Evaluation of Pancreatic Exocrine Function and Zinc Absorption in Alcoholism

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Summary: Zinc absorption in alcoholism was studied by a combination of zinc tolerance tests in 382 male patients with alcoholism (more than 140 g/day of ethanol) who had alcohol-induced disease of the liver or pancreas. In study 1, the serum zinc level was measured in all patients, and serum zinc and fecal chymotrypsin levels were compared in various disease groups. In study 2, 14 patients with liver cirrhosis (LC), 15 with chronic pancreatitis (CP), 7 with LC+CP, and 7 controls underwent oral zinc tolerance and zinc dipicolinate tolerance tests, zinc absorption and disorders of pancreatic exocrine functions were examined. In study 1, the serum zinc concentration was significantly lower in the CP and LC groups than in the control group, and the fecal chymotrypsin activity was significantly lower in the CP than in the control groups. In study 2, during the oral zinc tolerance test, the serum zinc concentration 3 hours after administration was significantly lower in the LC, CP and LC + CP groups than in the control group. In these groups, the serum zinc concentration was significantly lower in the abnormal fecal chymotrypsin group than in the control group at 2 and 3 hours after administration of zinc sulfate. In the oral zinc dipicolinate tolerance test, the serum zinc levels 2 and 3 hours after administration were significantly elevated in the control and all disease groups; there were no significant differences between the control and each disease group. These results suggest that reduction of pancreatic exocrine functions by alcohol and chronic reduction of synthesis of ligands such as picolinic acid in the liver are involved in the reduction of serum zinc in alcoholism.

Key words alcoholism, pancreatic exocrine function, zinc tolerance test, zinc dipicolinate tolerance test

INTRODUCTION

Zinc, one of the minor metallic elements, plays a very important role in the maintenance of metabolic functions. A deficiency of zinc causes a growth disorder, dermatopathy, and dysgeusia [1]. Since zinc acts as a coenzyme for carboxypeptidase, one of the pancreatic enzymes [2,3], and is closely related to pancreatic functions, it is considered to be an important factor in digestion and absorption.

Zinc is abundantly present in food and drinking water, and a deficiency of it is rare. However, oligotrophy and abnormalities in digestion and

absorption are frequent complications of alcoholism, causing abnormal metabolism of minor elements [4]. Nakamura et al. [5] has reported that a reduction in pancreatic exocrine functions causes a reduction in zinc absorption. Zinc is excreted primarily from the pancreas together with digestive enzymes [6] and is reabsorbed in the intestinal tract by the action of picolinic acid. Picolinic acid is one of substances that enhances absorption of zinc by its strong chelating ability, but the mechanism is unknown [7].

In this study we examined serum zinc levels and zinc absorption using an oral zinc tolerance test in patients with alcohol-induced disorders of the liver

and pancreas.

SUBJECTS AND METHODS

We studied 382 male patients with alcoholism (more than 140 g/day of ethanol) who were hospitalized for withdrawal from alcohol. The mean patient age was 46.5±11.2 years. Liver cirrhosis (LC) was present in 166 patients, chronic hepatitis (CH) in 57 patients, hepatic fibrosis (HF) in 94 patients, fatty liver (FL) in 65 patients, and chronic pancreatitis (CP) in 42 patients. Of 42 patients with CP, 19 had LC, 2 had CH, 13 had HF, and 5 had FL. The diagnosis of liver diseases, except clinically obvious LC, was made by liver biopsy, and CP was diagnosed according to the 1983 chronic pancreatitis criteria (JSGE) [8]. The control group comprised 29 normal volunteers.

Serum zinc (Zn) concentrations were measured by atomic absorption spectrophotometry of serum collected immediately after hospitalization. Pancreatic exocrine functions were examined by the fecal chymotrypsin test (FCT) and measured by colorimetric analysis using Monotest Chymotrypsin [9].

Oral zinc tolerance test

- 1) In the oral zinc tolerance test, 106 mg of zinc sulfate was orally administered together with 300 ml of water after an overnight fast. The serum Zn concentration was serially measured before administration and 1, 2 and 3 hours after administration.
- 2) In the oral zinc dipicolinate tolerance test, 120 mg of zinc dipicolinate was administered 1 week

after the oral zinc tolerance test, and the serum Zn concentration was serially measured according to the same timetable. Zinc dipicolinate consists of two picolinic acid molecules bound to one zinc atom by chelate bonds [7].

The amount of Zn in the reagents used in both tolerance tests was 24 mg. Informed consent for both the oral zinc and zinc dipicolinate tolerance tests was obtained in writing.

Analysis

- Study 1: The serum Zn level was measured in all patients to determine whether there were differences in the serum Zn concentration between disease groups. Pancreatic exocrine functions were similarly evaluated by measuring fecal chymotrypsin activity.
- Study 2: The 14 LC, 15 CP, and 7 LC+CP patients along with 7 controls who underwent the oral zinc tolerance and zinc dipicolinate tolerance tests were also examined for zinc absorption activity to investigate whether there was any correlation between this activity and the disease type or the kind of pancreatic exocrine disorder.

Statistical analysis was performed with Student's t test, and P< .05 was regarded as significant.

RESULTS

Evaluation of the serum Zn concentration and fecal chymotrypsin activity in the various liver and pancreatic disease groups

The serum Zn concentration was 75.3±18.7 µg/dl in the CP group, and 72.5±19.7 µg/dl in the LC

TABLE 1.
The serum Zn concentration and fecal chymotrypsin activity
in the various liver and pancreatic disease groups

N	Control 29	Chronic Pancreatitis 42	Liver Cirrhosis 166	Chronic Hepatitis 57	Hepatic Fibrosis 94	Fatty Liver 65
S-Zn (µg/dl)	88.6±18.7	75.3±18.7*(33%)	72.5±19.7*(35%)	79.0±17.7 (21%)	83.5±21.9 (17%)	80.4±19.4 (25%)
FCH (U/g)	50.3±20.5	28.4±19.8*(40%)	33.2±26.7 (25%)	57.1±33.4 (14%)	35.4±22.9 (24%)	44.1±30.4 (20%)

FCH: fecal chymotrypsin activity
*P<0.01 compared to control group
Mean±SD (abnormal rate)

group, both significantly lower than the control group ($88.6 \pm 14.4 \mu\text{g/dl}$) (Table 1).

The fecal chymotrypsin activity in the CP group was significantly lower than that in the control ($p < 0.01$).

Evaluation of the oral zinc tolerance and zinc dipicolinate tolerance tests in the LC and CP groups

After administration of zinc sulfate, the serum zinc concentration was lower in the disease groups than in the control group. Of these disease groups, the LC, CP and LC+CP groups showed significantly lower serum zinc concentration than the control group at 2 hours after administration (Fig. 1a).

There was no significant difference in the serum zinc concentration between zinc sulfate and zinc dipicolinate in measurements obtained 1 hour after administration, while those obtained 2 and 3 hours after administration showed significant elevation of

the serum zinc concentration in all disease groups. There were no significant differences between controls and any of the disease groups (Fig. 1b).

Evaluation of the oral zinc tolerance and zinc dipicolinate tolerance tests in the normal and abnormal fecal chymotrypsin subgroups of LC patients

During the oral zinc tolerance test the serum zinc concentration was lower in both the normal and abnormal fecal chymotrypsin groups than in the control group. The serum zinc was significantly lower in the abnormal fecal chymotrypsin group than in the control group 2 hours after zinc sulfate administration. Three hours after administration, the serum zinc was significantly lower in the normal fecal chymotrypsin group and in the abnormal fecal chymotrypsin group than in the control group (Fig. 2a).

Fig. 1a. The oral zinc tolerance tests in the liver cirrhosis and chronic pancreatitis groups.

Fig. 1b. The oral zinc dipicolinate tolerance tests in the liver cirrhosis and chronic pancreatitis groups.

Fig. 2a. The oral zinc tolerance tests in the normal and abnormal fecal chymotrypsin subgroups of liver cirrhosis patients.

Fig. 2b. The oral zinc dipicolinate tolerance tests in the normal and abnormal fecal chymotrypsin subgroups of liver cirrhosis patients.

There was no significant difference in the serum zinc concentration between zinc sulfate and zinc dipicolinate measured 1 hour after administration. At 2 and 3 hours after administration of zinc dipicolinate, the serum zinc concentration was significantly elevated in all disease groups, and there were no significant differences between the control and any of the disease groups (Fig. 2b).

Evaluation of the oral zinc tolerance and zinc dipicolinate tolerance tests in the normal and abnormal fecal chymotrypsin subgroups of CP patients

During the oral zinc tolerance test, the serum zinc concentration was lower in the CP group than in the control group. It was significantly lower in the abnormal fecal chymotrypsin group than in the control group at 2 and 3 hours after administration of zinc sulfate (Fig. 3a).

Fig. 3a. The oral zinc tolerance tests in the normal and abnormal fecal chymotrypsin subgroups of chronic pancreatitis patients.

Fig. 3b. The oral zinc dipicolinate tolerance tests in the normal and abnormal fecal chymotrypsin subgroups of chronic pancreatitis patients.

There was no significant difference in the serum zinc level between zinc sulfate and zinc dipicolinate if measured 1 hour after their administration, while at 2 and 3 hours after administration of zinc dipicolinate, the serum zinc concentration was significantly elevated in all disease groups, and there was no significant difference between the control and each disease group (Fig. 3b).

DISCUSSION

Insufficient intake of zinc in alcoholism is considered to be due to an unbalanced diet [4]. In this study, however, the serum zinc concentration was significantly lower in the LC and CP patients. This result cannot be explained solely by insufficient intake of zinc because zinc is present in drinking water as well as food. The results of the oral zinc tolerance test showed that zinc absorption ability was significantly lower in the LC and CP groups than in the control group. The serum zinc concentration in LC patients is considered to be reduced by enhancement of zinc excretion in the urine [10,11], reduction of binding proteins in the serum [12], and reduction of absorption in the gastrointestinal tract [12-14]. Unlike patients with viral LC, many patients with alcoholic LC have pancreatic disorders even though they do not satisfy the diagnostic criteria for CP. These patients were classified into the normal and abnormal groups according to the fecal chymotrypsin level, and the serum zinc level was examined. There was no significant difference between the two groups, but there was a greater difference between the control group and the abnormal group than between the control group and normal group. Similar results were obtained for the CP patients. Reduction of the serum zinc concentration in alcoholism was more often observed in the abnormal fecal chymotrypsin group than in the normal fecal chymotrypsin group, suggesting that it is related to the reduction of pancreatic exocrine function. The mechanism of reduction of the serum zinc level by reduction of pancreatic exocrine function may be that zinc absorption is reduced by the decrease of picolinic acid secreted into the intestine. The mechanism of the action of picolinic acid is unknown, but it is thought that picolinic acid is produced from tryptophan in the liver and kidney, secreted with the pancreatic juice into the intestine, and bound to Zn to generate zinc dipicolinate, thus enhancing the absorption of zinc [7].

Based on the results of animal experiments,

Suzuki et al. [13] have proposed that zinc absorption is divided into two phases; diffusion and active transport [15,16]. Transport of zinc within 1 hour after administration is considered to be due to diffusion because of the concentration difference between the interior and exterior of the intestine. Thereafter, active transport by carriers such as histidine and picolinic acid becomes the major pathway of zinc transportation. In the present study, the serum zinc concentration was significantly lower in both CP and LC groups than in the control group only on measurements obtained 2 and 3 hours after administration. However, there were no differences between the control and the CP and LC groups in serum zinc concentration measured 2 and 3 hours after administration of zinc dipicolinate, suggesting that chelated zinc was actively absorbed. In LC patients without reduction of pancreatic exocrine function, zinc absorption was also improved by administration of zinc dipicolinate. This suggests that the reduction of serum zinc in patients with alcoholic LC is caused by a reduction of synthesis of picolinic acid in the liver in addition to the potential disorder of pancreatic exocrine functions.

These results suggest that the alcohol-induced reduction of pancreatic exocrine function and chronic reduction of ligands such as picolinic acid synthesized in the liver are involved in the reduction of serum zinc in alcoholism.

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