Berberine therapy of hypertyraminemia in patients with liver cirrhosis.

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Abstract

Plasma tyramine concentrations were abnormally high in cirrhotic patients with hepatic encephalopathy. Oral administration of berberine hydrochloride corrected hypertyraminemia in cirrhotics and also prevented the elevation of plasma tyramine levels following the oral tyrosine load, probably because of berberine-inhibition of bacterial tyrosine decarboxylase in the intestine. This is a new approach as Anti-amine therapy for cirrhotic patients.

KEYWORDS: tyramine, berberine, liver cirrhosis, tyrosine load

*PMID: 7136858 [PubMed - indexed for MEDLINE]
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BERBERINE THERAPY OF HYPERTYRAMINEMIA IN PATIENTS WITH LIVER CIRRHOSIS

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Received January 8, 1982

Abstract. Plasma tyramine concentrations were abnormally high in cirrhotic patients with hepatic encephalopathy. Oral administration of berberine hydrochloride corrected hypertyraminemia in cirrhotics and also prevented the elevation of plasma tyramine levels following the oral tyrosine load, probably because of berberine-inhibition of bacterial tyrosine decarboxylase in the intestine. This is a new approach as “Anti-amine” therapy for cirrhotic patients.

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Plasma tyramine concentrations have been recently reported to be abnormally elevated in patients with liver cirrhosis (1) and in dogs with portacaval shunt (2). Hypertyraminemia may result in cardiovascular and neurologic complications of liver diseases, since tyramine has various pharmacologic actions on these systems as an indirect sympathomimetic amine (3, 4). Tyramine is also the precursor of octopamine, which acts as a central “false neurotransmitter” (5). Tyramine can be formed by decarboxylation of tyrosine mainly by bacterial aromatic amino acid decarboxylase within the large intestine (6). Berberine inhibited tyrosine decarboxylase and tryptophanase activities of Streptococcus faecalis and Escherichia coli but not those of the animal enzymes (7, 8).

In this communication, changes in plasma tyramine concentrations following an oral tyrosine load were examined in cirrhotic patients with hypertyraminemia and berberine was administered orally to the patients for correcting the elevated plasma levels. This is the first report that berberine can be used as a therapeutic agent for hepatic encephalopathy.

SUBJECTS AND METHODS

Three control subjects, a case of fulminant hepatitis and 14 cirrhotic patients with (9 cases) and without hepatic encephalopathy (5 cases), who were admitted to Okayama University Hospital from 1978 to 1980, were used for this study. Various oral doses of berberine hydrochloride (600-800 mg/day, Nihon Kayaku Co. Ltd., Tokyo) were administered to these patients. Clinical findings such as the electroencephalogram (EEG), neurologic symptoms and signs were examined during the treatment. Fifty mg of tyrosine per kg body weight was administered orally in the early morning to a cirrhotic patient without encephalopathy, and the effects of oral berberine administration on plasma tyramine concentrations
were studied.

Blood samples for tyramine determination were drawn from a peripheral vein in the early morning and the plasma separated was quickly frozen at −80 °C until analysis by the method of Faraj et al. (1).

RESULTS

Fasting plasma tyramine level was determined in normal subjects and in

<table>
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<tr>
<th>Table 1. Plasma tyramine concentration in cirrhotic patients with and without hepatic encephalopathy</th>
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<td>No. of patients</td>
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<td>Control</td>
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<td>Liver cirrhosis</td>
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<td>Without encephalopathy</td>
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Results are shown as Mean ± SE. *P < 0.01

Fig. 1. Effect of berberine administration on plasma tyramine concentrations in a cirrhotic patient (M. M., 48-year-old man) following the oral tyrosine loading test. Arrows indicate the oral tyrosine load at a dose of 50 mg/kg body weight in the early morning. Plasma tyramine concentrations were determined one and a half h, and 3 h, after the load. Berberine hydrochloride was administered orally at the time indicated by symbols (●, 200 mg) before and/or after tyrosine load. Oral intakes and intravenous injections were not made until the 3rd h of the load.
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cirrhotic patients with and without hepatic encephalopathy. The levels were significantly higher in cirrhotic patients with hepatic encephalopathy (2.56 ± 0.25 μg/dl) than in normal controls (1.53 ± 0.08 μg/dl). In non-encephalopathic patients with cirrhosis, the value of 1.88 ± 0.13 μg/dl was also higher than in normal controls, but the difference was not significant (Table 1). One and a half h after oral loading doses of tyrosine to a patient with compensated cirrhosis (50 mg/kg), the plasma tyramine level rose from 1.9 to 2.3 μg/dl. The level then fell to 2.1 μg/dl 3 h after the load (Fig. 1). In the same patient, given 200 mg berberine orally five times with an 8 h interval for 1.5 days, however, the fasting plasma tyramine level decreased from 2.0 μg/dl (before berberine administration, i.e. 2 days before the tyrosine load) to 1.4 μg/dl (just before the oral load of tyrosine). Then the oral dose of tyrosine was given after berberine administration had already been discontinued. Plasma tyramine concentrations following tyrosine administration again rose slightly to 1.7 μg/dl in the 3rd h of the load. When berberine administration was continued for longer periods even after tyrosine was given, the plasma tyramine level after the tyrosine overload was rather lower in the 1.5th h of the load and then only slightly increased in the 3rd h.

Although the clinical efficacy of berberine administration alone was not evaluated because of other simultaneous therapeutic maneuvers such as amino acid infusion and oral administration of lactulose, five out of eight patients with

![Graph](image)

**Fig. 2.** Clinical course of Case Y. N. with decompensated cirrhosis of the liver (49-year-old man). Berberine hydrochloride was administered at a dose of 600 mg/day for 64 days. No encephalopathy occurred even after discontinuation of berberine.
hepatic encephalopathy (one fulminant hepatitis and 4 with liver cirrhosis) showed arousal during berberine administration. A 49-year-old man with liver cirrhosis and diabetes mellitus is shown as a representative case (Fig. 2). Disorientation, drowsiness and muscle weakness were observed shortly after admission. The EEG findings revealed diffuse slow waves ($\theta$ wave dominant). The blood ammonia level was 268 $\mu$g/dl. Berberine (600 mg/day), lactulose and fradionycine were administered simultaneously by gastric tubing at the time of precoma. Arousal from hepatic encephalopathy was rapidly obtained, and the EEG findings and neurologic abnormalities also markedly improved.

DISCUSSION

Berberine is a plant alkaloid contained in Berberis vulgaris and B. aristala Linn, which belongs to the group of isoquinoline derivatives with a quaternary base in the molecule. Berberine exhibits a potent bacteriostatic activity and is frequently used as an effective remedy for various enteric disorders. Inhibition of bacterial tyrosine decarboxylase by berberine has been reported to be the result of competition between pyridoxal phosphate, a coenzyme of this enzyme, and berberine for the apoenzyme at the optimum pH (5.5) (7, 8).

Marked elevation of plasma tyrosine concentrations in patients with liver cirrhosis may induce accumulation in the central nervous system of its minor metabolites, tyramine and octopamine, which may be responsible for hepatic encephalopathy (5). Abnormal metabolism of tyrosine as shown by impaired tyrosine tolerance may be due to decreased activities of the initial rate-limiting enzymes of the tyrosine oxidative pathway such as tyrosine transaminase, 4-hydroxyphenylpyruvic acid oxidase and homogentisic acid oxidase (9). The hypertyraminemia of cirrhosis resulted primarily from overproduction of tyramine, but not from the decreased clearance rate of the amine (10). Most of the tyramine overproduction from tyrosine could result from the gastrointestinal bacterial tyrosine decarboxylases, and the amine may enter the systemic circulation via portal-systemic shunts. Increasing dietary protein from 40 to 80 g per day raised the fasting tyramine concentration by 30 to 70 % within 3 days in both encephalopathic and non-encephalopathic cirrhosis (1). Since tyramine crosses the blood-brain barrier only slowly, this amine may not be delivered to the central nervous system even in the presence of chronic hypertyraminemia. Tyrosine transport into the brain has been reported to be accelerated in encephalopathic cirrhotics (11). In liver failure, therefore, elevation of the brain tyrosine content (12) may be related to the accelerated synthesis of tyramine and octopamine.

The accumulation of tyramine and octopamine may cause lowering of peripheral resistance with resultant high cardiac output, reduction in renal function, and cerebral dysfunction in cirrhotic patients (5). Normalization of plasma tyramine elevation can be obtained by oral berberine administration, probably
due to berberine-inhibition of bacterial tyrosine decarboxylase in the intestine. This new approach might be evaluated as "Anti-amine" therapy in cirrhotic patients for preventing and treating hepatic encephalopathy and other complications, which are often observed in cirrhotics. Direct correlations between berberine administration and plasma tyramine levels in cirrhotic patients are now in progress using a larger number of patients.

REFERENCES