50 days, and the levelling off of the AFP at this time may well reflect a second short period of synthesis. The mechanism by which the adult non-malignant liver is stimulated to synthesize this fetal protein is not clear. Our data suggest that synthesis may well occur as a result of regenerative activity.

REFERENCES


Vitamin B₆ and Aspartate Aminotransferase Activity in Chronic Liver Disease

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SUMMARY

Serum aspartate aminotransferase (AST) concentrations are commonly determined to detect hepatocellular damage. However, discrepancies between serum AST values and histological signs of active liver damage sometimes occur in patients with cirrhosis.

The enzyme AST requires pyridoxal-5-phosphate (PLP) (active vitamin B₆) as a co-enzyme to express its activity. Since approximately 90% of patients with severe cirrhosis are vitamin B₆-deficient, it has been suggested that vitamin B₆ supplements given to these patients might cause an elevation of falsely low serum AST concentrations.

Treatment of 8 vitamin B₆-deficient cirrhotic patients with pyridoxine hydrochloride (50 mg intravenously twice daily for 1 week) increased their serum AST concentrations from 121 ± 18 (mean ± SEM) to 136 ± 26 IU/l, while treatment of a second group of 9 patients with the active co-enzyme PLP increased AST concentrations from 118 ± 17 to 146 ± 20 IU/l. Neither of these increases was statistically significant. Plasma PLP increased from 2.4 ± 0.7 to 18.5 ± 7.6 ng/ml after pyridoxine, and from 3.3 ± 0.7 to 27.0 ± 6.2 ng/ml after PLP supplementation.

It is concluded that B₆ deficiency is unlikely to be an important determinant of serum AST concentrations in patients with chronic liver disease.


Serum aspartate aminotransferase (AST) concentrations are widely used to detect hepatocellular damage. Elevated serum AST values in hepatic injury are presumably due to leakage of the enzyme from damaged hepatocytes. In acute hepatic damage, e.g. viral hepatitis, the rise in serum AST values precedes hyperbilirubinaemia. Serial AST estimations have been proposed for the early detection of hepatic drug reactions. Serum AST concentrations are used to monitor the progress and response to treatment of patients with chronic active hepatitis. In cirrhosis, serum AST is usually only minimally elevated, or it may even be normal. A normal AST value in cirrhosis is explained by calling the cirrhosis ‘inactive’
or 'well-compensated'. However, on occasion histological signs of activity do not correlate with the AST values, which may be normal even in the presence of histologically proven chronic active hepatitis.  

One possible explanation for variable serum AST values, especially in chronic liver disease, is deficiency of vitamin B₆. AST activity depends on the presence of its co-enzyme, pyridoxal-5-phosphate (PLP). Deficiency of the co-enzyme may thus possibly lead to a falsely low AST estimation. Alternatively, apo-enzyme synthesis may be depressed by co-enzyme deficiency. Controlled vitamin B₆ depletion studies in humans have shown a fall in plasma, erythrocyte and leucocyte AST activities. In vitro addition of PLP increases AST in erythrocytes and in whole blood in direct relationship to the degree of vitamin B₆ deficiency. Administration of the vitamin to B₆-deficient rats increases hepatic transaminase activity. In acute hepatocellular necrosis, a positive correlation between serum AST and PLP is found. Since vitamin B₆ deficiency is common in chronic liver disease, it has been suggested that the administration of pyridoxine to cirrhotic patients might increase serum AST concentrations. In this way falsely low AST estimations would be exposed and the value of serum AST as a marker of hepatic damage would be enhanced.

In this study the effect of vitamin B₆ supplementation on serum AST concentrations in patients with decompensated chronic liver disease was studied.

**PATIENTS AND METHODS**

Pyridoxal-5-phosphate and aspartate aminotransferase were measured by means of an AutoAnalyzer in samples of heparinized blood from 17 patients with decompensated chronic liver disease (biopsy-proven cirrhosis or submassive necrosis with two or more of the following features: encephalopathy, ascites, jaundice, hypo-albuminaemia or prolonged prothrombin time not responding to vitamin K). Blood was taken on admission and again after 7 days of supplementation with thiamine (100 mg intravenously twice daily), ascorbic acid (500 mg intravenously twice daily) and either pyridoxine hydrochloride or PLP (50 mg intravenously twice daily). When possible, blood was again taken 7 days later. Eight patients (6 alcoholics, 1 with secondary biliary cirrhosis, 1 with schistosomiasis) received pyridoxine hydrochloride, and 9 patients (3 alcoholics, 3 with chronic active hepatitis, 1 with primary biliary cirrhosis, 1 with submassive necrosis, 1 with haemochromatosis) received PLP.

**RESULTS**

All the patients had subnormal or borderline plasma PLP concentrations (mean 2.9 ± 1 SE 0.5 ng/ml, normal range 6-20 ng/ml) at the onset of the study, while mean serum AST was moderately elevated at 119 ± 12 IU/l (normal range 5-40 IU/ml). There was no correlation between PLP and AST concentrations. Supplementation with pyridoxine increased serum AST from 121 ± 18 to 136 ± 26 IU/l (13% increase) while serum AST increased from 118 ± 17 to 146 ± 20 IU/l (20% increase) in the group receiving PLP (Fig. 1). Neither of these increases were statistically significant (paired t test). However, the response in individual patients was very variable (Fig. 2). In the group receiving pyridoxine serum AST values increased in 5/8, and in the group receiving PLP serum AST values increased in 6/9. The increases were small, except in 1 patient with chronic active hepatitis.

![Fig. 1. Plasma PLP and serum AST in patients with decompensated chronic liver disease after pyridoxine or PLP (100 mg/24 h for 7 days).](image1)

![Fig. 2. Individual serum AST concentrations in patients with decompensated chronic liver disease after pyridoxine or PLP (100 mg/24 h intravenously for 7 days).](image2)
receiving PLP, in whom AST increased from 80 to 250 IU/l. In this case the AST value decreased to 90 IU/l 1 week later. In 2 other patients with chronic active hepatitis who received PLP, the serum AST values increased from 140 to 165 and from 114 to 142 IU/l. In all, 11 patients showed increased serum AST values, 5 showed decreased values and 1 showed no change after supplementation. One week after supplementation was stopped, a similar variability of response was evident, although mean AST concentrations fell to presupplementation levels.

Plasma PLP concentrations rose from 2.4 ± (1 SE) 0.7 to 18.5 ± 7.6 ng/ml (P<0.05, paired t test) after pyridoxine hydrochloride and from 3.3 ± 0.7 to 27.0 ± 6.2 ng/ml (P<0.005) after PLP. In all 9 patients who received PLP the plasma PLP values increased to normal or supranormal concentrations, but only 4/8 of the pyridoxine-supplemented group responded. However, there was no correlation between changes in plasma PLP concentrations and changes in serum AST values.

**DISCUSSION**

The results of this study do not support the conclusions of Ning et al. that vitamin B therapy will increase circulating transaminase activity in cirrhotic patients with vitamin B deficiency. While transaminase activity may be increased in some patients (9/15 in their study, 11/17 in the present study) others show no increase or may even show a decrease. The severity of the liver disease did not appear to influence the AST response to vitamin B supplementation and the changes in AST concentrations were also independent of circulating PLP levels achieved by supplementation. It therefore appears that vitamin B administration does not consistently alter AST concentrations in patients with decompensated liver disease.

The reasons for the lack of effect of vitamin B on serum AST are not clear. In patients with severe cirrhosis there is malutilization of vitamin B, illustrated by the poor response to pyridoxine in the present study, which is contributory to defective conversion of pyridoxine hydrochloride to PLP and by increased degradation of PLP. However, this is unlikely to explain the present findings regarding AST, since even the PLP-treated group of patients failed to show a significant increase in AST concentrations. Nevertheless, normal plasma PLP levels do not necessarily imply normal tissue levels, for very little is known about hepatic uptake and binding of vitamin B in cirrhosis. As the transaminase apo-enzyme normally combines intracellularly with PLP co-enzyme, persistence of low intrahepatic PLP might offer an explanation for these findings. It is of interest that Frank et al. were unable to increase vitamin B concentrations in rat livers damaged by carbon tetrachloride.

It is possible that AST apo-enzyme continues to be produced and is liberated into the circulation by damaged hepatocytes, but that conditions do not favour combination with exogenous PLP. The half-life of the apo-enzyme in the plasma is likely to be very short since the holo-enzyme AST has a half-life measured in hours; apo-enzymes may be more unstable and therefore more liable to degradation than the complete enzyme. Alternatively, the absolute amount of apo-aspartate aminotransferase in the serum may remain relatively constant over a wide range of enzyme activities, as has been demonstrated by in vitro techniques for apo-alanine aminotransferase. When the baseline AST activities are abnormally elevated, as in the present study, the percentage increase achieved by saturating the apo-enzyme may appear relatively insignificant.

Patients with chronic active hepatitis may be expected to show the greatest rise in AST after PLP supplementation, since hepatocyte necrosis is more prominent in this condition. In this study only 1 such patient had a marked rise (213%); 2 others had more modest rises of 18% and 47%. Nevertheless, it may be of interest to study a larger group of patients with chronic active hepatitis, and such a study is presently underway.

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**REFERENCES**