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Abstract

The author has described modern thrombolytic therapy of arterial and venous thrombosis and emboli by therapeutic fibrinolysis and other drugs also methods and effects of local and parenteral application of fibrinolysin preparations, dosage, control, indications. Contraindications, side-effects and their treatment with fibrinolysin antagonists and therapy with fibrinolysin combined with anticoagulants and antibiotics are discussed.

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VARIOUS ASPECTS OF THROMBOLYSIS AND FIBRINOLYSIS

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There is no essential difference between thrombolysis and fibrinolysis. The use of these two different words in the literature was necessary for practical reasons. We use the expression "thrombolysis" clinically. The term "fibrinolysis" has been used for the lytic substrates of fibrin *in vitro* by ASTRUP, GROSS and others. It is better used because the blood clotting thrombus can be dissolved by the lysis of fibrin. The so-called mixed thrombus is composed of cellular elements, particularly containing many platelets. Further, these cellular components can hardly be influenced by plasmin (fibrinolysin), or other proteolytic substance. Some problems of lysis with fibrinolytic substances may be solved using radioactive I^{131} streptokinase and by labelling clot autoradiographically. It is also possible to label fibrin by radioactive iodine and to observe the fibrinolysis.

Enhanced "fibrinolysis" is very often accompanied by enhanced fibrinogenolysis. It should be stressed, furthermore, that the clinical hemorrhagic diathesis which we see is not due to lysis of fibrin, but to proteolytic change in the clotted fibrin.

One has noted in several cases associated with operation or delivery that not only is fibrin deficient, but also other important blood clotting factors, e. g., Factors V or VII are altered.

GOETHE has said that the history of a science is the science in itself. Hence I will make a brief description of the history of "fibrinolysis". In the 4th century B. C. HIPPOCRATES had already made observations which could have been related to fibrinolysis. Later, in the 17th century MALPIGHI, and DENIS in 1838, had noted that in some diseases blood would not coagulate. The term "fibrinolysis" as such was first used by DASTRE (1883). NOLF (1905) and OPIC (1911) have written on proteases in serum, TILLETT (1933) on a fibrinolytic substance, MILSTONE (1941) on an agent of indirect effect, CHRISTENSEN (1945) on plasmazymogen (plasminogen) and INNERFIELD (1950) on trypsin. In 1955 TILLETT gave streptokinase intravenously, in 1957 CLIFFTON plasmin intravenously, while SEEGERS

injected "Thrombin E". So besides plasmin (or activators of plasminogens) some other proteases have also been applied to clinical use. TILLETT (1933) was the first to observe that filtrate of some haemolytic streptococci can dissolve human blood clots, but intensive research in this field began only in 1945. SZIRMAI in 1955 published a scheme from which it is very easy to study fibrinolysis. (Table 1)

Fibrinolytic processes can be divided into four phases, viz: pre, 1st, 2nd and 3rd phases. The pre-phase is a study of formation of different activators and inhibitors. The first phase consists of the activation of profibrinolysin, the second of the formation of fibrinolysin and the third of thrombolysis.

As activators of fibrinolysis there are physiological and foreign-body compounds which are of therapeutic use. According to the great Swiss haematologist, R. FEISSLY, who died in January, 1966, polybrenes seem to be excellent activators of fibrinolysis.

Concerning inhibitors of fibrinolysis, we again have two groups as with the activators, i. e., physiological and therapeutic substances. In the second group we have E-aminocaproic acid, inhibitor of soya, cystein and mercaptol + tanolamin, although there are not many data relating to these latter substances. With fibrinolysis and blood-clotting we note the formation of a proteolytic ferment, i. e., thrombin which decomposes fibrin into small units, viz: fibrin-polypeptide. The enzyme of fibrinolysis, fibrinolysin, also decomposes fibrin, but into different polypeptides. Both proteolytic ferments are found in plasma in their inactive pre-phases which are activated by the influence of tissue-and blood-activators.

There are many papers relating to methods of determination of fibrinolysin.

I will now discuss the principal data relating to therapeutic aspects of fibrinolysis.

Treatment by Fibrinolytic Agents

For clinical purposes fibrinolytic agents may be divided into two grups, viz: those used locally and those used parenterally.

In treating patients with these agents, especially parenterally, the following should be taken into consideration:

(1) The mechanism of the effect of the preparation.
(2) The method of effective treatment and of its control.
(3) Indications for treatment at a given time.
(4) Contra-indications.
(5) Possible side-effects, especially haemorrhage and its treatment by fibrinolysin-antagonists.

Table 1 Schema of the Fibrinolysis after SZIRMAI (1961)

		Prophase Activation of the Froactivators	1st Phase Activation of Profibr.	2nd Phase Formation of fibrinolysin	3rd Phase The thrombolysis
Positive factors of the fibrinolysis	Therapeutic	Pyrexal, Adrenalin SK+SD, Chloroform Antidiabetica: Tolbutamid Carbutamid etc ··· (indirect Fibrinolysis-activation by pyrexal nicotinic acid, nicotinic acid+ heparin)		Direct activation of fibrinolysin lysokinase streptokinase staphylokinase urokinase polybrenes	
Activators	Physiologic	Proactivators I. Tissue-activator (Tissue-fibrinokinase) II. Blood-activator Thermolabil→=activator Serum Co. proactivator (urokinase from human urin) milk, tears, etc.	Inactive profibrinolysin = → Plasminogen	Fibrinolysin = Plasmin	Lactoglubulin, Caseine gelatine Hormons: ACTH & STH Thrombolysis → fibrinogen → fibrin → factor V & VIII → prothrombin
Negative factors of the fibrinolysis Inhibitors (-Inhibition of the fibrinolysis)	Physiologic Inhibitors	I. Tissue antifibrinokinase II. Serum-antifibrinokinase		Antifibrinolysin (Antiplasmin) Pancreas inhibitor (=antifibrinolytic action) Cohn. Fr. IV-1, IV-4, V. ACTH, cortisone (?) prednisolone (?)	
	Therapeutic Antidotes	E-aminocaproic acid)=Antiactivator+ antiplasmin) trypsin, kunitz, zinc, Cu } Inhibitor of		sojainhibitor E-aminocaproic acid (antiactivator + antiplasmin) protaminsulfate, trypsin K 1-vitamin, zinc, Cu	

Local Fibrinolytic Therapy

Antibiotics become less useful when applied locally because of the increase of resistant colonies of proteus, pyocyaneus, etc., to antibiotics. However, fibrinolytic therapy using streptokinase or streptodornase becomes more useful. The lytic substance of the steptococcus from which streptokinase and streptodornase are prepared promotes the inflammatory reaction of the organism, because the formation of fibrin and leukocytosis inhibit diffuse infiltration of the tissues. In our clinic for over 11 years we have used streptokinase and streptodornase with good effect in the toilet of wounds. Unfortunately it occasionally induces meningitis, haemothorax with empyema, etc,

If the expected effect is not obtained, some foreign body like bits of bandage or cotton may be found inhibiting fibrinolysis. It is also noted that mucoproteins and fibrinous or collagenous tissues cannot be dissolved by streptokinase-streptodornase. It is of importance that the enzymes really come into contact with tissues directly. Therefore, it is necessary to remove the tissue by aspiration of other means before the application of fibrinolysin every 24 hours.

Parenteral Therapy

Animal experiments do not give uniform results with parenteral therapy, because the blood of some kinds of animals does not react with fibrinolysin in the same way as in the human. The early preparations of fibrinolysin were not pure enough for clinical use. They often provoked fever and shock-reactions when given parenterally. In more recent years better products have been produced making parenteral treatment more feasible (Reports by FLETSCHER, JOHNSON and later of ENGLER, CHRISTOPHER, MORETZ, MOSER and KENNETH, etc). These latter authors discuss the successful treatment of thrombosis and embolism by intravenous injections and infusions.

Intramuscular and peroral or sublingual fibrinolysin therapy with early products did not give satisfactory results. Only in the past few years have the good effects like those reported by Innerfield in 1958 been obtained.

Intravenous fibrinolysin therapy is a new and efficient way for the treatment of thrombosis and embolism. Fibrinolysins should not be used instead of anticoagulants. Fibrinolysins do not replace the dicoumarin and indanedione drugs in this regard, nor do they inhibit the expansion of a thrombus unlike heparin. They dissolve thrombus on intravenous injection due to fibrinolytic activity. This fibrinolytic ferment system

attacks not only fibrin and fibrinogen, but also inactivates factors V, VIII, and particularly prothrombin (Factor II). By the proteolysis of fibrinogen with the enzymes an antithrombin is formed. This had a strong effect. The production of this antithrombin is of great importance in fibrinolytic therapy.

Many publications on experiences with fibrinolytic therapy exist, but I will mention here only some results of GROSS, HARTL, KLOSS and RAHN, and of our own with the material of I and II Streptase of BEHRING-WERKE, Germany, (1962—1964).

1. *Preparations :*

Preparations which act as activators of fibrinolytic systems when given intravenously may be divided into two groups according to their actions :

1. Fibrinolytic agents acting directly *in vivo* and *in vitro.*
2. Those acting indirectly.

A. The direct acting substances may be divided further into :

a) Streptokinase, an activator of the fibrinolytic systems and its end-product.

b) Active plasmin resp. fibrinolysin. This may be isolated from human plasma by the help of streptokinase.

The new fibrinolytic preparations still contain some streptokinase, but it is more purified to such an extent that febrile reactions are rarely encountered and if so, are harmless. Normal human urine also contains a substance having fibrinolytic activity, i. e., urokinase. It is, however, still in an experimental stage and no clinical data are available at the present time.

B. *Substances having indirect fibrinolytic activity*

Substances belonging to this group show no fibrinolytic activity *in vitro*, but they cause *in vivo* activation of fibrinolytic systems by a still unclear mechanism. These substances include

(a) nicotinic acid.
(b) adrenalin.
(c) lipopolysaccharide from some bacteria, e. g. pyrexal isolated from salmonella equi.
(d) Oral antidiabetic drugs, e. g., tolbutamide and carbutamide.

In connection with the indirect active fibrinolytic agents, several authors have reported good results using nicotinic acid treatment which induces activation of the body's own fibrinolytic system. This preparation, already in use here in our clinic for the treatment of other diseases, is now

found to be useful in the treatment of thrombosis and embolism. It is particularly useful because it is unaccompanied by dangerous side effects.

I have wide experience with the preparation called "Solcosal". It contains fibrinolysin activating nicotinic acid and also vitamin P (Rutin) for the protection of tone and permeability of the vessel-wall. Besides these, "Solcosal Forte" contains also 1,000 units of heparin per 5 ml. The addition of heparin supports the fibrinolysin-activation and enhances the effect of nicotinic acid on the circulation. At the same time heparin possibly inhibits the further formation of thrombus.

2. *The dosage of direct fibrinolytics*

In treatment with streptokinase some patients show increased resistance and others require lower dosage. Hence the determination of streptokinase tolerance is important before the commencement of therapy proper. we have several different methods for the determination of individual dosage, e. g. the plate test of ASTRUP, and MULLERTZ, the methods of MARBET. of WITTE and DRINBERGER, of FISCHBAUER, etc. Among these the thrombelastograph is the best method for such determination. The method is as follows: In a cell of the thrombelastograph 0.23 ml of the patient's oxalated plasma to be tested is taken. Then 10 units are added, while coagulation after adding calcium is checked. If fibrinolysis is not so powerful, though the greater part of fibrinogen is destroyed, a clot will be formed. In such a case the thrombelastogram shows the form of a pear. By observing clot formation in 3 cells containing different concentrations of streptokinase it is possible to determine how many units of streptokinase are necessary to result in a complete suppression of clot 10 minutes after adding calcium. This number is the so-called "streptokinase tolerance" according to FISCHBAUER, as applied to 0.23 ml of plasma. The total amount of streptokinase to be injected into the patient should be obtained by multiplying the value about 10, 000 times, but experience has shown that this dosage of streptokinase is not adequate to obtain a beneficial effect *in vivo*. Hence the "streptokinase tolerance" must be multiplied by 30, 000 instead of 10, 000. This will provide an effective therapeutic dosage. With this method an expert worker takes a total of about 20 minutes, while in contrast, with the plate-method, he may require several hours for obtaining the same result.

The determination of the individual dosage before treatment is very important (MARX, etc.). According to SHERRY and his associates, 5 % of the population show a significant level of antistreptokinase.

According to KOLLER and others the streptokinase tolerance may vary

from 2 to 76 units and it can reach 720 units after streptokinase treatment. Even more streptokinase will be needed for a second treatment to reach effective lysis. The duration of therapy is also different from case to case. It is essential to perform individual treatment in each case according to his streptokinase tolerance.

I will not quote different theoretical and practical data concerning this problem, but experience has shown that clinical results give the best information for the duration of streptokinase application. Threatment over a period of 12 hours is recommended, but according to SHERRY and his collaborators it may be continued up to 32 hours. The dose per infusion could be decreased in the second infusion in comparison with the initial dose of 50, 000, but it should not be less than 20, 000—30, 000 units. It is important after such fibrinolytic treatment to follow with anticoagulant therapy, first using heparin and later oral anticoagulants. Some authors, e. g., GROSS, HARTL, KLOSS and PAHN, separate compatibility and clinical results. According to clinical experience 40, 000—100, 000 units of fibrinolysin per infusion gives the most successful results. The above-named authors used in general 40, 000 nnits in 400—500 ml of glucose or saline solution, or in smaller dosage, 200—250 ml, if necessary. The duration of treatment is about 6 days and not more than 5—6 infusions, because, with aging of the thrombus, lysis becomes more difficult and the host may be sensitised with antibody formation.

GROSS, HARTL, KLOSS and RAHN, and ourselves, made the following investigations at the beginning and at the end of infusion therapy : -

1) Thrombelastography.
2) Thromboplastin time.
3) Determination of Factor V.
4) Thrombin coagulation time.
5) Fibrinogen determination.
6) Euglobulin lysis time, and
7) Fibrin plate test (according to ASTRUP and MULLERZ). Besides these techniques some authors also carried out fibrinogen electrophoresis.

In some patients it is desirable to check also antistreptokinase and antistreptolysin values. BEHRING-WERKE, Germany, recommend the so-called streptokinase resistance test for obtaining better scientific therapeutic information. We have many data available on succesful treatment with fibrinolysin in cases of thrombosis and embolism, e. g., pulmonary embolism, cerebral thrombosis, sinus thrombosis, thrombophlebitis and phlebothrombosis, etc. The earlier experiences in this field were published first by twelve American authors in 1959 in the Journal of Angiology (Vol.

10, 244). These authors used the fibrinolytic preparation, actase.

Mention must be made of Varidase (Lederle/USA and in Germany Cyanamid GmbH, Munich) and the excellent fibrinolysin (human), LYOVAC von MERCK, Sharp and Dohme Inc., RAHWAY, N.J. (USA). The latter is made by activating a fraction of human blood plasma with streptokinase. The human plasma is fractionated by the COHN ethanol method. One MDS unit of fibrinolysin Lyovac is the quantity which is sufficient to dissolve within 10 minutes a clot of about 5 mg. weight under constant conditions of PH, temperature and molar concentration. We have also other valuable and excellent preparasions like Streptase of Behring in Germany. In haemorrhagic disorders and including afibrinogenaemia fibrinolysin therapy is contra-indicated.

3. *Indidations for fibrinolysin therapy :*

According to our present-day knowledge, the indications for fibrinolysin therapy are as follows : —

1. Acute venous thrombosis. Several authors have reported dissolution of venous thrombi in arms and legs when fibrinolysin therapy is used.

2. Fresh pulmonary emboli.

3. Arterial thrombosis and embolism. As reported by KOLLER and other authors, not only is the success of therapy dependent on the age of the thrombus, but also on consecutive necrosis of the infarct. The occlusion of arteries or veins in the brain for some minutes gives rise to irreversible damage—similarly in coronary thrombosis after two hours and in the arteries of the extremities after 6 hours. After these periods the infarct does not recover even though the embolus is dissolved. Some authors have reported the dissolution of microthrombi in the vicinity of the infarct, thus preventing further tragedy.

It is possible to commence fibrinolytic therapy some hours after the formation of the infarct. However, several authors (AMBRUS, FISCHBACHER, JÜRGENS, MARX, FLETSCHER, etc.,) reported rather poor response to fibrinolysin therapy in the treatment of arterial thrombosis and emboli under these conditions.

Contra-indications :

Contra-indications may be divided into two categories :

(a) Those in which fibrinolytic therapy is not effective and

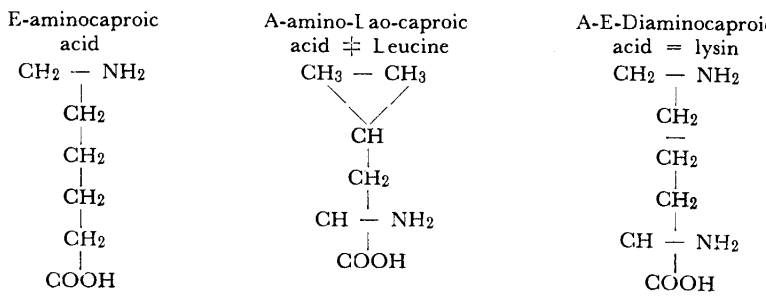
(b) Those in which fibrinolytic therapy could be dangerous.

The first group contains cases with thrombosis and emboli older than 3 days and the second group those with ulceration, wounds, operative procedures and haemorrhagic disorders. Fever associated with coronary

thrombosis or circulatory disturbance associated with pulmonary emboli are not contra-indications to therapy. Side effects, especially haemorrhages, can be treated with fibrinolysin antagonists. Modern therapeutic fibrinolytic therapy, especially of thrombosis and emboli is relatively harmless. As already pointed out, the most important and dangerous side effect seen in these cases is haemorrhage. Complications such as high fever have seldom been encountered in recent years. With therapeutic doses of fibrinolysin, fibrinogen disappears as in afibrinogenemia, but Factors V, VIII and prothrombin are acarcely influenced. A severe decrease in platelets does occur. If, in spite of all measures taken, a haemorrhagic tendency appears, patients should be treated with an excellent fibrinolysin antagonist, viz. E-aminocaproic acid in dosage of 30 gr. per os or several grams intravenously. This treatment will effectively inhibit haemorrhage in a few minutes.

E-aminocaproic acid is in the first place an activator and in the second an antifibrinolysin. The mechanism of action is according to the opinion of several authors a competitive inhibition. E-aminocaproic acid as shown in Fig. 1, is a physiological amino acid. This was discovered by Japanese investigators and first used by my friends T. ABE and K. HAYASAKI, T. ABE and K. SATO, etc. In Europe P. de NICOLA, SOARDI, GIBELLI, KOLLER and SZIRMAI were the first to work with this compound. Besides E-aminocaproic acid and some other aminoacids we have the inhibitor from pancreas (TRASYLOL-BAYER in Germany) and soya inhibitor. KLINE, SHERRY, FLETSCHER, GROSS, HARTL, KLOSS and RAHN reported on side effects of fibrinolysin infusion as follows: headache, painsin joints, shivering, restlessness and hypotonia. According to thc experience of these authors, well controlled fibrinolytic therapy is no greater risk in relation to haemorrhage than is the case with anticoagulant therapy. However, it must be stressed again that thrombolysis by fibrinolysin does not work in the same way as in thrombosis. Therefore, it is very important to combine fibrinolytic therapy with very careful coagulation controls by using anticoagulants.

Fig. 1



Similarities of fibrinolysin antagonist, E-aminocaproic acid to leucine and lysine.

Our Experiences :

The author has made researches and treatment since 1961 with Varidase or fibrinolysin Lederle. So-called "Buccal" tablets (1 Tabl. = 10, 000 U. streptokinase and 2, 500 U. streptodornase, bottles with 25, 000 U from these 20, 000 U. streptokinase, 5, 000 U. streptodornase for injections and different buccal tablets). These compounds obtained from Lederle/USA and Lederle Cyanamid/Munich, were also used for research purposes. Broad outline of practical and experimntal data follow.

Some of this work has been reported at the 8th Congress of the European Society of Haematology in Vienna (1961), to the World Congress for Gynaecology and Obstetrics in Vienna in 1961, the Congress of the Swiss Society of Haematology in Lugano in 1962, the Congress of the European Society of Haematology in Strasburg in 1965 and in some publications (1955, 1956, 1962, 1963 and 1964). I gave some lectures at the Universities in Würzburg, Zürich, Madrid, Helsinki, and some American universities (1965), and these data will be described briefly here.

Varidase Buccal-tablets were given to 195 patients. Among these 127 patients had phlebitis and thrombophlebitis of different aetiologies (rheumatic, traumatic, and infectious). 51 patients with chronic tonsillits, pharingitis and laringitis, and 17 patients with different skin infections were treated. Also treated were 10 cases of repcated furunculosis and 25 patients with thrombotic states, such as varicose ulcer.

Included are all those treated up to 1965. Treatment varied from case to case and some patients have also been treated in combination with other drugs. In Table II are brief descriptions of some cases. By comparison, data obtained by expcrience in the past twenty years with other treatments of the same diseases are poor. Among 127 cases of thrombophlebitis and phlebothrombosis 122 patients were successfully treated with medicaments. Quicker healing, resolution of post-thrombotic oedema and quicker reduction of inflammation were obtained. The patients treated in combination had butazolidin, phenylenedandione and dicoumarin preparations, heparin, hirudoid, cortisone and antibiotics, Naturally, strict indications and contra-indications were followed. Controls of blood-clotting factors and liver function, etc., were made. In 44 patients with pharyngitis laryngitis, and a variety of forms of tonsillitis, also had very good and quick recovery. Patients who have been sick for a long time should also be treated. Quick healing was noted in 8 patients with celluli-

tis, 7 of 10 patients with furunculosis and 21 cases with varicose ulcer, and other 8 post-thrombotic states.

Together with the results of my later experiences it could be said that Varidase (Streptokinase-Streptodornase) treatment is very effective in inflammatory thrombophlebitis and phlebothrombosis, varicose ulcer and thrombotic states. It may also be added that colleagues have had similar results when advised by me.

My experiments with fibrinolysin plasmin and blood-clotting factors including platelets in healthy and sick persons are reported as follows:

METHODS, MATERIALS AND PATIENTS:

Examinations of activators and inhibitors have been made using the method of DUCKERT and KOLLER, as well as our own method published elsewhere. Platelet determinations were made using the method of SPITZ, FEISSLY and LÜDIN. For determining the effect of fibrinolysin on blood clotting factors we used oxalated plasma at 37°C in blood clotting thermostat as devised by the author in 1953. The plasma was incubated with 400 units/ml. fibrinolysin at 37°C. in the thermostat. At varying lapses of time blood samples were taken. The coagulant fibrinogen and the physiological activity of blood-clotting factors in experimental solutions or in the patient's blood have been observed. The method described by FONIO using citrated plasma was used for platelet determinations. For the examination of the degree of fibrinolytic effect (1) citrated plasma from 8 healthy women (not pregnant) between the ages of 25 and 30 years were used as a standard. Repeated investigations were made on these during a period of 10 days. (2) Plasma from eight normal people having no haematological disorder were used on the second day of the period. (3) Plasma from seven patients with acute venous thrombosis prior to treatment with drugs was investigated. (4) Plasma from 6 patients with thrombocytopoenia WERLHOF's Disease) were investigated.

RESULTS

In the experiments with normal bloodplasma the formation of fibrinogen war completed by 27 minutes. Besides fibrin formation we also checked plasma Factors V and VII, both of which showed initial activation at 65—100 minutes. Thereafter they had lost their physiological functions. The data are consistent with those reported by JUNG, DUCKERT and KAPELLER. Factors VII, IX and X are stable, and showed no change in plasma or in serum even in thepresence of fibrinolysin. Prothrombin was diminished by 50 to 60 %. I also found an increase in heparin-like antithrombin due, according to JUNG and DUCKERT, to reduction in fibrinogen. The number of platelets dd not change significantly, as was

revealed by checking the sediment of the oxalated plasma incubated with 400 units/ml. of fibrinolysin at 37°C.

Experiments with blood and plasma taken at this time revealed slightly reduced levels of platelet numbers and prothrombin initially, but the level of antithrombin was twice as high as previously.

My earlier experiments in 1961—1962 indicated that this could be explained by an increasein fibrinolytic effect and in the tendency to haemorrhage.

In 7 patients suffering from acute venous thrombosis there was no fibrin formation at the beginning of treatment during 38 minutes. Factor V needs 80 minutes and AHG 65 minutes on an average for the loss of their physiological functions. Prothrombin was reduced to a level of 60—70 %, but antithrombin inereased during a period of 38 minutes by about the same rate as is seen in healthy persons after the fibrinolysin effect. We thought that we would have had a slower value similar to thrombosis without fibrinolysis effect. The numbcr of platelets was not significantly changed.

In the experiment with blood from those patients suffering with thrombocytopenia (Werlhof's disease) fibrinolysin effected a quicker reduction in fibrinogen level after about 16 minutes, especially marked in 4 cases. Factors V and VIII had also lost their physiological function after 40—80 minutes. Prothrombin was reduced by 65—73 % and the quantity of antithrombin was twice as high as in normal plasma. The low platelet count of the patients with thrombocytopoenia was further reduced by 20 % in 4 patients and by 15 % in 2 further patients, by the effect of fibrinolyin. All the experiments were made under strict aseptic conditions using the method of FONIO with citrated plasma in reagent tubes. The decrease in thrombocyte count by fibrinolysin was as rapid as in healthy persons on the second day of the period and as in the patients with thrombosis.

DISCUSSION

My experiments have shown that there are differing fibrinolytic effects on clotting factors and on antithrombin formation in healthy persons during and after the pcriod of thrombocytopoenia and thrombosis. This effect is very important especially during the period of thrombocytopoenia in relation to the activation of fibrinogen, factors V and VIII and the partial activation of prothrombin becoming more rapid, while the antithrombin is significantly higher. By some thromboses fibrinolytic

effect is also decreased by the already-named factors, but the antithrombin level is not always less than normal.

According to FONIO, the effect of fibrinolysin can be measured by the degree of retraction of fibrin clot and by the degree of reduction in platelet count. These experiences also seem to confirm my observations that thrombocytopoenia and during the period, fibrinolytic decrease is more rapid. It may be worthwhile mentioning thc experiments of A. KAPERT on fibrinolysin and blood clotting. He examined before and during treatment at varying times the blood of 39 patients (22 ♂, 17 ♀) Middle age: 59, 5 yearr (43—72 years old).

These patients suffered from the following diseases:

Nine patients had obliterative arteriosclerosis (Stage II-III) of the extremities of brain vessels.

Eight patients had acute or sub-acute thrombosis of femoral and carotid arteries.

Eight patients had infarcts of heart and post-infarction states.

Two patients had "myopathia cordis".

Two patients had pulmonary emboli.

Two patients had thrombophlebitis and phlebitis of varicose veins.

Four patients had post-thrombotic syndromes.

Six different patients had other diseases.

All these patients were divided into three groups, viz. A, B and C.

Group A: Peroral application 3 times/day, 1 or 2 dragees. Two patients were treated with mean daily doses of 100 mg. Duration of treatment was 3—4 weeks. During the trial time 12 patients also took Dicoumoral (Marcumar).

Group B: Parenteral administration to 12 patients. Injections of 100 mg. i. m. twice daily in 6 cases, 3 times daily in two cases and once daily in one case. The mean daily dose was 200 mg. Duration of treatment was 8—10 days.

Group C: Patients were treated with rectal application as suppositories, 100 mg of effective elements, 200 mg, once in the morning and also in the evening, per day. Duration of treatment was 8—10 days.

During the oral (100 mg per day) and reetal (200 mg per day) therapy he observed marked reduction of euglobulin-lysis time. With both forms of application a good effect was observed in 30% during treatment. Nearly the same effect qualitatively and quantitatively was obtained with parenteral application of 100—200 mg per day. With qualitative technique (total-lysis of plasma clot or total-blood) one has only few really positive

reactions. Examination of blood-clotting (method of LEE and WHITE, test of heparin-tolerance, test of thromboplastin-tolerance) have shown measurable effects which have little anticoagulant action by all forms of application. The prothrombin index was not significantly influenced. The reactions observed in the test of heparin-toleranee using the oral application are very interesting.

Fibrinolysis in Paediatrics :

In general, all that has been mentioncd above about fibrinolysis and thrombolysis is applicabte to paediatrics, although the dose has to be modified as in all other fields of medicine. Preparations of fibrinolysins are used in various fields of paediatrics such as surgery, oto-rhino-laryngology, dental surgery and treatment of accidents.

Successes have been reported by several authors in the treatment of sagittal sinus thrombosis of the new-born with streptase/Behring. Good results have also been reported in post-operative mesenteric occlusion of veins using Streptase and Varidase and in adults with Varidase, and in arterial or central venous thromboses after accidents both in adults and children with Streptase and Varidase.

In 1962 at a meeting of paediatricians in Leipzig, KAKDLER reported on the treatment of purulent meningitis with streptokinase-streptodornase. He observed marked amelioration of the thick cerebro-spinal fluid using Varidase by intrathecal or lumbar application. The thick cerebo-spinal fluid was thinned by Varidase which makes it possible to obtain C. S. F. by puncture. As the C. S. F. is liquified by Varidasse very quickly it is of great help in treatmcnt with antibiotics which are made to disperse quickly. Four doses of 10,000—15,000 units are recommended for newborn children and 20, 000—25, 000 units for little children. One makes a puncture 6 hours after the application and the thin C. S. F. can be released. It is possible to give immediately another instillation of Varidase. The Varidase can be continued for a week. Generally, treatment with Varidase is combined with antibiotic treatment.

KOHNLEIK also describes the use of Varidase in osteomyelitis (1962). He recommends the use of Varidase-Buccal especially in chronic osteomyelitis in order to dissolve fibrin around the inflammatory focus, thus, making it easy for antibioties to permeate into the focus. By using broad spectrum antibiotics sasisfactory healing was hastened in the patients treated with Varidase.

The number of cases of chronic osteomyelitis increased from 20—40% in combined treatment with Varidase. Complete healing of acute osteo-

myelitis in the era before antibiotics was 8 %, 64 % during the penicillin period and 76 % with wide spectrum antibiotics only.

MAPPES and VOLK reported also on general and local antibiotic long-term treatment of post-thrombolytic osteomyelitis of several cases in adults and children. He discussed the treatment of the disease with Varidase in cembination with Ledermycin. According to MILLER, GODFREY, MILTOK, GINSBERQ and PAPASTRAT who reported on their clinical experiences with Buccal Streptokinase treatment with Buccal Varidase effects a more rapid reduction of oedema by quick dissolution of fibrin sediment resulting in suppression of the inflammatory process. Varidase Buccal could also be used for prophylaxis of oedema and is very helpful in operations on the face and mouth. The oedema inhibits wound-healing both in adults and in children and the application of Varidase Buccal in combination with antibiotics promotes wound-healing. Thus Varidase is useful in a variety of conditions, viz. abscesses, haematoma, oedema (post-operative and post-traumatic), thrombophlebitis, various infections, operations of all kinds, amputations, etc.

MANNEL reported the fermentative dissolution of necrotic tissues by Varidase. According to him, Varidase Buccal ameliorates the application of Varidase because of its optimal effect and because it is simplest in the way of application.

But already in 1958 INNERFIELD reported at the Meeting of the American Medical Association that both in adults and children Varidase reduces the duration of the inflammatory reaction of patients by its Buccal application. The human organism reacts to trauma with an in flammatory response so as to localise the various toxins.

Besides these, experimental observations revealed that the Schwartz-mannphenomenon is inhibited by Varidase. Clinical examination shows that the tuberculin reaction is largely suppressed by Varidase. In patients with urticaria, contact dermatitis and bronchial asthma their allergic symptoms were improved by the buccal application of Varidase.

Varidase also proved to be effective for periorbital oedema, haematomas and ecchymosis due to trauma of face and head, acute inflammation of joints and oedema following injuries and in thrombophlebitis inrelation to operations. Besides investigatiog the clinical value, we have made some experiments on animals with Buccal Varidase in combination with antibiotics in the treatment of experimentally induced abscesses and cellulitis. Among these observations a marked effect was obtained on staphylococcus infection, although infections were often multiple.

Forty-eight hours after the application of Varidase Buccal (1 tablet

every 4 hours), the inflammatory focus showed a tendency to localisation of purulent exsudate so that it was easily removed by incision and drainage. In acute infections of the respiratory tract the sputum was lipuified and coutd be coughed up very easily. Chronic bronchitis showed an increase in weight, improved feeling of well-being and a better sleep record.

WEGNER in Munich reported on the possibility of avoiding post-operative complications in plastic surgery: post-operative haemorrhage, haematoma and oedema. For many years these post-operative complications were a big problem in plastic surgery, esrecially in children, and it was very difficult to avoid them in spite of careful operations. Therefore, Varidase treatment is very important in this field. It promotes physiological phagocytosis and regeneration in the healing-process of wounds by dissolution of fibrin, by the resorption of the viscous exudates and by the diminution of capillary bleeding and venous stasis.

HEIDSIECK and GABKA reported in 1962—1963 on the application of Varidase in thc field of dental surgery in both children and adults. In this field extraordinarily good effects were observed in the cases of infection treated with Varidase, especially when combined with antibiotics. About one half of the cases treated with Varidase showed very puick amelioration of symptoms by the sccond day of treatment.

BETHGE, HORATZ and STURTZBECHER reported on the intrapleural use of streptokinase-streptodornase in post-operative empyema of adults and children. They treated 60 patients with post-operative empyema with Varidase. By adequate application of Varidase they could successfully inhibit the formation of fibrin, blood clots and the purulent process. Those already formed could be dissolved. Thus an excellent effect was observed in 32 cases out of 60 patients. Four teen showed moderate improvement and there was no recognizable effect on the remainder. In the cases refractory to treatment they did not find that the streptokinase-streptodornase was of inferior quality. Hence its ineffectiveness is probably due to some other factor.

EAGLE reported on Varidase Buccal treatment of oedema in the oto-rhino-laryngology field both in adults and children. The application of ferment-preparations obtained since 1949 showed a very good effect when given by local, intravenous, intramuscular and oromucal routes in dental extractions, tonsillitis, purulent otitis media, haematoma of the tongue and various kinds of dermats.

BLAHA and WORN reported on the fermentative breakdown of extrapleural and intrapleural haemothorax by Varidase. Its good effect was shown in most cases when the haematoma di ssolved after one or two

injections.

Many other excellent papers and books have been published on fibrinolysis in the last decade, but this paoer may serve as a brief summary of our up-to-date knowledge in this field of study.

SUMMARY

The author has described modern thrombolytic therapy of arterial and venous thrombosis and emboli by therapeutic fibrinolysis and other drugs also methods and effects of local and parenteral application of fibrinolysin preparations, dosage, control, indications. Contraindications, side-effects and their treatment with fibrinolysin antagonists and therapy with fibrinolysin combined with anticoagulants and antibiotics are discussed.

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