulation defect and the nature and severity of the bleeding strongly suggested that although defective fibrin polymerization and depression of coagulation factors contributed, the major factors responsible for the bleeding episodes were a combination of a local vascular defect (usually iatrogenic) and an active fibrinolytic state. Control of bleeding was readily obtained in three patients (two who bled from sites of arterial puncture and one with hematemesis) merely by stopping treatment, and in one patient who required urgent pulmonary embolectomy the fibrinolytic effect was rapidly reversed with intravenous epsilon amino caproic acid and the operation was performed without unusual blood loss. Furthermore, bleeding from venepuncture sites often occurred in patients with only minimal elevation of the thrombin clotting time, and neither of the two patients with transient hypofibrinogenemia developed hemorrhagic manifestations. These findings indicate that with this therapeutic approach serious bleeding is uncommon unless the patient is exposed to trauma or has an underlying local lesion such as a peptic ulcer. However, it should be recognized that patients treated with streptokinase are always at risk from bleeding, and therefore this treatment is not recommended unless adequate medical supervision is available at all times.

In the initial stages of the study, before prophylactic corticosteroids were used, approximately 40 per cent of the patients became febrile after 12 to 24 hours of therapy. These pyrexial reactions which were usually mild, but sometimes severe, especially in patients with acute myocardial infarction, were virtually abolished by the use of prophylactic corticosteroids. One patient (in the total of 80 now treated with streptokinase) developed a severe allergic reaction during the infusion of the inducing dose despite the fact that she had been given 30 mg. of prednisolone orally 10 minutes earlier. The clinical manifestations of perioral edema, stridor and hoarseness, responded to intravenous hydrocortisone. It is of interest that the streptokinase resistance was not particularly high in this patient, and that there was no history of allergy. One patient who had an acutely infected finger developed severe lymphangitis and rigors eight hours after commencing streptokinase therapy; it is quite likely that the spread of infection was augmented by the fibrinolytic effects of streptokinase.

The exact place of thrombolytic agents in the management of thromboembolic disease is still not clearly defined. However, if well-controlled trials confirm the results obtained from the now considerable experimental and clinical experience, it will be important to ensure that these drugs are administered in pharmacologically effective doses. It is quite clear that a predictable thrombolytic effect with streptokinase would be obtained most consistently if the inducing dose of streptokinase was individualized for each patient. However, occasionally it may be inconvenient or indeed imprudent to delay treatment until the result of the resistance test is available, and in such circumstances a standard inducing dose is a reasonable alternative. This may be particularly so if the initial reports on the value of thrombolytic therapy in acute major pulmonary embolism12-15,18
are confirmed by clinical trial. The routine use of a standard dosage schedule would be acceptable only if it is shown by appropriate testing that a thrombolytic state could be achieved in a very high percentage of the community with a reasonably low inducing dose. If the distribution of streptokinase resistance in the community shows a very wide scatter with a significant proportion having a very high resistance, it would be far more economical and perhaps safer, to individualize treatment than to treat all patients with a very high inducing dose.

SUMMARY

The safety and effectiveness of a standard dosage schedule of streptokinase was evaluated in 50 patients with thromboembolic disease. A streptokinase resistance test was performed, and each patient was then treated with 250,000 units of streptokinase infused over 30 minutes followed by 100,000 units per hour. The results of serial tests of fibrinolytic activity were then correlated with the streptokinase resistance in each patient. Forty-six of the fifty patients had a resistance of 250,000 units or lower and all these developed an active thrombolytic state with rapid plasminogen depletion. The four patients with a streptokinase resistance in excess of 250,000 units showed a delayed fibrinolytic response; however, once obtained, the fibrinolytic effects were similar to those found in the other 46 patients.

It is concluded that an active thrombolytic state would be obtained most consistently if the inducing dose of streptokinase is individualized for each patient. The thrombolytic effects of a standard dose schedule are less predictable, but its routine use may be an acceptable alternative in a particular community if the range and distribution of the streptokinase resistance have been determined and have been shown to be relatively low in a large percentage of the community.

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REFERENCES

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