in cerebrovascular disease is presently available. Of the two statistically controlled therapeutic trials that have been published, the first with a plasmin/streptokinase mixture (Thrombolysin) suggested that the treatment was without value, while the second trial of streptokinase plus anticoagulants versus a control group of anticoagulant-treated patients suggested that though lysis of the causative thrombus occurred more frequently in the treated than in the control group, judged by mortality and morbidity criteria, the treated group responded less well to therapy than did the control group.

However, for various well known reasons, streptokinase is a far from ideal drug for use in acute cerebrovascular disease and serious exploration of the potential of thrombolytic therapy in this area required the availability of a superior thrombolytic agent such as urokinase.

Urokinase therapy does not appear to present any special difficulty or hazard in the patient with acute cerebrovascular disease. Urokinase dosage requirements, calculated on a patient body-weight basis, are

similar to those of patients suffering from other thromboembolic disease states. High levels of plasma thrombolytic activity are induced by the therapy with only minimal disturbance to blood coagulation function.

Clinically, no unusual haemorrhagic phenomena were observed except that, similarly to other patients treated with urokinase, haemorrhage sometimes occurred at surgical incision sites or at sites of recent arterial catheter insertion.

While no valid assessment of urokinase therapeutic effect can be made with this small number of stroke patients, it should be mentioned that there was only one death (not attributable to the treatment). Deterioration of patients during the time of treatment infusion was not observed, and, five patients suffering from severe venous sinus thrombosis recovered following therapy, in three instances, with apparently unusual rapidity and completeness.

These findings suggest that a larger trial of urokinase therapy in acute cerebrovascular disease is certainly feasible and should be undertaken.

Observations of enzyme elevations in the serum during streptokinase treatment

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Side effects of fibrinolytic therapy with streptokinase are well known. Casual observations of enzyme elevations in the serum of patients with chronic arterial obstruction of the lower extremities during streptokinase treatment (Martin, Schoop, and Zeitler, 1969) suggested that a planned study of 24 unselected patients should be performed (Schmidt, Poliwoda, Buhl, Alexander, and Schmidt, 1969).

The enzymes were chosen with regard to their value in differentiating distinct cellular lesions: the amino transferases (GOT and GPT), together indicating disturbed permeability of liver cells, the mitochondrial glutamate dehydrogenase (GLDH) as an index of severe cellular damage, alkaline phosphatase (SAP) and γ -glutamyl transpeptidase (GGTP) for the evaluation of cholestasis and

cholinesterase (CHE) as a measure of the capacity of protein synthesis in the liver. Lactic dehydrogenase (LDH) and creatinephosphate kinase (CPK) were added to the profile as indices of a possible involvement of red blood cells and skeletal muscle. Enzyme determinations were done at least twice before therapy in order to establish reliable initial values. With few exceptions the activities of all enzymes were within the normal range. During streptokinase treatment determinations of enzyme activities were done at 12-hour intervals from the first to the fifth day, daily up to the eighth day, and after this, at varying intervals up to three months.

The response of our patients to fibrinolytic therapy as reflected by their enzyme patterns in serum can be divided into three different stages.

Fig. 1.

Fig. 1 Changes in serum levels of pseudocholinesterase (CHE), γ -glutamyl transpeptidase (GGTP), alanine amino transferase (GPT), and glutamate dehydrogenase (GLDH) in a patient treated with streptokinase. Similar changes were seen in seven other patients.

Fig. 2.

Fig. 2 Changes in serum levels of pseudocholinesterase (CHE) γ -glutamyl transpeptidase (GGTP), alanine amino transferase (GPT), and glutamate dehydrogenase (GLDH) in a patient treated with streptokinase. These changes are representative of those observed in a group of 10 patients.

One quarter failed to develop a substantial elevation of enzyme activities in serum.

An increase of GGTP and depression of cholinesterase values were just outside the normal range. The remainder fell within the normal range.

The next group of eight patients showed an early significant rise of GGTP up to four times the initial values, and a less important but substantial increase of transaminases, GLDH, and alkaline phosphatase (Fig. 1). For clarity the course of only four representative enzymes in one individual is shown in this figure. It can be seen that concomitant with the elevation of cellular enzymes and the depression of the cholinesterase values a marked retardation of BSP elimination from the serum took place.

In the last group (Fig. 2), comprising 10 patients, immediately after the beginning of streptokinase treatment a very pronounced increase of transaminases, of the mitochondrial GLDH, and the enzymes which indicate cholestasis occurred. The maximum

was reached after two to four days, and was followed by a rapid decrease of transaminases and GLDH, whereas GGTP and to a minor extent alkaline phosphatase became more elevated and then fell more slowly to reach normal ranges later. The diminution of cholinesterase activity in this group is similar to that in the second group. However, the retention of BSP is striking; its values are comparable to those seen in anicteric acute hepatitis.

The source of the elevated enzymes in serum must be the liver. This is evidenced by the very similar levels of GOT and GPT. It is proven by the increase of GLDH and GGTP, which is virtually liver specific, and is supported by the concomitant delay in BSP elimination and the fall in cholinesterase activity, as well as by the invariably low activities of LDH and CPK, which exclude muscle or erythrocytes as tissues of origin.

Regardless of the absolute levels, the type of the enzyme pattern resembles that of severe acute toxic

injury or acute hypoxic liver damage. The typical features are the disproportionate increase of GLDH as compared to that of the transaminases, the rapid and relatively high elevation of the enzymes indicative of cholestasis, and the early decrease of cholinesterase activity.

Thus we are dealing with the coincidence of disturbances of cellular and subcellular membrane permeability as well as intrahepatic cholestasis and a reduced protein synthesis and/or secretion.

As to the mechanism of the lesion, three possibilities are to be considered foremost: a sudden disturbance of the microcirculation of the liver, hepatotoxicity of streptokinase in itself, or a direct action on the membranes of the parenchymal cells due to the enhanced proteolytic activity of the plasma. Up to now we have investigated the last two possibilities. Figure 3 shows the results of some studies on the effect of streptokinase, plasmin and plasmin activator on the isolated, haemoglobin-free and volume-constant perfused rat liver. After one hour of perfusion we added one of these com-

pounds in a dose comparable to the concentration reached in human blood, and followed the release of cellular enzymes into the perfusion medium. Streptokinase was without a significant effect. The addition of plasmin as well as of activator, however, led to a marked acceleration of enzyme release.

This suggests that streptokinase itself does no harm to the liver, whereas the activated proteolytic enzymes increase the cellular permeability significantly.

For practical use, these observations demonstrate that frequent but fortunately transient liver lesions have to be taken into account during streptokinase treatment.

Abstract

Some Experiments with Streptokinase in Recent Aortic Prostheses in Dogs and Cats

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Streptokinase was infused into 18 dogs and 13 cats four days to six weeks after the insertion of aortic prostheses. Control studies with saline infusion were carried out with eight dogs and six cats.

With streptokinase treatment almost all animals experienced severe bleeding within one week and in cats within up to three weeks of insertion of the prosthesis. Histological examination in these cases showed complete lysis of fibrin deposits within the lumen of the prosthesis.

Fig. 3. Enzyme release of the isolated perfused rat liver.