Effect of oxpentifylline on blood viscosity and cerebral blood flow in man

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The effects of intravenous oxpentifylline on blood viscosity and cerebral blood flow were studied in eight patients with cerebrovascular disease using a double-blind placebo controlled design. A single dose of 200 mg oxpentifylline in 10 ml saline was given by intravenous injection over 10 min and compared with 10 ml saline alone. Whole blood and plasma viscosity were measured in a Contraves LS 30 coaxial viscometer at shear rates of 0.7 and 94.5 s^{-1} . Cerebral blood flow was measured by the non-invasive intravenous xenon¹³³ clearance method. The measurements were made before and then 30 min after the start of the injection of drug or saline alone. Oxpentifylline was found to have no significant effect on blood viscosity or cerebral blood flow.

Keywords oxpentifylline blood viscosity cerebral blood flow cerebrovascular disease

Introduction

Reduction of blood viscosity has been proposed as a treatment for stroke on the grounds that this will improve cerebral blood flow (CBF) and oxygen delivery to ischaemic areas of the brain (Gilroy *et al.*, 1969). Under normal conditions, alterations in blood viscosity have little influence on CBF because the cerebral circulation adjusts to the changes in viscosity to maintain constant oxygen delivery (Brown & Marshall, 1985). However, this regulatory process has an upper limit imposed by the maximum capacity of the circulation to vasodilate and in areas of ischaemia, the flow of blood in maximally dilated collateral vessels is likely to be dependent on the viscosity of the blood (Schmid-Schonbein, 1976). These considerations led to the treatment of acute stroke by haemodilution (Gottstein, 1979). As well as lowering blood viscosity, haemodilution has the unavoidable effect of lowering the oxygen content of the blood dependent on haemoglobin concentration, which may account for the failure of two recent large multicentre trials to show a benefit of haemodilution in patients with acute stroke (Italian Acute Stroke Study Group,

1987; Scandinavian Stroke Study Group, 1988).

An agent which reduced blood viscosity without altering the oxygen carrying capacity of the blood might increase both CBF and oxygen delivery and therefore be of more value than haemodilution in the treatment of stroke. The viscosity of whole blood samples determined *in vitro* depends on several factors including the sample haematocrit, the viscosity of the plasma, the shear rates at which the measurements are made and the aggregability and deformability of the red cells (Begg & Hearn, 1966). Oxpentifylline (pentoxifylline; Trental-Hoechst) is a xanthine derivative which has been reported to reduce blood viscosity by a direct action on red cell deformability (Leonhardt & Grigoleit, 1977; Theis *et al.*, 1978). This paper reports a study of the action of oxpentifylline on blood viscosity and CBF using a double-blind cross over design. The immediate effects of a single intravenous injection were examined as this would be the most desirable use of the drug in the early treatment of stroke.

Methods

Subjects

Eight patients with established cerebrovascular disease were studied. Four gave a history of transient ischaemic attacks, three had suffered a minor or moderate stroke and one a severe stroke. Two of these patients had unilateral internal carotid artery occlusion. The mean age of the group was 57 years (range 42 to 71). Six were male and two female.

Study design

Each patient was studied on 2 days separated by a period of 48 h. On each day the patient had a baseline measurement of CBF and immediately afterwards received either an intravenous injection of 200 mg oxpentifylline made up to 10 ml with 0.9% saline or an injection of 10 ml 0.9% saline alone, as placebo. The intravenous injections were given slowly over 10 min and a further CBF measurement made starting 30 min after the onset of the intravenous injection. Four patients received oxpentifylline on the first day and saline on the second. The sequence was reversed in the other four patients. The order of the treatments was randomized and was not known to the patients or the investigator until the trial was completed. Measurements of pulse rate and blood pressure were made before and 30 min after the injections.

CBF measurement

CBF was measured by the non-invasive intravenous xenon¹³³ clearance technique, described by Thomas *et al.* (1979). A bolus of approximately 7 mCi of xenon¹³³, dissolved in 5 ml saline was injected into an arm vein of the recumbent patient and the clearance of isotope from the cerebral hemispheres monitored with six external scintillation detectors, each 25 mm in diameter. Expired concentrations of xenon¹³³ were measured with a seventh detector and the end-tidal counts used to estimate recirculating arterial xenon¹³³ concentration. Regional CBF was calculated from a bi-compartmental analysis of 11.5 min of the clearance curves. This analysis produced a measure of volumetric perfusion through the fast clearing tissues of the brain (known as F fast), representing flow predominantly in cortical grey matter. Arterial carbon dioxide tension (P_{CO_2}) was estimated from the end tidal expired P_{CO_2} measured by a Datex CD300 capnograph over the first 5 min of the CBF study.

Measurement of blood viscosity

Blood samples for viscosity measurements were taken immediately prior to the CBF measurements from a forearm vein without stasis with the arm horizontal and the subject recumbent. Samples were anticoagulated with lithium heparin and the determination made within 30 min. Whole blood and plasma viscosity were measured at 37°C in a Contraves LS30 coaxial cylinder viscometer coupled to a Rheoscan programmer and a graph recorder. The samples were subjected over periods of 1 min to a logarithmic increase in shear rate from 0 to 1.29 s⁻¹ (the low shear range) and then from 0 to 128.5 s⁻¹ (the high shear range). Whole blood viscosity values were calculated from the shear stress readings at shear rates of 0.7 s⁻¹ (chosen to represent the low shear range where the effects of red cell aggregation are most important) and 94.5 s⁻¹ (chosen as the maximum convenient value in the high shear range where the effects of red cell deformability are more important). Plasma viscosity was measured at a single shear rate of 94.5 s⁻¹. Packed cell volume (PCV) was determined in triplicate using a Hawksley microhaematocrit centrifuge.

Results

The mean results are given in Tables 1 and 2 and were compared using a paired *t*-test. Oxpentifylline had no significant effect on any of the parameters measured. The baseline measurements were not significantly different on either of the study days. There was no difference between the effects of the drug on regional CBF in the symptomatic hemisphere compared with the asymptomatic hemisphere.

Discussion

This study has failed to show a significant effect of a single intravenous injection of oxpentifylline, given in the maximum recommended dosage, on blood viscosity or CBF. This lack of demonstrable effect on blood viscosity contrasts with the results of previous studies of the intravenous preparation (Heidrich *et al.*, 1976; Stormer *et al.*, 1977). In these earlier studies oxpentifylline was given by infusion in a relatively large volume of fluid and the reported fall in whole blood viscosity may have been secondary to haemodilution. The failure of the current study to show an effect on measurements

Table 1 Comparison of the effect of intravenous oxpentifylline and saline on blood viscosity in eight patients (mean $\pm$ s.d. pre- and post-injection; no difference was significant)

	Effect of saline		Effect of drug	
	Pre	Post	Pre	Post
Packed cell volume	0.41 $\pm$ 0.03	0.41 $\pm$ 0.03	0.41 $\pm$ 0.03	0.40 $\pm$ 0.03
Whole blood viscosity at shear rate of 0.7 s ⁻¹ (mPa.s)	23.5 $\pm$ 5.5	22.9 $\pm$ 6.1	23.0 $\pm$ 5.4	23.3 $\pm$ 5.1
Whole blood viscosity at shear rate of 94.5 s ⁻¹ (mPa.s)	4.74 $\pm$ 0.59	4.70 $\pm$ 0.62	4.63 $\pm$ 0.59	4.64 $\pm$ 0.57
Plasma viscosity (mPa.s)	1.41 $\pm$ 0.07	1.39 $\pm$ 0.07	1.40 $\pm$ 0.09	1.40 $\pm$ 0.07

Table 2 Comparison of the effect of intravenous oxpentifylline and saline on cerebral blood flow (CBF) in eight patients. (mean $\pm$ s.d. pre- and post-injection; no difference was significant)

	Effect of saline		Effect of drug	
	Pre	Post	Pre	Post
Mean arterial BP (mm Hg)	104 $\pm$ 12	100 $\pm$ 16	99 $\pm$ 19	98 $\pm$ 14
Pulse rate (beats min ⁻¹)	67 $\pm$ 10	63 $\pm$ 6	67 $\pm$ 8	65 $\pm$ 7
Arterial P _{CO} ₂ (kPa)	4.9 $\pm$ 0.4	4.9 $\pm$ 0.3	4.9 $\pm$ 0.5	4.9 $\pm$ 0.4
CBF (ml 100 g ⁻¹ min ⁻¹)	62.0 $\pm$ 7.5	62.9 $\pm$ 10.9	63.4 $\pm$ 8.9	60.4 $\pm$ 6.3

of whole blood viscosity does not exclude a beneficial effect of oxpentifylline on red cell deformability *in vivo*. Such an effect, if present *in vitro*, would have been expected to result in a reduction in whole blood viscosity measured at the higher shear rate, which was not found. However, it has recently been suggested that measurements in rotational viscometers of the type used in this study might miss changes in red cell deformability detectable by other techniques, such as filtration or laser diffractometry (Stuart, 1985).

This study also contradicts earlier studies of the effects of oxpentifylline on CBF in cerebrovascular disease. Methodological differences may explain this discrepancy. Koppenhagen *et al.* (1977a,b) measured cerebral transit time, which is dependent on cerebral blood volume and correlates poorly with more exact measures of CBF (Rowan *et al.*, 1970; Smith *et al.*, 1971). The other study of intravenous oxpentifylline to report an increase in CBF used a similar method of measuring CBF to the current study, but the trial was uncontrolled and oxpentifylline was given with other medication, leading to uncertainty about the conclusions (Gabaschwili *et al.*, 1979). In contrast to previous human studies, the results of the current study are more consistent with two carefully controlled

animal studies which showed that acute administration of oxpentifylline did not alter CBF in the anaesthetised dog (Steen *et al.*, 1981) and reduced CBF in hypertensive rats (Johansson, 1986).

The results of the current study may not be applicable to acute stroke. All the patients were in a stable phase of their disease to avoid the confounding effects of the spontaneous and unstable fluctuations in CBF, known to occur in acute stroke (Heiss *et al.*, 1975). Although oxpentifylline did not increase mean CBF, measured in relatively large regions of each hemisphere, improvements in flow in areas of focal ischaemia may have been missed. In such areas the low partial pressure of oxygen may increase the rigidity of red cells and impair blood fluidity (Weed *et al.*, 1969). Oxpentifylline appears to correct this deficit *in vitro*, and it is possible that it would do so in capillaries within areas of ischaemia without influencing measures of blood viscosity performed on mixed venous blood at normal oxygen tension. A recent *in vivo* study of patients undergoing neurosurgical revascularisation demonstrated an increase in tissue oxygenation following intravenous oxpentifylline, consistent with such an effect (Schultheiss *et al.*, 1987).

Prolonged oral therapy with oxpentifylline

may have beneficial effects not seen after a single intravenous injection. One study of patients with peripheral vascular disease demonstrated a significant effect of oral oxpentifylline on blood viscosity after 10 days oral treatment (Volker, 1976) and another showed an effect only after the medication had been given for 60 days (Mueller, 1985). Measures of blood fluidity also seem to be improved by prolonged oral therapy in patients with cerebrovascular disease (Ott *et al.*, 1983). Four weeks oral therapy has also been reported to increase CBF in patients with dementia, but this study was not blind and the patients did not act as their own controls, diminishing the value of the results (Hartmann, 1981). Prolonged oral therapy with oxpentifylline also lowers fibrinogen in normal volunteers (Jarrett *et al.*, 1977).

This could reduce red cell aggregability, lower plasma and whole blood viscosity and reduce coagulability. In addition, oxpentifylline appears to have beneficial effects on platelet aggregation as well as a direct antithrombotic action (Schroer, 1985). Further studies of oxpentifylline in cerebrovascular disease may therefore be justified.

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