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IMPROVEMENT OF SICKLE CELL DEFORMABILITY BY PIRACETAM IN VITRO AND IN VIVO

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Piracetam (P) (2-oxo-pyrrolidine acetamide) has rheological properties and has been used at various dosages over the past decade for the management of psychosenescent syndromes.On maintenance therapy, at the oral dosage of 160 mg/kg/day, in four divided doses, P reduces the number of vaso-occlusive crises in sickle cell homozygous patients, to about a fifth of what could be expected without drug. After oral intake at the latter dosage P's bioavailability in the blood ranges from 0.5 to 1 m mol/l. Microsieving on polycarbonate filters, 5 μm pore size, of diluted suspensions (haematocrit 1%) of oxygenated HbSS cells previously incubated with P 0.5 to 1 m mol/l, shows that the drug strongly improves their deformability. Similarly, microsieving of oxygenated HbSS cells obtained from patients on maintenance therapy with P, shows that the drug enhances the deformability of these cells as actively as it does in in vitro experiments in the same range of concentration. On the other hand the drug only poorly restores the loss of deformability of physiologically deoxygenated HbSS cells. From these experiments, it seems that P works rather on the outer viscoelastic properties of the HbSS red cell membrane than on the inner HbSS content of these cells.

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EFFECT OF PIRACETAM ON THE MEAN INTRASPLENIC RED CELL TRANSIT TIME (MST) IN SICKLE CELL DISEASE AND SICKLE CELL THALASSAEMIA

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The effect of Piracetam on the MST has been evaluated in 3 children with homozygous sickle cell disease, and in 1 child and 2 adults with sickle cell β thalassaemia. The MST was measured using 99 Tcm labelled autologous red cells before and during treatment with Piracetam (160 mg/kg/d). Tests for in vitro filterability of red cells were performed and an improvement of the in vitro deformability was observed in all the patients.

A shortening of the MST was also observed :

Patient		MST before Piracetam (min)	MST during Piracetam (min)
1	HbSS	5.6	4.9
2	HbSS	1.7	1.2
3	HbSS	5.5	2.5
4	HbS/βo	7.0	4.5
5	HbS/βo	5.3	4.4
6	HbS/βo	3.8	1.5
	$\bar{x}$	4.82	3.17
	SD	±1.83	±1.64

Student's Test "t" ($t = 3.77$) $p = 0.013$*

We conclude that Piracetam shortens the MST by improving red cell deformability.

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HAEMATOCRIT REDUCTION CONCOMITANT WITH ACUTE PHASE REACTANT RISE.

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The study aimed to investigate haematocrit variation as acute phase reactants rise in myocardial infarction.

Serial measurements of haematocrit were undertaken in a cohort (N = 60) of patients over periods ranging from 6 to 28 days. Concurrent measurements of plasma fibrinogen were made by the method of Clauss. Patients with clinical or radiological evidence of heart failure were excluded as were patients with history or evidence of bleeding for any cause.

Results showed a small initial transient rise in haematocrit above baseline of 3% within the first 12 hours post-infarction, followed by a mean decrease below baseline of the order of -16%. The decrease was maintained at the time of discharge from hospital (mean 9.5 days) at a level of -11%. In the single case where serial haematocrits were measured up to 28 days, haematocrit was still reduced by -12%. The maximum individual percentage decrease measured in any patient exceeded -30% and occurred at 3 days post-infarct. The decrease parallelled the rise in plasma fibrinogen but apart from the early post-infarct period, the correlation was poor because of the rise in other acute phase reactants subsequently.

A postulated mechanism for the fall in haematocrit is that it reflects haemodilution. This is in part a physiological compensatory mechanism for the increase in colloid osmotic pressure that is attendant on the increase in acute phase reactants due to myocardial tissue destruction. The blood loss due to serial diagnostic phlebotomies cannot explain the magnitude of the decrease.

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NOVEL TECHIQUES FOR QUANTIFICATION OF RBC-SHAPE (RS) AND SHEAR INDUCED RBC ELONGATION (SIRE): APPLICATION FOR ANALYSIS OF DRUG INDUCED ALTERATIONS.

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In the past, red cell resting shape could only be assessed by subjective scaling, red cell deformability by a variety of rheological tests that are extremely difficult to standardize and which all subject the RBC to high deforming forces. None of the latter have been accepted as reference in haematology, haemorheology or pharmacology. A recent development from our group now allows objective, numerical analysis of red cell membrane curvature (i.e. the echinocytic or stomatocytic deviation from the discocytic resting shape) by a tangent count procedure in optical sections through freely suspended, randomly oriented RBC: (Grebe et al. Biorheology 22(6), 1985). Also, the deformation of point attached erythrocytes under the influence of extremely low shear stresses (0.05 Pa to 0.5 Pa, ARTMANN: Clin.Hemorheology 6, 1986), which are at least two orders of magnitude lower than that in any routinely available filtration method allows for the first time to model in vitro the extreme low flow states that occur in severe forms of haemodynamic insufficiency.

These two methods in combination are ideally suited for routine tests of drug effects on normal human RBC: the drug action on RS can be monitored continuously during the action of drugs in the suspending medium: likewise, RISA can be recorded automatically on one population of adherent RBC while altering the composition and the drug concentration in the superfusate. The two methods were applied in combination to test rheological and membranological effects of two distinctly different compounds, namely Bencyclan (Bencylan-Hydrogen-Fumarate) and Vinpocitin (Aethyl vincamin) in normal cells and in cells after exposure to "stress conditions", i.e. hyperosmolarity and lactacidosis. Both drugs given to n o r m a l RBC produce stomatocytosis in a dose dependent fashion (1-100 uMolar). At shear stresses above o.6 Pa, the RISA is identical to controls, but is considerably less pronounced at lower shear stresses (T < 0.2 Pa). Thus, drugs of completely different pharmacological action produce clear cut rheological effects on RBC in the micromolar concentration range; the combination of methods employed opens new possibilities for the systematic development of haemorheologically active drugs.

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