EFFECTS OF RANITIDINE ON PLASMA CLEARANCE OF INDOCYANINE GREEN IN PATIENTS WITH LIVER CIRRHOSIS

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Summary

The effects of ranitidine on plasma clearance of ICG were investigated in 68 cirrhotic patients (9 were positive for HBsAg, 33 were alcoholics and 26 had cryptogenic cirrhosis). The ICG clearance test was performed before and after ranitidine administration.

In 31 patients treated with ranitidine (150 mg perorally), the plasma ICG clearance were 233.6 ± 20.4 ml/min (mean ± S.E.) and 239.2 ± 20.5 ml/min before and after ranitidine, respectively. In the 37 treated with intravenous ranitidine 50 mg, the corresponding values were 205.4 ± 17.7 ml/min and 206.4 ± 17.9 ml/min. There was no significant change in the plasma clearance of ICG or the elimination rate constant after ranitidine administration. Even in patients with decompensated liver cirrhosis, no significant change was demonstrated in the plasma ICG clearance after ranitidine.

These results led to the conclusions that ranitidine does not reduce the hepatic blood flow and that it is a safe and useful drug for the treatment of gastrointestinal tract bleeding in patients with liver cirrhosis.

Key Words: Liver cirrhosis, Plasma ICG clearance, Ranitidine.

Introduction

It is well-known that in fulminant hepatic failure and in the terminal stage of liver cirrhosis, respiratory insufficiency, renal failure, gastrointestinal tract bleeding (GI tract bleeding) and multi-organ failure are occasionally encountered in addition to hepatic insufficiency. GI tract bleeding is the most frequently seen of these disorders, and it can significantly worsen the prognosis. Therefore, it is important to prevent GI tract bleeding in patients with hepatic failure.

Macdougall et al. reported that cimetidine,
a well-known histamine H₂-receptor antagonist, prevented GI tract bleeding in patients with fulminant hepatic failure, although the survival rate was not improved. Since that report, histamine H₂-receptor antagonists have been used for prophylaxis and treatment of GI tract bleeding, even in patients with hepatic failure. Feely et al.⁵,⁶, however, questioned the use of histamine H₂-receptor antagonists in these situations, suggesting that they reduce the hepatic blood flow. Their conclusion was based upon the results of the indocyanine green (ICG) clearance test, which showed impairment in 8 healthy volunteers given cimetidine. Many investigators do not accept Feely's results, reasoning that the reduced ICG clearance after treatment with cimetidine or ranitidine does not reflect a reduction of the hepatic blood flow and in fact arises from decreased hepatic extraction of ICG⁵,⁶.

The generally accepted view is that hepatic blood flow plays an important role in the maintenance of hepatic cell functions, particularly in diseased states. Accordingly, if a histamine H₂-antagonist reduces the hepatic blood flow, it should not be used in the treatment of GI tract bleeding accompanying hepatic failure. In view of this concept, the authors investigated the effects of ranitidine, a new histamine H₂-receptor antagonist, on ICG clearance in patients with liver cirrhosis.

**Subjects and methods**

This clinical study investigated the effects of ranitidine on plasma ICG clearance in patients with chronic liver diseases at 8 institutions. The subjects consisted of 68 patients (49 males and 19 females) with liver cirrhosis (Table 1). Informed consent to inclusion in this study was obtained from each patient. The mean age of the patients was 54.1 years (ranging from 19 to 74 years). Regarding the etiology of liver cirrhosis, 9 patients were positive for HBsAg, 33 were alcoholic and thought to have alcoholic liver cirrhosis and 26 had cryptogenic cirrhosis.

As shown in Table 1, 53 of the 68 patients were assessed as being in the compensated stage of liver cirrhosis, while the remainder were thought to be in the decompensated stage because of ascites and/or jaundice.

**ICG clearance test:** A dose of ICG (0.5 mg/kg body weight) was rapidly injected into the antecubital vein of the fasting patients early in the morning. Blood samples were taken from the vein of the opposite arm before and at 5, 10 and 15 minutes after the injection. The patients were kept in the supine position during the ICG clearance test. Two weeks after the first ICG clearance test, 31 patients ingested one tablet containing 150 mg of ranitidine, while 37 patients received 50 mg of

| Number of patients | 29 | Compensated stage | 24 | Oral administration |
| Number of patients | 8 | Decompenated stage | 7 |
| Sex Male | 22 | 6 | Intravenous administration |
| Sex Female | 7 | 2 | Oral administration |
| Age (Mean ± S.E.) (years) | 53.3±1.8 | 53.9±2.8 | 52.7±3.2 | 59.0±2.8 |
| Causes: Alcohol | 16 | 12 | Intravenous administration |
| Causes: HB | 4 | 3 | Oral administration |
| Causes: Unknown | 9 | 9 | Intravenous administration |
| Causes: Unknown | 5 | 3 | Oral administration |