Thrombolytic Therapy with Streptokinase Using a Standard Dosage Scheme

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The term "thrombolytic therapy" refers to the attempted removal of preformed intravascular fibrin occlusions using fibrinolytic agents. Several substances have been described as inducing a fibrinolytic state in the peripheral blood ; however, for only a few of these (namely, the plasminogen activators streptokinase and urokinase) was it proved beyond reasonable doubt that administration resulted in an increase in fibrinolytic activity to the point of dissolving intravascular thrombi.

After critical clinical evaluation the overall results with streptokinase-plasmin mixtures were rather disappointing and it was still unclear which of the two agents was responsible for the action.

The purpose of this paper is to demonstrate that where a standard dosage scheme which has been proved to induce thrombolysis can be used for streptokinase administration, cumbersome laboratory controls become non-essential, thus making clinical trials accessible to a larger group of investigators.

Experimental Data Leading to the Adoption of a Standard Dosage Scheme

Search for a Standard Initial Dose of Streptokinase

A prerequisite for the induction of a fibrinolytic state in man is that the lytic activity produced overcomes the endogenous inhibitors present in the circulating blood. If therapeutic thrombolysis is to be induced with streptokinase (S.K.), the activity of antibodies and inhibitors to this enzyme has to be neutralized. The purpose of the initial loading dose of S.K. is therefore to neutralize these antagonists by the infusion of an amount of S.K. equivalent to the measured amount of circulating inhibitor.

Various titration methods for computing this dose (commonly termed "titrated initial dose" (T.I.D.)) have been developed and do not differ substantially (Deutsch and Fischer, 1960 ; Fischbacher, 1961 ; Nilsson and Olow, 1962 ; Amery *et al.*, 1963).

Based on published results of eight investigators (Fletcher *et al.*, 1959 ; Deutsch and Fischer, 1960 ; Deutsch *et al.*, 1961 ; Stacher and Boechnel, 1961 ; Nilsson and Olow, 1962 ; Olow, 1962, 1963 ; McNicol *et al.*, 1963 ; Helle, 1963 ; Winckelmann and Heimeyer, 1964 ; Abastado, 1964) it was found that the titrated initial dose may vary from 25,000 units of S.K. in one individual to 1,500,000 units in another. The average initial doses in these eight series ranged between 152,000 and 359,000 units S.K. The mean initial dose for the whole group of 99 subjects was found to be 294,000 units S.K. Johnson *et al.* (1957) measured the priming dose in 149 individuals and found that 500,000 units S.K. would be sufficient to neutralise inhibitors and antibodies in 82% of this group.

Using one single method (described by Amery *et al.*, 1963), we determined the initial dose in 132 persons. The mean initial dose (352,000 units S.K.) was in the same range as the average in the literature. The individual T.I.D. in our series varied between 25,000 and 3,000,000 units S.K., which corresponds to the variation from individual to individual of over a 100-fold range previously noted by Johnson *et al.* (1957). When the data of the literature and our series are combined, it appears that 224/231 (97%) persons have a T.I.D. below 1,250,000 units S.K. Therefore it may be expected that administration of 1,250,000 units S.K. as standard initial dose will be sufficient to induce a fibrinolytic state in at least 97% of the population.

The prerequisites for the routine administration of high doses of S.K. in man are numerous. First, it should be demonstrated that the batches of S.K. used are pyrogen-free. At present the European manufacturers of S.K. have been successful in producing preparations which fulfil this requirement. The second prerequisite is that the drug should be well tolerated when infused at a rate of 800,000–1,250,000 units over 15–30 minutes. So far it has been our experience that with the S.K. used, and under a cover of 25 mg. prednisone given immediately before the S.K. infusion is started, major and even minor side-effects are exceptional—and definitely not more frequent than when the titrated priming dose is given. The third prerequisite for the routine use of a high dose is that the S.K. given in large excess to the opposing materials should not inhibit activator formation or plasmin activity in the clot. In all our patients a high plasmin and activator content was found in the first hour of therapy and the same incidence of thrombolysis in acute peripheral arterial occlusions was obtained independently whether the initial dose was calculated individually (18 of 23 arterial occlusions) or standardized at 1,250,000 units S.K. (12 of 15 arterial occlusions). The standard dose was so chosen as to minimize the risk of bleeding.

Standardization of the Maintenance Dose

In previous trials (Verstraete *et al.*, 1964b) we came to the conclusion that maintenance of a high plasma activator level (as measured on unheated fibrin film) and nearly complete depletion of circulating plasminogen are associated with arterial clot dissolution in 78% of patients, provided that the occlusion was not older than 72 hours and that the thrombolytic therapy was pursued until thrombolysis occurs or for three days' continuous treatment. A low circulating plasminogen level during S.K. administration being associated with a high incidence of thrombolysis, it was our purpose to maintain a state of nearly complete plasminogen depletion (that is, below 5% of the normal value corresponding to 250 units/ml. plasma) throughout the thrombolytic treatment. The plasminogen assay used was the method of De Vreker (1965).

After administration of the initial dose the amount of S.K. required to reduce the plasminogen level below 5% of the normal value, and to maintain this reduction for several days, was found to be independent of the T.I.D.

The Chart demonstrates that the minimum perfusion rate of S.K. must exceed 70,000 units/hour in order to maintain the plasminogen under the 5% level. As a perfusion rate of approximately 100,000 units/hour was adequate in all our

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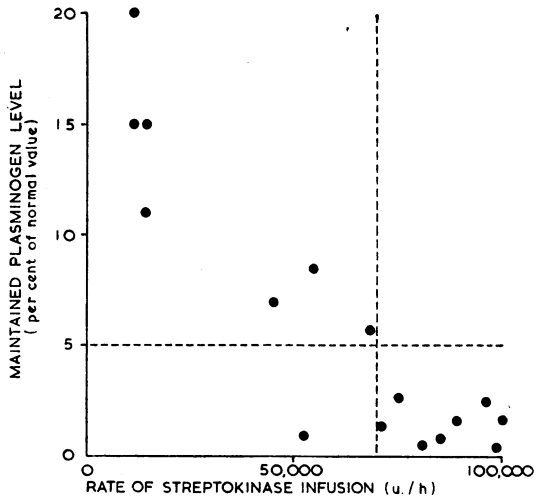
patients to maintain the plasminogen at this level, we selected this amount of S.K. as the standard maintenance dose.



Relation between rate of streptokinase infusion (units S.K./hour) and the plasminogen level maintained in plasma.

Results with the Standardized Dosage Scheme

Fifteen patients with peripheral arterial occlusions of no more than 72 hours' duration were treated according to this standardized scheme. In all patients the S.K. was administered using the standard scheme for the initial dose (1,250,000 U.) and the maintenance dose (100,000 U./hour). The initial dose was perfused intravenously over a period not exceeding 30 minutes. This large initial dose was well tolerated in all patients ; 25–50 mg. prednisone was given as cover.

The variations in the plasminogen level during the administration of S.K. by the standard dosage scheme are summarized in Table I. From this table it is apparent that the plasminogen level was maintained below 250 units/ml. from the second hour of infusion onwards in most patients tested. On three occasions a plasminogen level above 250 units/ml. was noted ; in each case this was due to an accidental decrease of the infusion rate ; when this was corrected the plasminogen level again fell below the 250 units/ml. level.

TABLE I.—*Variations of Plasma Plasminogen Level During Streptokinase Administration (Standard Dosage Scheme)*

Hours after Start	No. of Patients in whom Assay was Performed	Plasma Plasminogen Level (units/ml.)	
		Mean	Extremes
0	11	5,800	3,500–12,000
0–1	10	468	≤50–2,800
1–2	4	70	≤50–90
2–4	5	55	≤50–65
4–8	3	115	≤50–240
8–16	10	95	≤50–440
16–32	9	116	≤50–660
32–64	9	154	≤50–390

Table II summarizes the variations of the whole blood fibrinogen level during administration of S.K. by the standard dosage scheme. The fibrinogen concentrations were measured by the fibrin-polymerization-time-test and expressed in mg./100 ml. of blood (Vermylen *et al.*, 1963). The value of this test for evaluating the coagulation defect during S.K. administrations has been discussed previously (Verstraete *et al.*, 1964a).

TABLE II.—*Variations of Blood Fibrinogen Level During Streptokinase Administration (Standard Dosage Scheme)*

Hours after Start of Administration	No. of Patients in whom Assay was Performed	Blood Fibrinogen Level (mg./100 ml.)	
		Mean	Extremes
0	14	300	142–498
0–1	11	61	≤10–232
1–8	6	33	≤10–57
8–16	6	38	≤10–91
16–32	11	71	25–198
32–64	12	115	52–282

Clot dissolution was obtained in 12 of the 15 occlusions treated with the standard dosage scheme as demonstrated by sudden return of previously absent pulsations. A control arteriography was not performed in all cases, but the clinical improvement was confirmed by this method in nine patients.

As this standardized scheme of S.K. administration has also been applied to a number of patients with coronary occlusions, more experience was gained on the subject of side-effects. In this series there was no evidence of venous thrombosis and no haemorrhagic complications were seen.

Comments

In previous studies evidence has been presented that in the presence of a low concentration of circulating plasminogen the administration of a large amount of S.K. will result in an important level of activator activity without measurable free plasmin activity (Johnson and McCarty, 1959). The standard scheme used in the latest group of our clinical experiments aims at obtaining a high level of circulating activator activity which would activate plasminogen trapped in the fibrin web (Alkjaersig *et al.*, 1959). At the beginning of thrombolytic therapy it has not been possible to avoid an initial phase of hyperplasminaemia with consequent fibrinogen breakdown and the appearance of polymerization inhibitors (Verstraete *et al.*, 1964b). However, after 24–32 hours, provided that the plasminogen concentration remains very low, preventing new formation of free plasmin activity, the fibrinogen level reaches the safe level of 50 mg./100 ml. blood. Therefore it is our opinion that it could be more dangerous to give as maintenance dose to small an amount of S.K. than too much.

In 1959 Johnson and McCarty reported a high incidence of re-thrombosis of occlusions induced in superficial veins by intimal damage when plasminogen-exhausting amounts of S.K. were administered. In our series of patients with spontaneous arterial occlusion no evidence of re-thrombosis was obtained.

The main disadvantage of a high standard dose of S.K. is the prohibitive price of the product. For this reason we have limited our clinical trial almost completely to patients with occlusions of peripheral arteries. Considering the financial implications, one could to some extent decrease the present cost of S.K. therapy by giving as standard initial dose 750,000 U. S.K. and a maintenence dose of 80,000 U. S.K./hour. With this substantial decrease in priming dose, 9% (20/231) instead of only 3% of the overall population would have an insufficient initial dose. As it appears that a maintenance dose of 70,000 U. S.K./hour is the lower limit required to maintain the plasminogen below 5%, one could consider it satisfactory to limit the security margin and give 80,000 U./hour instead of 100,000 U./hour. Other vascular occlusions, such as deep venous thrombosis, present a less critical situation and were not included in this trial.

Steroids were administered prior to the S.K. infusion in the hope of preventing the occurrence of an occasional pyrogenic reaction. We believe that the rare incidence of this side-effect should not deter from using this potentially limb-saving drug.

The main hazard of the therapy is haemorrhage, as all S.K.-treated patients are potential bleeders during the first 24–32 hours of thrombolytic therapy. Bleeding does not occur unless traumatic procedures such as surgical operations or venepunctures are performed, or potential bleeding conditions are present: thus patients with active peptic ulceration or with diastolic hypertension should not be subjected to S.K. treatment.

An important advantage of a standard administration scheme of S.K. is that the laboratory control is greatly simplified and is not even essential. This burden of control, and the lack of good assay systems, have in the past been major problems in fibrinolytic therapy. The required facilities for plasminogen determinations and other assays are not necessarily present in smaller hospitals and the accuracy of laboratory assessments only occasionally performed may be questioned.

Using intense and prolonged S.K. administration, properly conducted according to the criteria mentioned above, pulsative blood flow was restored in 12 of the 15 treated cases. In nine cases where the pulsative flow was restored, arteriographic series were taken before and after the S.K. administration. In all of them clearing of the main artery was found.

It was hoped that rapid restoration of blood-flow would prevent irreversible tissue necrosis. However, in some cases, though pulsative blood flow was restored, amputation of at least some part of the involved extremity was necessary. Therefore any modification of S.K. treatment which restores the blood-flow more rapidly could be of crucial importance. This might be a further reason for presenting a standard administration scheme for S.K., rather than a scheme varying according to the patient, where the necessary laboratory controls would delay the start of S.K. administration.

We are aware that this new administration scheme may result in very widespread use of this material in hospitals. At present, however, only a high incidence of thrombolysis *in vivo* by streptokinase administration has been proved. Comparative studies of the mortality rate, limb amputation rate, and the incidence of recurrence with S.K. therapy and other forms of treatment of recent peripheral arterial occlusions are not available at this time. This information should be available before the widespread use of S.K. can be justified.

Summary

The feasibility and efficiency of a standard administration scheme have been explored, using experience gained from previous experiments and clinical trials with streptokinase (S.K.) as a thrombolytic agent in man. With a set initial dose of 1,250,000 U. S.K. administered intra-arterially or intravenously in less than 30 minutes and a maintenance dose of 100,000 U. S.K./hour for three days, restoration of arterial blood-flow was obtained in 12 of 15 arterial occlusions.

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Exercise Performance and Electrocardiographic Changes as Indices of Effect of Long-acting Nitrates in Angina Pectoris

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Evaluations of anti-anginal drugs are usually based on electrocardiographic changes observed after a standard exercise test. Since there is little correlation between angina and electrocardiographic evidence of myocardial ischaemia (Katz, 1935 ; Russek *et al.*, 1955), the conclusion is often drawn that anginal pain is a poor criterion of the effect of a drug in improving myocardial ischaemia (Russek, 1955 ; Sandler *et al.*, 1963). This is obviously true for drugs acting on pathways of pain transmission. Alcohol, sedatives, tranquillizers, and monoamine oxidase inhibitors may favourably influence angina without electrocardiographic improvement (Russek *et al.*, 1950, 1955). On the other hand, the validity of the electrocardiographic method in identifying effective agents, such as glyceryl trinitrate, is based on the observation that such drugs increase the exercise tolerance (Sandler *et al.*, 1963, Russek and Howard, 1964). Angina and electrocardiographic changes may both reflect ischaemia in a minute area of the myocardium. The choice of method for evaluating less potent long-acting nitrates depends, therefore, on which method is most sensitive and reproducible when applied on a population with angina pectoris.

Most patients with coronary insufficiency believe that they are able to state quite exactly the onset of pain, and often develop pain in their daily life after the same amount of exercise. Whether this reflects coronary insufficiency at identical work loads or is due rather to a psychological reaction to the situation when pain is known to occur has not been settled. By using a Master two-step technique (Sandler *et al.*, 1963) the patients may count the number of circuits accomplished. In the present study exercise was therefore performed on a bicycle ergometer. The ordinary controlled double-blind technique was modified in so far that the patients were told that the drugs had different potency and were likely to delay the onset of pain differently. This was done in order to minimize the placebo effect. The order of administration was of course kept secret. On three consecutive days one hour before exercise a placebo tablet or one of two long-acting nitrates (pentaerythritol tetranitrate and methylpropylpropandioldinitrate) was administered according to a permutation scheme (Kiil, 1960). Methylpropylpropandioldinitrate is synthesized by Apothekernes Laboratorium for Specialpraeparater, Oslo, and marketed as Nitral.

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