

## ANTITHROMBIN III TREATMENT IN ACUTE LIVER FAILURE

G.E. Vogel, P. Bottermann, M.v. Clarmann, Ch. Komm, \*A. Oberdorfer. II. Medical Clinic and \*Institute for Clinical Chemistry and Pathobiochemistry, Technical University Munich, Munich, G.F.R.

In acute liver failure (alf) there is a defect in synthesis of coagulation factors in addition there is a disseminated intravascular coagulation which is followed by an impairment of the microcirculation. With an early substitution of Antithrombin III (AT III) we tried to stop this situation. In 22 patients (10 female, 12 male, age 10-68) with alf presenting with hepatic coma (grade I-IV) we studied the time course of AT III plasma activity (the study started in December 1978 and is continued until now). AT III was measured with the chromogenic substrate method. When AT III activity fell below the level of 80% of normal, we started to substitute AT III and to give low dose heparin (125-500 U/hrs). In addition in case of bleeding or a decrease of coagulation factors or fibrinogen under the hemostatic active concentration, complexes of prothrombin and fibrinogen were administered. Besides the usual conservative treatment for alf, patients in coma (grade IV) were undergoing baboon liver perfusion. The rapid fall of the hepatic coagulation factors stopped. In patients, who still were able to synthesize coagulation factors a reincrease of these factors after administration of AT III was seen and there was a further fall in fibrinogen. The dosage of AT III in alf required to bring AT III to normal values depended on the degree of intravascular coagulation. The average dose in our study was 250 U/3 hrs. The clinical course of alf was prolonged in all patients and 7 patients with the prognostic deleterious colombindex (sum of factors II + V + VIII) < 75% eventually survived the alf. The coagulation disorders in alf can be treated with an early substitution of AT III; thus, there is more time for liver regeneration. Our results suggest an improved prognosis of the acute liver failure.

ANTITHROMBIN III SUBSTITUTION IN ACUTE HEPATIC FAILURE DUE TO CCl<sub>4</sub> INTOXICATION. R. Egbring, H.-G. Klingemann, N. Heimbürger\*, H.E. Karges, J. Beule, R. Seitz, K. Havemann. Department of Haematology, Medizinische Universitätsklinik and \*Behringwerke AG, 3550 Marburg, W. Germany.

In patients with acute severe hepatic failure the synthesis of clotting factors and inhibitors is considerably diminished. The decrease of clotting factors may be enhanced by liberation of thromboplastic substances from liver cell debris, leading to thrombus formation in the sinusoids and to further cell damage. At the low levels of clotting factors and inhibitors signs of disseminated intravascular coagulation as well as hyperfibrinolysis have been demonstrated. Treatment with heparin to prevent coagulation is insufficient at low levels of antithrombin III (AT III). Therefore, Vogel und Fritzsche 1979 suggested the substitution of AT III in these cases.

We now report about 3 patients who were admitted to the clinic together with severe signs of liver damage after oral uptake of CCl<sub>4</sub>.

On the day of admission several clotting factors plasminogen and alpha<sub>2</sub>-antiplasmin were significantly diminished; AT III levels between 25-45% of the norm were found. (Diss. Eckhardt-Klaßnitz). Therefore we started treatment with AT III concentrate from Behringwerke (1000-2000 I.U. daily for 3 to 14 days) and fresh frozen plasma (total volume of 2 l within the first 3 days).

AT III was simultaneously determined by clotting test, a chromogenic substrate test, and immunologically. Hemodialysis was necessary in 2 patients. Under treatment with AT III and fresh frozen plasma no bleeding tendency occurred. Though two of the patients showed severe intoxication on admission all could be dismissed with only slight histological signs of liver alterations. Treatment with AT III concentrates, therefore, seems of value in patients with acute yellow liver dystrophy.

## BIOLOGICAL CHARACTERISTICS OF ANTITHROMBIN III IN AN ANTITHROMBIN III DEFICIENT FAMILY.

S. Kondo, T. Matsuo, Y. Ohoki and O. Matsuo. Department of Internal Medicine, Hyogo Prefectural Awaji Hospital, Sumoto and Department of Physiology, Miyazaki Medical College, Miyazaki, Japan.

In the familial AT III deficiency of a Japanese family, the propositus (a-39-yr old female) and her mother had episodes of recurrent thrombosis and their AT III levels as measured immunologically and biologically were below the normal value. In the plasma of her brother, the AT III concentration as measured immunologically was half of the normal value, but his biological antithrombin activity was within the normal range. The progressive antithrombin activity and antifactor Xa activity of plasma samples in this familial AT III deficiency were within the normal range. Measurements of the rate of thrombin neutralization activity revealed that the brother's plasma was in the normal range, but the plasma of the propositus and of her mother showed rates of thrombin neutralization activity which were somewhat below the normal value. The rate of thrombin neutralization activity per mg protein of AT III was highest in the plasma of the brother, and became slower in the mother, propositus, and pooled normal plasma in that order. In the plasma of this familial AT III deficiency, the rate of Xa neutralization activity was much slower than the normal value. It is postulated that since the antithrombin of the brother of the propositus was found to react as normal in the neutralization of thrombin, he does not have episodes of thrombosis. Such characteristic hyperfunction of antithrombin in the plasma of the brother may be due to some molecular abnormality of AT III within this hereditary deficient family.

CHANGES IN BIOLOGICALLY AND IMMUNOCHEMICALLY MEASURED ANTITHROMBIN III (AT III) IN TOTAL HIP REPLACEMENT WITH SPECIAL REGARD TO TYPE OF THROMBOEMBOLIC PROPHYLAXIS. H.O. Fredin and L. Tengborn. Department of Orthopaedic Surgery and Coagulation Laboratory, Allmänna Sjukhuset, Malmö, Sweden

The plasma levels of AT III were studied in 71 patients operated with total hip replacement. AT III was determined with amidolytic assay using the chromogenic substrate Coatest S-2238 (KabiDiagnostica, Sweden) as well as electroimmunochimically. Samples were drawn before the operation and 4-5 times the first week postoperatively. The results were adjusted to the hematocrit (Hcr) for each sample.

The patients were randomly allocated to thromboprophylactic prevention with either Macroder (Pharmacia, Sweden) or heparin with dihydroergotamine (Sandoz, Switzerland). Phlebography of the operated leg and perfusion/ventilation lung scanning was performed on the 10-14th postoperative day.

Results. No difference in the AT III levels were seen in patients who developed postoperatively deep venous thrombosis and/or pulmonary embolism (DVT/PE) as compared to those who did not develop DVT/PE.

No decrease of AT III was found postoperatively, when adjusted to Hcr.

The frequency of DVT/PE did not differ significantly between the two types of thromboembolic prophylaxis.

Conclusion. Pre-operative determination of AT III, whether biologically or immunochemically, did not seem to be successful as screening method of patients to develop DVT/PE.