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Blood flow changes with naftidrofuryl in systemic sclerosis and Raynaud's phenomenon

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SUMMARY

Blood flow was measured in patients with Raynaud's phenomenon, systemic sclerosis and in normal controls by venous occlusion plethysmography on the forearm and calf, and changes in blood flow in the finger were followed by calorimetry.

Intravenous naftidrofuryl oxalate (praxilene) improved blood flow to the skin of the finger as measured calorimetrically in seven of sixteen patients with Raynaud's phenomenon and systemic sclerosis. The drug markedly reduced blood flow in the finger in all ten normal control subjects. However, naftidrofuryl increased blood flow as measured by venous occlusion plethysmography in the leg both of normal subjects and of those with Raynaud's phenomenon. In addition to these findings, no significant change in blood flow in response to the drug was observed in the forearm. The reasons for these regional differences are discussed and considered to be due to redistribution of blood flow as a result of differences in pharmacological receptor activity in different parts of the body and possibly also due to effects of central control.

Naftidrofuryl oxalate (praxilene) has been shown to increase blood flow and to be devoid of side-effects, such as hypotension and flushing. It has been used successfully in the treatment of intermittent claudication but there are no reports of its effect in systemic sclerosis and Raynaud's phenomenon. We have, therefore, studied blood flow and its response to naftidrofuryl in patients with these conditions and compared the findings with those of control subjects. The blood flow in the arm and leg was studied with venous occlusion plethysmography and the heat output from the finger was measured calorimetrically.

PATIENTS AND METHODS

Nine patients aged between 26 and 59 with Raynaud's phenomenon, and seven aged between 63 and 68 with systemic sclerosis, were studied. Seven male and five female volunteers between the ages of 21 and 54 were controls. Naftidrofuryl, 40 mg as a 5 ml intravenous injection, was used. Five millilitres of normal saline was given as control i.v. before naftidrofuryl administration. Peripheral blood flow in the finger was measured using calorimetry (Tan, Gaylarde & Sarkany, 1978). Venous occlusion

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plethysmography using a mercury strain gauge was the method for the study of the blood flow in the calf and/or forearm. Blood flow was measured at 1 min intervals and the average of at least ten readings was used. The patients and volunteers were kept in a draught-free room at $24{\cdot}5 \pm 0{\cdot}5^{\circ}C$ for at least 30 min, but longer if indicated by unstable readings, to allow the subject to become familiar with the experimental apparatus and to come into thermal equilibrium with the surroundings. The patients and subjects were not allowed to smoke for at least 4 h before the start of the study. The stirrer and chart recorder produced a continuous background noise which helped to mask external noises that might suddenly disturb the subject.

RESULTS

The mean heat output from subjects with systemic sclerosis and Raynaud's phenomenon was less than that of the control group (Table 1). There was no correlation between heat output and age in any of these groups. Naftidrofuryl produced an increase of heat output from the middle finger in seven of sixteen patients with peripheral vascular disease and reduced it in four. All control subjects were found to have a marked reduction of heat output after intravenous naftidrofuryl. The reduction in heat output was rapid in onset and was stable at the decreased value within 2 min whereas the increase in patients with vascular disease was delayed by 10–20 min and the blood flow improved gradually. The reduction in heat output in normal subjects was apparent for at least 40 min, with little diminution in

TABLE 1. Heat output from the finger measured calorimetrically showing the effect of naftidrofuryl on the superficial blood flow of normal and diseased subjects

	Heat output before naftidrofuryl (W)		Heat output following 40 mg naftidrofuryl as percentage of control values	
Subjects	Mean	s.e.	Geometric mean	s.e. geometric mean
Normal controls (N = 10)	2·312	0·509	46·7	1·115
Raynaud's patients (N = 9)	0·633	0·100	110·6	1·216
Systemic sclerosis patients (N = 7)	0·410	0·105	138·2	1·264

TABLE 2. Effects of saline and naftidrofuryl on blood flow in the forearm and calf measured by venous occlusion plethysmography

	Geometric mean of change in blood flow expressed as percentage of control flow					
Subjects and treatment	Leg	s.e.	N	Arm	s.e.	N
Saline controls after 5 ml saline	103·3	1·047	13	85·5	1·064	12
Normal controls after 40 mg naftidrofuryl in 5 ml saline	113·7	1·053	11	103·2	1·136	7
Raynaud's patients after 40 mg naftidrofuryl in 5 ml saline	111·8	1·035	9	87·3	1·045	5
Systemic sclerosis patients after 40 mg naftidrofuryl in 5 ml saline	95·7	1·061	6	98·2	1·094	6

effect at the end of this time. Venous occlusion plethysmography showed increased blood flow following naftidrofuryl in legs of normal controls and in subjects with Raynaud's phenomenon and decreased flow in the legs of patients with systemic sclerosis. No significant change of blood flow occurred in the forearm in response to naftidrofuryl (Table 2). In contrast, intravenous saline reduced the blood flow in the forearm and had no effect on the leg.

DISCUSSION

These results show that the effect of naftidrofuryl on blood flow is complex. Since naftidrofuryl does not alter blood pressure and heart rate (Fontaine *et al.*, 1969), the reduction in skin flow in normal subjects is the result of either a fall in cardiac output or vasodilatation elsewhere. The injection of normal saline caused only a transient drop in heat output from the finger, lasting about 2 min, but some workers have noted a more long lasting effect on skin flow in man. We also found that the blood flow in the arm is reduced for at least 10 min after saline injection in the contralateral arm.

Blood flow in the arm varies rapidly with time. This variation is a result of normal homeostasis, external disturbance and the trauma of injection. The flow in the leg is more constant and Table 2 shows that the standard error of the results is not as great as in the arm. The increase in blood flow in the leg in response to naftidrofuryl is consistent with reports from clinical trials that the drug is of use in the treatment of intermittent claudication (Kappert, 1967; Sicard *et al.*, 1968; Czepak, 1973), although Ruckley *et al.* (1978) reported no improvement in their series.

Naftidrofuryl caused vasoconstriction in the fingers while producing an increased blood flow in the leg of normal subjects. This is not as unexpected as it might seem at first, since even the powerful vasodilator amyl nitrite causes an intense vasoconstriction in the fingers (Burton, 1961). The latter was considered to be due to centrally controlled mechanisms.

We have also recently found that ethanol causes different regional changes in skin blood flow and similar observations were previously made by Fewings *et al.* (1966) using hand and limb plethysmography. These results show that the effect of vasodilators is not uniform in all areas of the body and that the response of the hands in particular may be different from other parts. It is well known, for example, that blood vessels in the fingers constrict in response to adrenaline, where the blood flow in the forearm initially increases and subsequently returns to preinfusion values (Whelan, 1954). Other factors causing differential flow in the hand and forearm include nicotine, painful stimuli, CO_2 inhalation, hyperventilation and acetyl choline.

All these observations suggest that the use of vasodilators in Raynaud's phenomenon and systemic sclerosis has to be reappraised and based on both clinical response and objective measurement of blood flow. We agree with Coffman (1979) that an ideal drug for the treatment of peripheral vascular diseases would dilate blood vessels and increase blood flow only in areas of deficient blood supply but, unfortunately, these agents do not yet exist. Fortunately, however, in vasospastic diseases, vasodilator drugs may have a beneficial effect in many patients by increasing cutaneous capillary blood flow through their action on the sympathetic nervous system.

We have shown that naftidrofuryl in some patients with systemic sclerosis and Raynaud's phenomenon produces an increase in blood flow and it would seem that this is due to its selective effect on abnormal blood vessels. We know of no other report which has suggested that diseased blood vessels respond to vasodilators in the opposite way to that seen in control subjects.

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