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Serotonin and the Flow Properties of Blood

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Summary: The effects of serotonin and its pharmacological antagonists on the physical flow properties of the blood have been studied far less than their effects on blood vessels, although they may be equally important. Indirect evidence suggests that in pathological circumstances serotonin may locally increase whole blood viscosity, particularly at low shear rates, decrease red cell deformability and increase the adhesiveness of white cells. Although the viscosity of the plasma alone is not affected, the rheological effects of serotonin on blood cells is probably dependent on the presence of platelets. These mechanisms may have a systemic effect in some forms of hypertension as well as in situations of local ischaemia such as Raynaud's phenomenon, atherosclerotic pregangrene of the leg or acute myocardial infarction. Specific serotonergic-antagonists, administered either orally or intravenously, normalize the increased whole blood viscosity and decreased blood filterability found in essential hypertension, following myocardial infarction and in severe leg ischaemia. The effect on red cell deformability is usually greatest when the cells are resuspended in platelet rich plasma. Ketanserin given intravenously for seven days to patients with very severe leg ischaemia, significantly improves whole blood viscosity, increases red cell transit time and most dramatically decreases pore clogging. This last effect was at least partly due to a change in the physical properties, but not the number of the white cells. The reported beneficial clinical effects of such an antagonist in various forms of peripheral ischaemia and essential hypertension may well be due, at least partly, to the normalization of the rheological properties of the blood. **Key Words:** Deformability—Erythrocytes—Hypertension—Ischemia—Ketanserin—Viscosity—White blood cells.

The effects of serotonin and its pharmacological antagonists on the flow properties of blood have been studied far less than their effect on the vessels carrying the blood, although they may be equally important. Indirect evidence suggests that in pathological circumstances, serotonin may have important haemorheological actions. Most experimental information about these possible effects has been inferred from data obtained using the serotonergic antagonist ketanserin.

De Cree and colleagues first showed that ketanserin significantly improves the filterability of patients' blood following myocardial infarction, when compared in a double-blind trial with patients taking placebo (1). This finding was supported by animal experiments performed by De Clerck et al., who showed a fall in blood pressure correlated with a parallel fall in whole blood viscosity in hypertensive dogs treated with ketanserin (2). Clinical trials have shown a significant improvement in haemorheological parameters both in the short term, after a single intravenous injection of ketanserin, and over a longer period of oral administration of the drug (3–5). These studies demonstrate a normalization of the increased whole blood viscosity and decreased blood filterability found in essential hypertension and also following myocardial infarction and severe leg ischaemia.

In our study we have attempted to assess the effect of ketanserin on the haemorheological parameters of patients with severe leg ischaemia using newer, more accurate, rheological techniques.

PATIENTS AND METHODS

Fourteen patients with severe leg ischaemia were entered into the trial. Patients with rest pain or trophic changes severe enough to warrant hospital admission were selected. The ischaemic aetiology was determined by clinical and Doppler examination, and arteriogram if necessary. Patients with coexisting diabetes or other systemic diseases such as vasculitis were not excluded, nor were those who had undergone a failed arterial reconstruction or balloon dilatation. Exceptions included those who required immediate amputation or emergency arterial surgery.

The history of the condition was recorded and a clinical assessment was performed. Biochemical and haematological

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TABLE 1. *Summary of findings*

	Placebo (n = 6)			Ketanserin (n = 14)			
	Before	After	Δ%	Before	After	Δ%	p
Whole blood viscosity at							
95 s^{-1}	5.25 ± 0.88	5.10 ± 0.61	−3	5.78 ± 0.89	5.22 ± 0.69	−10	<0.05
2.4 s^{-1}	18.3 ± 4.9	17.7 ± 3.6	−3	21.9 ± 6.0	18.1 ± 4.9	−17	<0.05
0.7 s^{-1}	36.1 ± 9.3	36.1 ± 7.4	0	42.7 ± 12.2	36.3 ± 9.6	−15	<0.05
Plasma viscosity	1.48 ± 0.16	1.46 ± 0.11	−1	1.43 ± 0.13	1.35 ± 0.09	−6	<0.05
Haematocrit	0.41 ± 0.06	0.40 ± 0.06	−2	0.44 ± 0.06	0.40 ± 0.04	−9	<0.05
Haemoglobin	138 ± 17	131 ± 16	−5	14.4 ± 2.2	13.1 ± 2.1	−9	<0.05
White cell count	6.8 ± 1.1	7.4 ± 2.8	+9	7.6 ± 4.0	7.5 ± 3.1	−1	NS
Transit time	11.9 ± 0.6	11.2 ± 0.7	+1	11.2 ± 1.3	10.3 ± 1.2	−8	<0.05
Clogging (10^6/ml)	0.21 ± 0.11	0.20 ± 0.11	−5	0.17 ± 0.08	0.08 ± 0.04	−53	<0.01
Residual white cell count	0.15 ± 0.11	0.13 ± 0.12	−13	0.11 ± 0.09	0.04 ± 0.06	−74	<0.05
H/V							
95 s^{-1}	2.64 ± 0.21	2.59 ± 0.25	−2	2.46 ± 0.28	2.58 ± 0.19	+5	NS
0.7 s^{-1}	0.39 ± 0.06	0.37 ± 0.05	−5	0.35 ± 0.07	0.39 ± 0.07	+11	<0.05

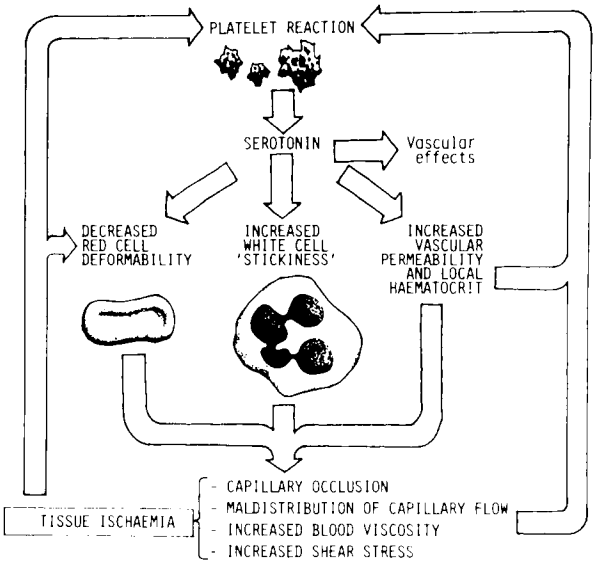

FIG. 1. Possible mechanisms by which serotonin may affect the flow properties of blood.

parameters were determined and haemodynamic measurements made using Doppler flowmetry, plethysmography, and transcutaneous oxygen measurements. Ten milliliters of blood was taken, without occlusion, and anticoagulated with lithium heparin. This sample was used for haemorheological testing. The clinical and haemodynamic results will be reported elsewhere.

After the initial assessment the patients were allocated randomly to either the treatment group or the placebo group. An intravenous infusion of ketanserin (2 mg/h), or matching placebo, was commenced and continued for 7 days. Blood pressure, analgesic usage, and subjective response were monitored daily, and at the end of the week the full assessment was repeated.

Haemoglobin, haematocrit, and white cell count were measured by standard Coulter analysis. Plasma viscosity was estimated using the Harkness capillary viscometer, and whole blood viscosity was determined with the Contraves LS-30 viscometer. Red cell filterability was measured with the new St. George's Filtrometer, which can distinguish between filter clogging and cell transit time through the filter pores.

RESULTS

There was a significant improvement in the whole blood viscosity over the period of treatment when compared with the control group. There was a parallel decrease in red cell transit time through the filter and, most dramatically, there was a decrease in pore clogging. This last effect was seen despite the fact that the total white cell count was not significantly changed by the infusion. These findings are summarised in Table 1.

DISCUSSION

The reported beneficial clinical effects of a specific serotonergic antagonist in various forms of peripheral ischaemia may be partly due to the normalisation of the rheological properties of blood. We have shown a significant reduction in whole blood viscosity after a 7-day infusion of ketanserin, despite no significant change in haematocrit. This implies a change in the flow properties of the red cells. Furthermore, there is evidence to suggest that the white cell rheology is altered by an infusion of ketanserin.

In the previous studies the techniques used could not distinguish between an effect on the true deformability of red cells (transit time through pores) and the effect on any particles in the suspension that blocked an increasing number of pores (clogging effect). Analyses of previous blood filtration techniques suggest that these two separate phenomena are involved but separation of one effect from the other has hitherto not been determined. White cells, for instance, even in very low concentrations, will decrease filtration rate by plugging an increasing proportion of pores in the filter used. A new filtration technique has been developed that can distinguish between the two effects. This method is based on measuring the change in the rate of flow beginning almost immediately at the start of filtration. The decrease

in filtration rate against volume filtered is a measure of the clogging rate, and by extrapolating to zero time, the filtration rate or transit time of cells in the absence of clogging may be determined. The most significant change with ketanserin is a decrease in pore clogging compared with the pretreatment value. This implies a change in the physical characteristics of white cells despite the absence of change in the absolute number of cells. The possible mechanisms by which serotonin may affect the flow properties of blood are demonstrated in Fig. 1.

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