SHORT REPORTS

Angiotensin converting enzyme: a tumour marker in malignant histiocytosis

Angiotensin converting enzyme is present in vascular endothelial cells and in cells of the monocyte macrophage series. Serum activities of the enzyme may be raised in active sarcoidosis, Gaucher's disease, leprosy, asbestosis, and silicosis,¹ in hyperthyroidism,² and in alcoholic liver disease and diabetes mellitus with severe retinopathy.³ Low serum activities of the enzyme have been reported in lung cancer, malignant lymphoma, leukaemia, and multiple myeloma.⁴ We report raised activities of the enzyme in two patients with malignant histiocytosis (histiocytic medullary reticulosis).⁵

Case reports

Case 1—A 52 year old man was referred to our hospital because of sustained fever, weight loss, progressive hepatosplenomegaly, and jaundice. Laboratory values were haemoglobin concentration 4.8 mmol/l (7.7 g/dl), platelet count $60 \times 10^9/l$, serum bilirubin concentration 166 $\mu\text{mol/l}$ (9.7 mg/100 ml), serum alkaline phosphatase activity 147 U/l, serum aspartate aminotransferase activity 162 U/l, serum alanine aminotransferase activity 7.7 U/l, and serum lactate dehydrogenase activity 1656 U/l. Bone marrow and liver biopsy showed infiltration with atypical, α -naphthylacetate esterase positive histiocytes and occasional erythrophagocytosis, which was also seen in a spleen biopsy specimen. The malignant histiocytes in the spleen showed ultrastructural characteristics of histiocytes—namely, abundant cytoplasm with small electron dense granules, large reniform nuclei with a moderate degree of nuclear chromatin condensation, and prominent nucleoli. Activity of serum angiotensin converting enzyme was greatly increased (167 U/l; normal 15–45). The patient died suddenly before treatment.

Case 2—A 27 year old man presented in September 1981 with fever, malaise, sweating, and weight loss. Spleen and liver were palpable 6 and 3 cm below the costal margins. Peripheral, intrathoracic, and abdominal lymph nodes were not enlarged. Laboratory measurements showed moderate pancytopenia and raised serum lactate dehydrogenase activity (928 U/l); serum values of urea, creatinine, bilirubin, alkaline phosphatase, aspartate and alanine transferases, and γ -glutamyltransferase were normal. Bone marrow biopsy showed increased cellularity and infiltration with atypical histiocytes, dispersed and in small foci. These cells showed phagocytosis of erythrocytes and granulocytes. The histiocytes were myeloperoxidase and periodic acid Schiff negative, acid phosphatase diffusely positive with inhibition by tartaric acid, and α -naphthylacetate esterase strongly positive, consistent with malignant histiocytosis. He was given combination chemotherapy with CHOP (1250 mg cyclophosphamide, 100 mg doxorubicin, and 2 mg vincristine intravenously on day 1, and prednisone 100 mg/day on days 1–5). Three courses of chemotherapy were unsuccessful but after removal of the still enlarging spleen peripheral blood values returned to normal. Further courses of chemotherapy failed because of intercurrent infections and lack of cooperation, but reinstitution of regular CHOP then resulted in good clinical remission. The malignant histiocytes, however, did not disappear completely from the bone marrow. Serum activity of angiotensin converting enzyme was measured at regular intervals (figure) and values fell to normal during initial chemotherapy, concomitantly with subjective improvement.

Serum angiotensin converting-enzyme activity in a patient with malignant histiocytosis (case 2). Shaded areas represent courses of CHOP.

The first relapse, with increased activity of the enzyme, responded favourably to splenectomy. The second relapse coincided with severe histiocytic infiltration of the bone marrow and greatly increased activity of the enzyme (137 U/l), which fell to 70 U/l after one course of CHOP and gradually decreased further during subsequent courses. At the end of each interval between treatments the angiotensin converting enzyme activity tended to

rise, probably owing to recurrent histiocytic proliferation. This accorded with the persistence of a small number of malignant histiocytes in the bone marrow and in a liver biopsy specimen at the end of the observation period.

Comment

These two patients with malignant histiocytosis showed increased activities of serum angiotensin converting enzyme. In case 2 the values correlated well with the activity of the disease. Histiocytoses are an ill defined group of disorders. The common characteristic is considered to be proliferation and in some cases activation of macrophages. Increased angiotensin converting enzyme activity may be a sign of increased macrophage activity.

We conclude that the serum angiotensin converting enzyme activity may be useful in the differential diagnosis of malignant histiocytosis and that its values may be used as a parameter of residual tumour during chemotherapy. Return to stable, normal values seems to indicate complete remission.

¹ Anonymous. ACE in sarcoidosis. *Lancet* 1980;i:804-5.

² Yotsumoto H, Imai Y, Kuzuya N, Uchimura H, Matsuzaki F. Increased levels of serum angiotensin-converting enzyme activity in hyperthyroidism. *Ann Intern Med* 1982;96:326-8.

³ Borowsky SA, Lieberman J, Strome S, Sastre A. Elevation of serum angiotensin-converting enzyme level. Occurrence in alcoholic liver disease. *Arch Intern Med* 1982;142:893-5.

⁴ Rømer FK, Emmertsen K. Serum angiotensin-converting enzyme in malignant lymphomas, leukaemia and multiple myeloma. *Br J Cancer* 1980;42:314-8.

⁵ Groopman JE, Golde DW. The histiocytic disorders: a pathophysiologic analysis. *Ann Intern Med* 1981;94:95-107.

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Seizures after infusion of factor VIII

Allergic reactions to blood products are not uncommon, but to our knowledge grand mal seizures after infusion of factor VIII concentrates have not been noted previously. We report on a haemophilic who sustained three epileptiform seizures after replacement treatment with factor VIII for muscle haemorrhage.

Case report

The patient was a 26 year old severe haemophilic who had received large quantities of factor VIII, in the form of cryoprecipitate or specific concentrates, frequently since the age of 12. On a few occasions he had experienced allergic reactions after an infusion, which usually consisted of appreciable pruritus or, rarely, bronchospasm. He had no family history of epilepsy but had sustained a head injury two years previously while under the influence of alcohol. A skull x ray film, a radionuclide brain scan, and the results of a study of cerebral flow were normal at that time.

In July 1981, while an inpatient, he had a grand mal seizure 40 minutes after the infusion of 2000 units of Edinburgh factor VIII concentrate (35 U/kg). It was noted later that he had injected the concentrate himself rapidly over about two minutes. Five months later he again had a tonic clonic seizure, in hospital, lasting four to five minutes and terminated by intravenous diazepam. This followed the rapid infusion of 1000 units of factor VIII one hour before. In June 1982 a further seizure lasting two minutes occurred one hour after rapid self administration of 2000 units of factor VIII.

Brain scans after these three episodes showed no abnormality, and no abnormality was detected on examination of the central nervous system. An electroencephalogram obtained after the last seizure showed a suggestion of an underlying seizure disorder, but no focal abnormality was detected. Anti-

convulsant treatment was never started. The patient also had severe brittle asthma and died later at home in status asthmaticus. Postmortem examination was not carried out.

Comment

We believe that the temporal relation of the seizures to the administration of factor VIII on three occasions makes the factor VIII the most likely aetiological factor in precipitating the seizures. Unusual intravascular particulate material has been noted in the cerebral white matter of a haemophilic treated with large quantities of factor VIII concentrates,¹ and deposition of such particles in a brain with an underlying tendency to seizures may perhaps have been sufficient stimulus to evoke these seizures. The prevalence of electroencephalographic abnormalities in adult haemophiliacs is normal²; the fact that seizures have not previously been noted after infusions of factor concentrates but were in this case may be because this patient, despite repeated warnings, occasionally injected the concentrate over a period of one to two minutes.

¹ Ghatak NR, Husain MM. Unusual intravascular material in the brain. *Am J Clin Pathol* 1976;**65**:508-12.

² Forbes CD, Renfrew S. Electroencephalography in haemophilia and Christmas disease. *Haemostasis* 1975;**4**:36-9.

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Effect of verapamil on enzyme release after early intravenous administration in acute myocardial infarction: double blind randomised trial

Verapamil has infarct reducing properties in experimental myocardial infarction and experimental myocardial ischaemia. In dogs comparisons of different agents with these properties showed a 20% reduction in infarct size after propranolol and a 40% reduction in size after verapamil.¹ Decreased elevation of the ST segment has been reported in several studies. Reduction of myocardial necrosis as quantified histologically and prevention of haemodynamic deterioration have also been described.² Nayler *et al* found that verapamil protected ischaemic rabbit hearts as shown by release of intracellular enzymes, depletion of adenosine triphosphate reserves, and diminishing ultrastructural cellular damage, the best results occurring after prophylactic use of the drug.³

We have conducted a clinical trial to assess whether verapamil administered early in acute myocardial infarction reduced infarct size as estimated by the release of creatine kinase into the circulation. The study was performed during the Danish Multicentre Study on Verapamil in Acute Myocardial Infarction.⁴

Patients, methods, and results

All patients aged up to 75 who had been admitted to the coronary care unit from July 1979 to August 1981 were assessed for the trial. Acute myocardial infarction was defined according to the WHO criteria. Contraindications to the trial were: treatment with beta-blockers, nifedipine, or verapamil; blood pressure below 90 mm Hg; severe pulmonary congestion; cardiac arrest before or at arrival; first degree atrioventricular block (PQ > 0.3 s); second degree or third degree atrioventricular block; bradycardia < 45 beats/min; valvular heart disease; and severe chronic disease. Patients were allocated at random to receive verapamil or placebo. The initial dose of verapamil was 0.1 mg/kg given slowly intravenously followed by 120 mg by mouth thrice daily. Blood samples were taken on arrival and every four hours for 72 hours. Serum total creatine kinase activity was assayed as described by the Scandinavian Committee on Enzymes. The patients received no intramuscular injections during the sampling period. Cumu-

lated creatine kinase value was calculated as described by Norris *et al*,⁵ the fractional disappearance rate being calculated for each patient.

During the trial period 417 patients were admitted to the unit. Two hundred were excluded from the trial and the remaining 217 began treatment. Of the 119 of these patients who fulfilled the WHO criteria for acute myocardial infarction, 19 were later excluded because cumulated creatine kinase values could not be calculated. Reasons were: admission after maximal values had been attained (nine patients), insufficient blood samples (five), death during first 72 hours (two), defibrillation (one), refusal to participate (one), and administrative mistakes (one). Of the 19 patients, 13 were in the verapamil group and six in the placebo group. Cumulated creatine kinase values were therefore available for 100 patients.

The median time from onset of pain to admission was four hours (range 0.5-12.0 hours). Fifty four of the patients received verapamil, and their mean cumulated creatine kinase value was $3711 \pm \text{SEM } 269 \text{ U/l}$. Forty six patients received placebo, and their mean cumulated creatine kinase value was $3436 \pm \text{SEM } 288 \text{ U/l}$. The difference was not significant ($t = 0.70$, $\text{df} = 98$, $0.4 < p < 0.6$) (figure). There was no difference between the treatment groups in age, sex, fractional disappearance rate of creatine kinase, or site of the infarct.

Cumulated creatine kinase values in 100 patients with acute myocardial infarction treated with placebo (n=46) and verapamil (n=54).

Comment

Using the cumulated creatine kinase value as an indication of myocardial damage, this study failed to confirm experimental evidence of infarct reducing properties of verapamil. Dosages of the drug were equivalent to those used in the animal experiments, and the delay before treatment was of the same magnitude as that in the beta-blocker studies reporting a reduction of infarct size. In the experimental studies, however, verapamil was administered either before or shortly after the induced coronary event. Hence the four hour delay in our study might have been responsible for the negative result.

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² Smith HJ, Singh N, Nisbeth HD, Norris RM. Effects of verapamil on infarct size following experimental coronary occlusion. *Cardiovasc Res* 1975;**9**:569-78.

³ Nayler WG, Gray A, Slade A. A protective effect of verapamil on hypoxic heart muscle. *Cardiovasc Res* 1976;**10**:650-62.