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Blood Viscosity, Finger Systolic Pressure and Effect of Dazoxiben Treatment in Primary Vasospastic Disease

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ABSTRACT

Whole blood viscosity, plasma viscosity, erythrocyte deformability, and finger systolic pressure (FSP) were measured in ten patients with primary vasospastic (Raynaud's) disease before and after a controlled double-blind prospective trial involving dazoxiben (a thromboxane inhibitor, Pfizer). Five of the patients were assigned to dazoxiben and five to placebo.

Before treatment, the FSP at 10 °C in the patient groups was significantly lower than that in a normal reference group, but all rheologic variables, measured at 37 and 10 °C, were normal. There was no significant correlation between FSP and rheology. Dazoxiben did not yield any subjective relief or give any objective effect.

INTRODUCTION

The mechanism of the vasospastic reaction to cold in Raynaud's phenomenon/disease is still unknown. Several studies in the literature have reported on altered blood viscosity in patients suffering from symptoms of primary Raynaud's disease (3, 4, 10). Goyle and Dormandy (4) suggested that this phenomenon may be caused by an abnormal increase in the viscosity and the yield stress of blood in response to a local fall in temperature.

We have measured blood viscosity and finger systolic pressure in ten patients with primary vasospastic disease in connection with a clinical trial on the effect of dazoxiben, a drug proposed to have a therapeutic vasodilating efficacy (6, 9, 11, 12).

MATERIAL AND METHODS

Patients

The participating subjects were out-patients, including seven women and three

men aged 21-50 and 24-48 years respectively.
The subjects were selected according to a criterion of a typical history of primary vasospastic disease which involve three or more classical attacks per week of Raynaud's phenomenon in both hands. None of the patients selected had a history involving the use of vibrating tools.

The following criteria of exclusion were used:
- age below 18 or above 65 years
- associated collagenic disease where history and serology were positive
- arterial hypertension, cardiovascular disease, gastroduodenal ulcer or diabetes mellitus
- a history of bronchial asthma, atopic skin disease or allergy to drugs
- inadequate anticonception (women), pregnant women or nursing mothers
- other drug treatment (anticonceptive pills allowed)

The therapeutic study was a prospective double-blind placebo-controlled trial, approved by the research-ethical committee of the medical faculty, Uppsala university. There was a two week run-in period involving a single-blind administration of placebo after which, five patients (3 women and 2 men) were assigned to dazoxiben (Pfizer, not registrered in Sweden, 6,9,11,12) and five (4 women and 1 man) to placebo treatment. The assignment was computer-randomized. Dosage of dazoxiben was 100 mg administrered four times per day.

Routine laboratory tests were made at two-week intervals. Blood rheology and finger systolic pressure were measured before, and after one and three months of treatment. The study began in February and was ended in May 1983.

Finger systolic pressure measurements

Finger systolic pressure (FSP) was measured during cooling of the digits. The cold test was performed on both hands using finger plethysmographs (model SB 2, Medimatic, Copenhagen, Denmark) with a 24 mm cuff perfused with fluid at a preset temperature.
Digit 4 was first exposed to 30 and then to 10 ^{o}C whereas digit 2 served as a control. The cuff was cooled for two minutes after which the FSP was measured successively. The procedure was repeated twice and the values averaged (13). FSP is expressed both in mm Hg and in percentage according to the formula of Nielsen (8):

$$FSP\% = \frac{FSP_{th,x}}{FSP_{th,c} - (FSP_{ref,c} - FSP_{ref,x})} \cdot 100$$

Finger pressure at the lower temperature (x) in the thermostated finger (th) is expressed as a percentage of the control pressure at 30 °C (c) corrected for changes in the arterial pressure, where FSP_{ref} is the pressure measured simultaneously from a reference finger of the same hand (5).

Erythrocyte volume fraction and blood rheology

Erythrocyte volume fraction (EVF) was analysed by centrifugation in microhematocrit tubes without correction for trapped plasma (trapping estimated as approximately 1 %).

Samples for EVF and rheology measurements were collected in heparinized vacutainer tubes after the patient had rested for 15 minutes.
Rheologic variables (whole blood viscosity, plasma viscosity and erythrocyte deformability) were analysed at 37 and 10 °C in a couette rotational viscometer, Low Shear 30 (Contraves AG, Zürich, Switzerland). A temperature of 10 °C was chosen to match the FSP cold test.
Whole blood apparent viscosity (B-viscosity) was analysed at a shear rate of 100 s^{-1} and plasma viscosity (P-viscosity) at 37.6 s^{-1}. B-viscosity was corrected to a standard EVF of 45 % by using a linear relationship between EVF and the logarithm of viscosity.

Erythrocyte deformability was estimated indirectly by the apparent fluidity at a shear rate of 0.945 s^{-1} and at an EVF of 55 %. The erythrocytes were washed and resuspended in isotonic saline phosphate glucose buffer at pH 7.4. Deformability was expressed as erythrocyte apparent fluidity (E-fluidity) using the unit $Pa^{-1} \cdot s^{-1}$.

Routine laboratory tests

Initially the S-acryl, S-ANF and S-electrophoresis tests were performed in order to eliminate those patients showing signs of collagenic disease.
For the trial samples were collected after the run-in period and thereafter at two week intervals for the following routine tests:
S-albumine, S-ALAT, S-ASAT, S-ALP, S-urea, S-creatinine, S-sodium, S-potassium, S-chloride, vB-bicarbonate, S-phosphate, S-calcium, fB-glucose, U-albumine and U-glucose.

RESULTS

A. FSP and rheology before treatment

Finger systolic pressure

As there was no significant difference between men and women, the FSP% from the ten patients were pooled. The mean of the right and left hand was used.

FSP% was significantly lower ($p < 0.001$, Student's unpaired t-test) in the Raynaud patients than that reported in a reference group of normal subjects (13) (Table 1).

Table 1. Finger systolic pressure

	FSP%	SD	n	
Raynaud group	62	28	10	(7 women, 3 men)
Reference group	90	11	56	(33 women, 23 men)

Rheology

The rheologic variables (Table 2) were not significantly different from normal subjects (healthy laboratory personnel, 8 women, 2 men) apart from fluidity at 37 ^{o}C, where the Raynaud group showed an uncharacteristic enhancement of fluidity compared to normal subjects ($p < 0.05$, Student's unpaired t-test). None of the rheologic variables were significantly correlated to FSP%.

Table 2. Rheologic variables
(B-viscosity corrected to an EVF of 45 %)

	Raynaud group			Normal subjects		
Variable	Mean	SD	n	Mean	SD	n
EVF (%)	41	4	10	43	3	10
B-viscosity,37 ^{o}C (mPa x s)	4.6	0.2	10	4.5	0.3	10
B-viscosity,10 ^{o}C (mPa x s)	11.4	2.2	10	10.9	0.8	10
P-viscosity,37 ^{o}C (mPa x s)	1.28	0.05	10	1.25	0.05	10
P-viscosity,10 ^{o}C (mPa x s)	2.5	0.3	10	2.4	0.3	10
E-fluidity,37 ^{o}C ($Pa^{-1} \times s^{-1}$)	122	9	9	114	8	10
E-fluidity,10 ^{o}C ($Pa^{-1} \times s^{-1}$)	68	6	9	66	6	10

B. Effect of dazoxiben treatment

None of the patients in the dazoxiben or placebo groups experienced any subjective relief during treatment. No side effects were registered and the routine laboratory tests were normal throughout the study. In Figure 1 the mean value and SEM are shown for both the dazoxiben (filled circels) and the placebo groups (squares) before, and after one and three months of treatment. A small but significant change in P-viscosity ($p < 0.05$, Student's paired t-test) was observed for the dazoxiben group during treatment. The reason for this change, indicated by an asterisk (*) in the Figure, is unknown. Otherwise no significant changes in blood rheology were observed.

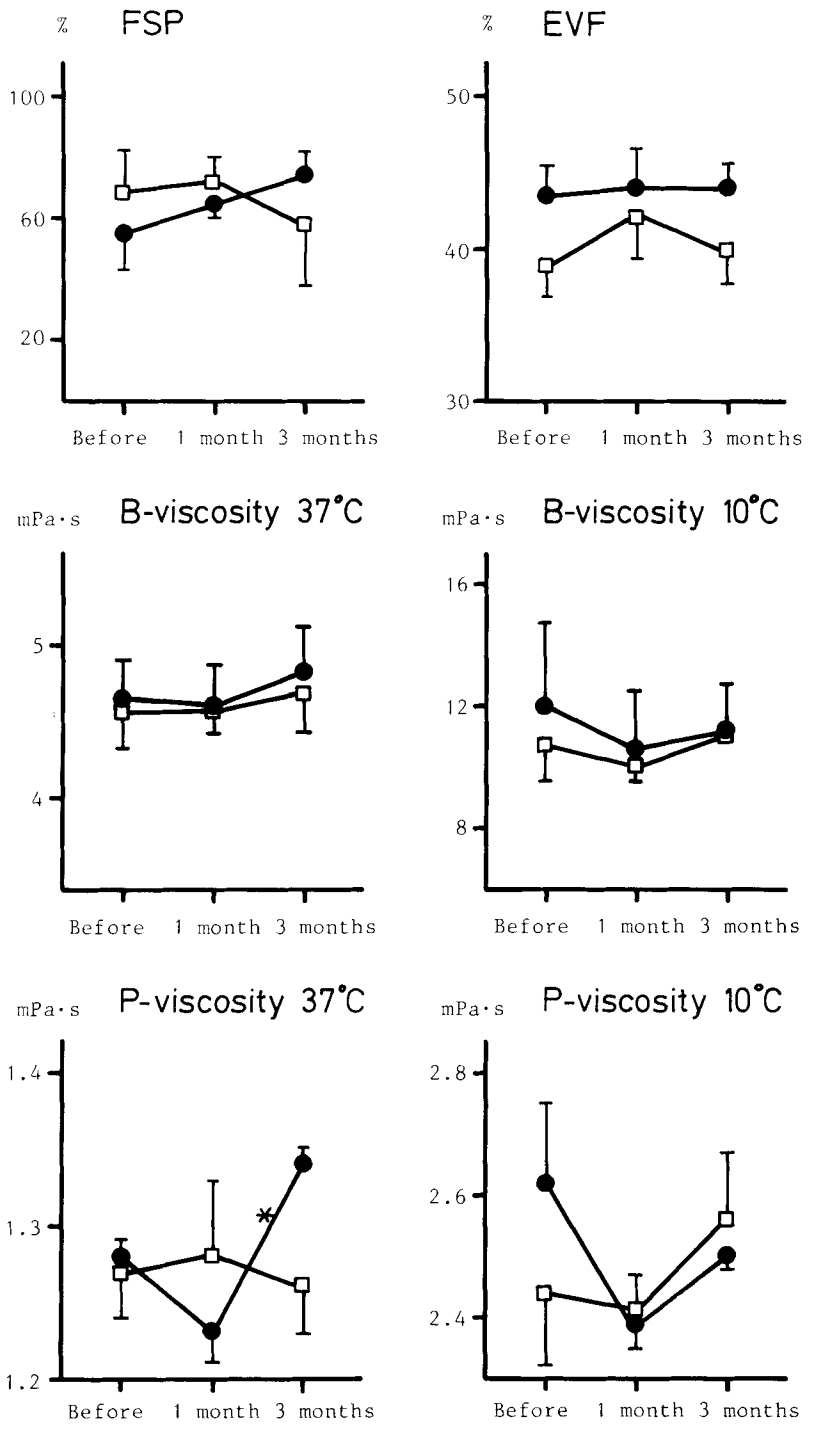

Fig 1. Viscosity variables in blood and plasma of the patients before and during therapy
FSP = Finger systolic pressure, EVF = Erythrocyte volume fraction

DISCUSSION

There was no subjective or objective improvement during dazoxiben treatment.

The previous published studies on blood rheology in patients suffering from primary vasospastic disease are contradictory. For example Pringle et al. (10) in 1965 found that 22 patients with "primary Raynaud´s disease" had a higher blood viscosity (as determined by Pirofsky´s continuous flow method at body temperature) than a corresponding control group of 22 normal subjects. Goyle and Dormandy (4) could not confirm this observation at 37 ^{o}C but did find that whole blood viscosity in "primary-Raynaud" patients was significantly increased at 27 ^{o}C and at low shear rates. Blunt et al. (3) however found that whole blood viscosity was significantly increased in 21 female patients with "idiopathic Raynaud´s syndrome" at both high and low shear rates at 37 but not at 22 ^{o}C. In contrast, McGrath et al. (7) reported that blood and plasma viscosities from patients with "Raynaud´s disease" were found to be normal at both high and low shear rates. The percentage increase in blood viscosity with cooling from 35 to 25 ^{o}C was also normal. Ayres et al. (2) also reported that blood viscosity from patients with "idiopathic Raynaud´s phenomenon" did not differ from that of a control group.

Since blood rheology in the present study was normal (Table 2) with no correlation found between the lowered FSP% and rheology, we conclude like both Ayres et al. (2) and McGrath et al. (7) that whole blood and plasma viscosities as well as red cell deformability (at either 37 or at 10 ^{o}C) in primary vasospastic disease (not related to vibrating tools) does not differ from that under normal conditions.

The variation reported in previous results may have been attributed to differences in the methods chosen for the rheologic determinations. Another possible reason for earlier differences may have been the inclusion of patients suffering from collagenic disease. The etiology of the vasospastic disease may also be of significance. It has been reported (3) that hyperviscosity may be found in patients suffering from traumatic (secondary) vasospastic disease caused by vibrating tools. This question requires further investigation.

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