Thrombolytic therapy: long-term enhancement with oral agents

Effect of treatment with combined phenformin and ethyloestrenol on the coagulation and fibrinolytic systems

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In certain diseases, such as arteriosclerosis, diabetes mellitus, and young female arteritis, the fibrinolytic activity in the blood tends to be abnormally low (Fearnley, 1965; Isacson and Nilsson, 1970), and this deficiency has been regarded as a contributory cause of the vascular lesion in these conditions. Isacson and Nilsson (1972) have recently shown that the majority of patients with idiopathic venous thrombosis have a decreased plasminogen activator content in the vein walls and/or a defective release of plasminogen activator from the vein walls. It is thus apparent that a substance or combination of substances capable of raising the fibrinolytic activity in the blood and the vessel walls would be a useful prophylactic. Fearnley and coworkers (Fearnley *et al*, 1967; Fearnley and Chakrabarti, 1968) have reported the use of phenformin combined with ethyloestrenol to stimulate the spontaneous fibrinolytic activity in the blood and to suppress platelet adhesiveness and the fibrinogen content. We considered it of interest to investigate the effect of this combination not only on coagulation and fibrinolysis in blood but also on the fibrinolytic activity of vessel walls.

Our material consisted of nine healthy volunteers, all men, aged 19-20 years. They received 100 mg phenformin plus 8 mg ethyloestrenol daily for 30 days. Blood samples were obtained on each of the last three days before the beginning and again on the last two days before the end of the trial. Biopsy specimens from superficial arm veins were taken the day before and the last day of the trial. Two new methods for the determination of fibrinolytic activity of the vein walls were used, namely, (1) the fibrinolytic activity occurring after venous stasis of the arms for 20 minutes in the way described by Nilsson and Robertson (1968), and (2) the content of plas-

minogen activators in the vessel walls in biopsy specimens from superficial arm veins with Pandolfi's modification of Todd's histochemical method (Pandolfi *et al*, 1967, 1968, 1969).

Treatment with combined phenformin and ethyloestrenol invariably suppressed the mean fibrinogen content (Table). All the other coagulation factors studied remained unchanged. Platelet adhesiveness decreased in seven and increased in two. The fibrinolytic activity in the circulating blood, as determined in resuspended euglobulin precipitate on unheated fibrin plates, increased slightly. These findings are in agreement with those of Fearnley. In addition, we found the combination to increase the plasminogen content and to decrease the α_2 macroglobulin. No change was found in the content of any

	Before	After
Platelet count (μ l)	205 000	207 000
Platelet adhesiveness (%)	33	23 ¹
Thrombin time (3 NIH U/ml-sec)	21	21
P & P (%)	88	96
Factor (%)	89	97
Factor VIII (%)	97	99
Fibrinogen (g/100 ml)	0.25	0.20 ²
Plasminogen (%)	100	136 ³
Spontaneous fibrinolytic activity on unheated plates (resusp. euglob. prec.-mm ²)	39	63 ¹
Fibrinolytic activity on unheated plates during venous occlusion of the arms (resusp. euglob. prec.-mm ²)	347	328
Urokinase inhibitors (%)	132	120
Antiplasmin (%)	107	113
α_2 macroglobulin (%)	127	112 ³
FDP (mg/100 ml)	0	0

Table Mean values for coagulation factors and fibrinolytic components before and after administration of phenformin combined with ethyloestrenol for 30 days

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The level of significance is 0.01 < P < 0.05¹; 0.005 < P < 0.01 P < 0.005³

of the other inhibitors of fibrinolysis. No fibrinogen degradation products were detected.

The treatment had no effect on the normal increase of the fibrinolytic activity during venous occlusion. This indicates that the drugs did not interfere with the release of the plasminogen activator. Of interest is that the combination caused a significant increase of the plasminogen activator content of the vein walls. This indicates that the combination stimulates the synthesis of the plasminogen activator in the vein walls.

In the coagulation and fibrinolytic systems, then, the combined treatment produced changes tending to counteract the development of thrombosis.

We have now started to give this combination to 26 patients with idiopathic recurrent venous thrombosis and with a decreased content of plasminogen activator in the vein walls. Biopsy specimens for determination of the plasminogen activator content of the vessel wall were taken before treatment and after three and 12 months' treatment respectively. In those 17 patients in whom the activator content was checked after three months the plasminogen activator content had increased in all but one. In most patients the activator content reached the normal level, which according to our grading is 6 arbitrary units. In those six patients who had taken the drug combination for 12 months an increase was noted in all. During the treatment period they had no new episodes of thrombosis.

Abstract

Fibrinolytic Enhancement by Stanozolol: A Double-blind Trial

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Thirty-four men with ischaemic heart disease were given 10 mg stanozolol per day, 10 mg stanozolol plus 100 mg phenformin per day, or a placebo for 12 months in a double-blind, randomized study. A panel of fibrinolytic and coagulation tests was performed at monthly intervals. Throughout the study the groups on active treatment showed significant enhancement of plasma fibrinolytic activity compared with their baseline values and compared with the placebo group. No significant difference was found in the enhancement of fibrinolysis which was produced by either active treatment regimen, and it is concluded that 10 mg stanozolol daily is as effective as 10 mg stanozolol plus 100 mg phenformin daily in increasing plasma fibrinolytic activity in men with ischaemic heart disease.