PHOSPHODIESTERASE INHIBITORS IN CEREBROVASCULAR DISORDERS

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Cerebrovascular disease is the third major cause of death in many countries, after ischemic heart disease and neoplastic disease (Gottstein, U., 1974). Clinical manifestations range from senile organic brain syndrome, depressive disorders, dizziness, sleeplessness, forgetfulness, to frank cerebral infarction.

Recent studies have shown that reduction of microcirculatory blood flow plays a most important role (Gray, S.D., et al 1968; Reid, H.L. et al 1976). This in turn depends on a number of hematologic factors including hematocrit, deformability of red blood cells, red cell and platelet aggregation. Red cells with a mean diameter of 7.4u have to squeeze through capillaries with a diameter of 5-6u.

Obviously deformability or flexibility plays an important role; it decreases in chronic cardiovascular disease, diabetes mellitus, acidosis, increased osmolarity, crisis of sickle cell anemia, reduced surface/volume ratio due to swelling, reduced intracellular ATP and AMP levels and in electrolyte imbalance (Gray, S.D., et al., 1968; Reid, H.L., et al., 1976; Schmid-Schonbein H., 1971). In addition, changes in the vessel wall, e.g., atherosclerotic narrowing, may influence microcirculatory blood flow. Distal to stenotic areas there is a certain degree of stagnant flow with reduced pressure. Inadequate oxygen supply favors aneorobic glycolytic processes resulting in acidosis and hyperosmolarity. This in turn increases red cell rigidity and decreased pressure can push these cells through the smaller capillary diameters only with difficulty (Gray, S.D., et. al 1968). Hypoxia will increase and cause increased capillary permeability with brain edema and local electrolyte imbalance (Meyer J.S., 1972). There will be serious interference with normal neuronal function and nutrition resulting eventually in infarction.

Realizing that the stenotic process is usually not amenable to medical therapy (except for surgery in certain instances) earlier therapeutic attempts were based on the use of vasodilators. Unfortunately the microcirculation where a major part of the pathophysiologic processes occur is not provided with vascular smooth muscle elements and thus does not respond to classical vasodilators. Moreover, vasodilation without increased pressure gradient may result in further slowing of peripheral blood flow. This essentially left us without effective drug therapy until recently. Inhibitors of phosphodiesterases interfere with intracellular decomposition of AMP resulting in decreased platelet aggregation and increased red cell deformability. This in turn decreases blood viscosity and reliaves the vicious cycles described above (Werner, U., 1975; Heidrich, H., Ott, M., 1974; Gastpar H, 1974). In experimental systems, these agents reduced brain edema and cerebral electrolyte shifts in response to cold injury (Ganser, V.; Boksay, L., 1974), increased intracellular ATP, AMP, and inhibited phosphodiesterases (Stefannovich, V.; 1974). These are probably the mechanisms on which the observed therapeutic results are based in cerebrovascular disorders as reported in this symposium and in the literature (Dominguez, D., et al 1977; Javanovic, U.J., 1976). Improvement of cerebral oxygenation induced by phosphodiesterase inhibitors appears to represent a new approach to cerebrovascular disorders.

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