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The Effect of *E. Coli* L-Asparaginase on Lipid Metabolism During Induction Chemotherapy of Childhood Acute Lymphoblastic Leukaemia

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S u m m a r y. In the present study we have compared the lipid status in 43 boys and girls with ALL, who were treated by the BFM 90 protocol. Blood samples were obtained for quantitation of serum proteins, lipids, lipoproteins and apoproteins, prior to the start of chemotherapy and after the 4th and the 8th intravenous administration of L-asparaginase in doses of 10,000 IU/m² per infusion. We have found the proteins levels strongly decreased, as L- asparaginase is a well Known inhibitor of the hepatic protein synthesis. The total serum cholesterol, the LDL, Apo-A and the Apo-B lipoproteins levels were elevated in the majority of the children. Further, total triglyceride levels were strongly increased. In contrast HDL levels were decreased. We conclude that, although the changes in lipids metabolism are reversible, the clinicians must be careful during the intravenous administration of L-asparaginase. It is necessary to identify the effect on protein and lipid metabolism because L-asparaginase produces unusual toxicity and sometimes serious morbidity.

INTRODUCTION

L-asparaginase is an enzyme with chemotherapeutic activity against human acute lymphoblastic leukaemia. It is being used successfully in combination with other drugs, for remission induction chemotherapy in childhood acute lymphoblastic leukaemia. L-asparaginase acts primarily by inhibiting protein synthesis in malignant cells, deficient in L-asparagine synthetase activity, and therefore depends on exogenous L-asparagine. We have observed changes of lipid metabolism in the serum of patients treated with L- asparaginase .We wanted to identify these lipids changes and wanted to know whether are due to L-asparaginase and whether or not are reversible.

PATIENTS AND METHODS

Forty three children, twenty four boys and nineteen girls, aged 3,5-13 years, were treated according to the ALL BFM 90 protocol, in which Prednisone was given as monotherapy for the first seven days. L-asparaginase was administered from the 12th to 33rd day, twice a week intravenously (10.000 U/m²) concomitantly with Prednisone and (at the day 15) with vincristine and daunorubicin. The blood was collected from the infusion and the samples were obtained for quantitation of serum lipids, lipoproteins, apoproteins (Al and B100), SGOT, SGPT, serum proteins and thyroid hormones, prior to the start of chemotherapy(A), after the 4th(B) and the 8th administration of L-asparaginase at the 35th day(C).All the children were in fat free diet at last 48 hours and they were also with no any food 12 hours before the blood collection. All the children with thyroid dysfunction or significant changes in the biochemical values during the first week of the chemotherapy, were excluded from the study.

RESULTS

We compare the pre-treatment values(A),to values during the L-asparaginase administration,

day 22, (B), (AB) and to values after the last L-asparaginase, day 35, (C) (AC). In this study the significance level used is P=0,05. Pre-treatment value (A) range of serum total triglycerides, was 8-200 mg/dl, the mean concentration was 96,6±5,7 mg/dl, SD 37,46 mg/dl and the SE 5,7 mg/dl. Significant elevations of mean serum concentration were found for total triglycerides in 14 children in AB measurement, p<0,03 and the range was 10,9-494,8%. In AC measurement we found an elevation of triglycerides values in 15 children which although were not statistically significant, the range was 10-1462,5%. Pre-treatment value range was 133-206 mg/dl of serum total cholesterol, the mean concentration was 167,8±4,2 mg/dl, SD 27,86 mg/dl and the SE 4,25 mg/dl. Significant decrease of mean serum concentration was found for total cholesterol in 15 children, in AC measurement (p<0,02). In measurements AB and AC, we found an elevation of total cholesterol values in 24 children. Although the changes were insignificant, the range was 7,5-143,6% in AB measurement and 3,2-173,7% in AC measurement. Non significant changes of serum concentrations of HDL, LDL, Apo-A, Apo-B 100, SGPT and SGOT were found. Despite these findings, the mean concentrations of Apo-A were elevated up to 11,06% in AB and 7,36% in AC measurements. The mean concentrations of Apo-B were elevated up to 16,16% in AC measurement. The mean concentrations of HDL were decreased up to 11,94%. In contrast the mean concentrations of LDL were elevated up to 1,88% in AB and up to 15,4% in AC measurements. The total proteins and albumins levels were strongly decreased. The mean concentrations of total serum proteins is significant, p<1,36E-0,6 in AB and p<9,97E-12 in AC measurements. Mean plasma albumin concentrations decreased (p<0,001) in AB and in AC, (p<8,87E-12) measurements. The mean concentrations of globulin level was significant (p<0,03) in measurement AC.

DISCUSSION

L-asparaginase is an effective antileukaemic agent and a well known inhibitor of hepatic protein synthesis (1). The decrease of the serum total proteins, albumins and globulins levels has been reported also in other studies (2,3). Further we have found a significant decrease of total serum cholesterol levels in some of the children in this study, as other studies also (1,2) showed. We believe that is mostly due to the impairment of protein synthesis. Thereby we have found the levels of Apo-B 100 and the LDL serum levels decreased as a sequel. It is still unclear the pathogenesis of hypercholesterolemia and the elevation af Apo-B100 and LDL serum levels, in some other children in this study. A possible cause is the decrease of LDL receptors. Cremer et al. (4) who studied the lipid metabolism of a group of children receiving L-asparaginase, concomitantly with prednisone and vincristine, found that the total cholesterol levels increased. The elevation cannot be attributed to L-asparaginase because it was observed, before initiation of the treatment with this drug. It is well known that corticosteroids are agents that elicit lipolysis of triglycerides. Despite their effect on lipid metabolism, plasma lipid changes, have been reporter rarely, with steroids. Total triglyceride levels were strongly increased, as other authors also reported (1,4,5,6). In contrast the serum levels of HDL and Apo-A were decreased. Although the pathogenesis of hypertiglyceridemia is unclear, a suppression of the lipolytic enzymes in plasma must be consider. The severe hyperlipidemia seen in children with ALL, treated with L-asparaginase was benign and transient. The treatment varied from simple observation and dietary fat restriction to drug discontinuation.

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