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EFFECT ON RHEOLOGICAL AND SOME PERIPHERAL HAEMODYNAMIC PARAMETERS OF DEFIBROTIDE IN POAD PATIENTS

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ABSTRACT

In ten POAD patients, 800 mg. of Defibrotide (polideoxynucleotide extracted from mammalian lung, with antitrombotic and fibrinolytic activity) were infused i.v. Blood and plasma viscosity, haematocrit, blood filterability and fibrinogen concentration were controlled, in basal conditions and after one hour from the end of infusion. Haemodynamic parameters: rest flow, peak flow, time to peak flow, half time and total time of reactive hyperemia by means of strain gauge pletismography, were controlled at lower limbs before infusion and after 1 h., 2 h., 6 h., from the end of infusion. The present investigation showed an improvement of rheological parameters and a decrease of total time and half time of reactive hyperemia. These data demonstrate a rheological activity of Defibrotide as well as the fibrinolytic one.

INTRODUCTION

The drugs with fibrinolytic activity are nowadays common tools for treatment of ischemizing pheripheral vascular diseases, particularly of acute trombotic disorders of the limbs. Streptokinase and Urokinase have been used in several clinical trials, in different doses, by loco-regional or systemic treatments (1-2-3-4-5). These drugs have been used also in chronic obliterative arteriopathies, with quite good improvement of the clinical conditions (6-7-8-9). However, several limits to urokinase and streptokinase terapy exist: the cost and the anaphylactic reactions and moreover hospitalization

KEY WORDS: Defibrotide, Haemorheology, Reactive hyperemia, Fibrinolysis

of the patients is required (10).
New drugs acting as moderate antithrombotic and profibrinolitic agents are now available, inclunding the so called Fraction P (Defibrotide). This drug is a polydeoxynucleotide extracted from mammalian lung;the fibrinolytic activity could be due to release of plasminogen activator factor, while the antithrombotic action probably also derives from the release of PGI_2-like substance (11-12-13-14-15). Previous studies showed this activity in vitro and in vivo in several patological conditions: deep venous thrombosis, acute renal failure due to thrombotic microangiopathy and peripheral arterial disease (POAD) (16-17-18). In POAD patients the increased tendency to thrombosis is usually associated with an impairment of blood rheological properties. A reduction of fibrinogen concentration is associated with an improvement of blood fluidity. The aim of our study was toverify wether Defibrotide shows a rheological action in addition to the well-known fibrinolitic activity.

METHODS

The study has been performed in ten patients aged 52 to 68 years (average age 59 $\pm$ 3.8) with peripheral obliterative arterial disease at Fontaine's second stage. Subjects affected by hepatic, renal or haematological disorders cardiac insufficiency, diabetes, hypertension, have been excluded from the study. Possible treatments interfering with the mechanisms of regulation of the cardiovascular system and of the fibrinolytic and coagulative systems, were interrupted at least 15 days before the beginning of the study.
800 mg. of Defibrotide in 100 ml of saline solution have been infused to every patient in 30 minutes.
The following parameters have been controlled in basal conditions and after one hour from the end of infusion:
-Blood and plasma viscosity by Rotoviscometer HAAKE (37° C at the shear rate of 150^{s-1}).
-Blood filterability by Reid and Dormandy's method which has been modified to keep the temperature constant at 37° C during the determination, using policarbonato Nuclepore filters 5 micron pores (19).
-Haematocrit by Wintrobe's method
-Fibrinogen by immunodiffusion
In basal conditions, after 1 h., 2 h., 6 h., from the end of the Defibrotide infusion, blood flow at rest and after 3 minutes of ischemia, at lower limbs level has been measured by means of a strain gauge plethysmograph taking the following parameters into consideration (20).
-Rest Flow (R.F.)
-Peak Flow (P.F.)
-Time to Peak Flow (t P.F.)
-Half time (t 1/2)
-Total time of reactive hyperemia (t T)
The statistical analysis of the results has been perfomed using Student's "t" test for the rheological parameters and AN.O.VA for plethysmographic parameters.

RESULTS

The analysis of the results showed a statistically significant decrease of blood and plasma viscosity, of fibrinogen concentration, with improvement of blood filterability. No changes of haematocrit were observed (Table I). With regard to the haemodynamic parameters were observed no significant modification of rest flow (R.F.) and peak (P.F.). However after one hour from the end of the infusion a significant decrease of half time ($t\frac{1}{2}$) and total time (t T) of reactive hyperemia appeared. Such parameters resulted decreased, as regards the basal values, even after six hours from the end of the infusion (Table II). Side effects referable to Defibrotide were not observed in any of the subjects examined.

TABLE I
Haemorheological Parameters

	Before Infusion	After Infusion	t	p
Blood Viscosity cPs 150^{s-1}	4.31 ± 0.22	3.68 ± 0.12	4.597	**
Plasma Viscosity cPs 150^{s-1}	1.44 ± 0.10	1.37 ± 0.10	4.209	**
Haematocrit %	38.85 ± 2.65	38.58 ± 2.14	0.810	n.s.
Fibrinogen mg.%	441.68 ± 21.23	418.28 ± 24.33	6.585	**
Blood Filterability ml/min	0.9018 ± 0.299	1.0544 ± 0.333	-3.583	**

N= 10 Means ± SE. Student's t test for paired data.
n.s. = not significant; * = $p < 0.05$; * * = $p < 0.01$.

TABLE II
Haemodynamic Parameters

	Basal	1 h.	2 h.	6 h.	
R.F. (°)	2.5 ± 0.8	2.6 ± 0.9	2.4 ± 0.6	2.5 ± 0.7	F=0.0422 p=0.0102
P.F. (°)	7.5 ± 2.1	7.8 ± 2.4	7.7 ± 2.2	7.8 ± 2.3	F=0.0694 p=0.1283
t P.F.(§)	18.8 ± 12.9	12.7 ± 7.7	11.9 ± 7.4	12.8 ± 8.4	F=0.4915 p=0.1827
t ½ (§)	171.4 ± 29.7	103.7 ± 26.1	101.9 ± 37.1	103.2 ± 36.5	F=7.2000 p=0.0004**
t T (§)	198.1 ± 46.1	138.8 ± 41.4	138.6 ± 47.8	137.6 ± 45.6	F=4.4649 p=0.0039**

N= 20 Means ± SE AN.O.VA $p < 0.05$ * $p < 0.01$ **
(°) = ml/min/100 ml (§) = second

DISCUSSION

Our findings confirmed the pro-fibrinolytic action of Defibrotide wich showed also rheological activity. The decrease of blood viscosity was closely correlated to blood filterability improvement, since no changes of haematocrit has been detected (21-22). According to the well-known pro-fibrinolytic activity of Defibrotide a significant decrease of fibrinogen concentration has been observed and consequently a decrease of plasma viscosity too.
The improvement of blood filterability could be explained by a direct action on erythrocyte membrane and/or by the reduction of fibrinogen concentration with subsequent reduction of erythrocyte-aggregates.
The drug doesn't show a vasodilating activity, in fact no change of rest flow has been detected after infusion, as we have seen in a previous pilot study where the maximal activity of the Defibrotide on rheological parameters one hour after the end of the infusion was observed. No modification of rest flow, continously measured for 60 minutes, has been observed in the first hour.
The behaviour of haemodynamic parameters seems particularly interesting. Both rest flow and peak flow did not changes throughout six hours observation.
On the contrary a considerable shortening of reactive hyperemia appeared. This effect, in our opinion (20), could be due to an improvement of the rheological properties of the blood with a reduction of the microcirculatory disorders.

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