Evaluation of the Long-term Administration of Rifaximin for More than Three Years in the Treatment of Repeated and Recurrent Overt Hepatic Encephalopathy

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Abstract:
The patient was a 65-year-old man with alcoholic liver cirrhosis who had been admitted to hospital 5 times for repeated and recurrent overt hepatic encephalopathy (HE) despite numerous therapies, including disaccharide, branched-chain amino acid (BCAA) formula, L-carnitine and zinc. After the additional administration of rifaximin (1,200 mg/day orally), his consciousness level was well controlled for 3 years without any adverse effects. The long-term administration of rifaximin may be useful and safe for managing recurrent overt HE, although the maintenance dosage and duration of rifaximin and safety should be evaluated in patients with ameliorated HE.

Key words: rifaximin, liver cirrhosis, overt hepatic encephalopathy, hyperammonemia

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Introduction
Hepatic encephalopathy (HE) is one of the most serious complications seen in patients with liver cirrhosis (LC) and is closely associated with a poor prognosis and a reduced health-related quality of life (1, 2). Since HE shows a wide spectrum of clinical signs, such as flapping tremor and consciousness disturbance, ranging from minor defects in orientation and coordination to deep coma, HE was recently classified into two categories: covert HE and overt HE (3). Covert HE involves minimal HE and grade I coma, while overt HE involves grade II-IV coma according to the West-Haven criteria (1, 3). Although the pathogenesis of HE in LC has not been fully clarified, neurotoxic substances, such as ammonia, mainly produced in the gut and portal-systemic shunting (PSS) are closely associated with the onset and recurrence of HE (2, 4). Thus, synthetic disaccharides (lactulose or lactitol) that decrease the production and absorption of ammonia in the gut have been historically used as first-line treatment for LC patients with both covert and overt HE worldwide (2, 5).

The oral administration of poorly absorbable antibiotics, such as neomycin, kanamycin, vancomycin, metronidazole, and polymyxin B, has also been performed with or without synthetic disaccharides in patients with HE and/or hyperammonemia (2, 5). However, these drugs cannot be administered over long periods of time, as they often induce severe and irreparable complications. Furthermore, according to the guideline of the Japanese Ministry of Healthy, Labor and Welfare, these drugs are not approved for insurance coverage in medical practice.

Rifaximin is a poorly absorbable oral antimicrobial drug that has been used in many countries to manage HE and/or hyperammonemia in LC and has shown few adverse effects, even with long-term administration (6). In Japan, the administration of rifaximin in the clinical setting has been approved since December 2016 (6). Recently, two studies reported the efficacy and safety of the long-term administration of rifaximin in Japanese patients with LC (7, 8). However, the clinical data on the efficacy and safety of the administration of rifaximin for over two years to LC patients

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with overt HE remain insufficient.

We herein report the case of a cirrhotic patient with repeated and recurrent overt HE that was well controlled by the administration of rifaximin for over three years.

## Case Report

The patient was a 65-year-old man who had been diagnosed with alcoholic liver injury since the beginning of May, 2004. He was admitted to the Department of Neurology in our hospital and received treatment for cerebral infarction in the right corona radiata with left numbness and weakness of the upper and lower limbs. His clinical symptoms associated with cerebral infarction completely disappeared with treatment, and he was discharged on the middle of May, 2004. However, he voluntarily stopped his medication and stopped attending follow-up appointments on the middle of November, 2011.

He was first admitted to our department on the middle of April, 2013, because of spontaneous hematemesis. Upper gastrointestinal endoscopy was immediately performed, and the focus of the bleeding was found to be esophageal varices (location, inferior to middle; form, 2; color, blue; red color sign, negative). We therefore performed endoscopic ligation therapy to treat his esophageal varices. At that time, we estimated the severity of liver damage and checked for other complications, such as hepatocellular carcinoma (HCC), with biochemistry and imaging tests [e.g., abdominal sonography and computed tomography (CT)]. The severity of liver dysfunction was Child-Pugh B, and the score was 8 points. The findings of imaging tests were incompatible with the diagnosis of LC without ascites and HCC. His estimated ethanol intake was >52 g/day for 40 years. Serum virus markers related to hepatitis B and C viruses were all negative, and serum titers of antinuclear antigen and antimitochondrial antigen were also negative. Based on these findings, we diagnosed the patient with alcoholic LC without HCC. Regarding the body composition analysis, his height was 170 cm, his body weight was 70 kg, and his body mass index was 24.22.

Following endoscopic treatment for esophageal varices, since no re-bleeding of the esophageal varices was noted and the liver damage was not exacerbated, he was discharged on the end of April, 2014, and followed up at the outpatient clinic of our hospital. At the first admission, he received branched-chain amino acid (BCAA) granules (12 g/day) for hypoalbuminemia and a proton pump inhibitor (PPI; esomeprazole magnesium hydrate; 20 mg/day). Later, as he complained abdominal distension due to ascites, diuretics (furosemide 20 mg/day and spironolactone 50 mg/day) were prescribed. At this point, he had completely discontinued alcohol intake since his first admission on the middle of April, 2013. However, he was again admitted to the hospital on the beginning of May, 2015, due to disturbance of consciousness. At this point, he was diagnosed with overt HE with coma grade III according to the criteria of Inuyama symposium in Japan (9).

The precipitating factors of HE were complex and included constipation due to decreased daily stool passage (once every two days several days before the onset of overt HE), dehydration due to overdosage of diuretics and protein overload, as he mentioned consuming roughly 200 g of roast meat 2 days before the onset of overt HE. His laboratory data on admission showed the following: red blood cell (RBC) count, 331×10^4 μL; hemoglobin (Hb), 12.6 g/dL; white blood cell (WBC) count, 3,310 μL; platelet count, 60×10^4 μL; total bilirubin (T-Bil.), 0.7 mg/dL; aspartate aminotransferase (AST), 37 IU/L; alanine aminotransferase (ALT), 34 IU/L; γ-glutamyl transpeptidase (γ-GTP), 114 IU/L; albumin, 3.6 g/dL; prothrombin time activity (PT), 69%; creatinine (CRNN), 1.07 mg/dL; and blood ammonia (B-NH3), 205 μg/dL. His Child-Pugh classification was B and his Child-Pugh score was 9. Dynamic CT showed a typical LC pattern with an irregular surface and atrophic liver, with a slight amount of ascites. We immediately performed the intravenous administration of BCAs-enriched amino acid solution (Aminoiban®; Otsuka Pharmaceutical, Tokyo, Japan) 500 mL/day with 24-h continuous administration of a glucose-electrolyte mixed solution and then prescribed lactulose (60 mL/day). After these treatments, his consciousness gradually improved to a normal state. He was discharged on the middle of May, 2015, and again followed up at the outpatient clinic of our hospital with periodic evaluations (monthly). For the management of HE, he was prescribed lactulose (60 mL/day) and enteral nutrition (Aminoiban EN®: total calories: 240 kcal/package, including 24 g of protein; 100 g/day) with a low-protein diet of 60 g/day, magnesium oxide (1.5 g/day) and PPI (20 mg/day).

However, he was again admitted on the beginning of July, 2015, and received treatments for overt HE (coma grade II). The precipitating factor of overt HE was constipation due to decreased daily stool passage. During this second admission period, he received kanamycin (oral, 500 mg/day) for 14 days; however, this treatment showed no apparent effect on his consciousness level. In addition, lactulose was changed to lactitol (18 g/day), due to the fact that the patient found the lactulose to be too sweet and as a result he consumed it irregularly. Furthermore, polaprezinc (150 mg/day, including 34 mg/day of zinc) was administered to prevent gastric mucosal injury and to improve the ammonia metabolism. Subsequently, from May 2015 to April 2017, he was admitted a total of five times because of overt HE with or without mild ascites. The final admission was the beginning of April, 2017, when he suddenly complained of disorientation early in the morning on the day of admission. The precipitating factor of HE in this instance was considered to be constipation and dehydration due to an overdose of furosemide. He immediately received infusion therapy with Aminoiban® and lactulose enema, and his coma grade improved from III to II. Although the dosage of lactitol was changed from 18 g/day to 36 g/day during admission, we decided to start rifaximin (orally 1,200 mg/day) along with other ammonia-
lowering agents from the end of April, 2017.

Table 1 shows the laboratory data obtained before the administration of rifaximin, including pancyclopenia, hypoalbuminemia, low prothrombin time-international normalized ratio, and hyperammonemia. The Child-Pugh score was 9 points. Tumor markers for HCC were almost within the baseline range. Abdominal CT showed an atrophic liver without HCC or ascites (small volume) with marked increase in serum tumor marker levels that was detected during a routine follow-up examination via abdominal sonography and dynamic CT in March 2020. These therapies for early gastric cancer and HCC were able to be performed safely without the exacerbation of HE or any other complications, such as infection or an exacerbation of the patient’s liver damage. At present, in May 2020, his consciousness level is almost normal, and his general condition is relatively well-maintained.

Table 1. Biochemical Data before Administration of Rifaximin.

| Hematology             | T-Protein (g/dL) | Blood Chemistry           | Blood coagulation       | Tumor markers            |
|------------------------|------------------|----------------------------|-------------------------|--------------------------|
| WBC (μL)               | 2,550 (3,000-8,600)* | T-Bil. (mg/dL) 0.7 (0.2-1.2) | PT activity/PT-INR 52 %/1.40 | AFP (ng/mL) 3.0 (0.0-13.4) |
| RBC (x10³μL)           | 255 (400-530)    | AST (IU/L) 87 (8-40)       |                          |                          |
| Hb (g/dL)              | 9.6 (13.5-17.5)  | ALT (IU/L) 35 (5-35)       |                          |                          |
| Ht (%)                 | 28.3 (40.0-50.0) | ALP (IU/L) 292 (112-334)   |                          |                          |
| Platelet (x10³μL)      | 44 (130-340)     | γGT (IU/L) 66 (8-65)       |                          |                          |
| T-Protein (g/dL)       | 6.6 (6.5-8.0)    |                            |                          |                          |
| Albumin (g/dL)         | 3.3 (3.9-4.9)    |                            |                          |                          |
| CRP (mg/dL)            | 0.35 (0-0.40)    |                            |                          |                          |
| BUN (mg/dL)            | 40 (8-20)        |                            |                          |                          |
| CRNN (mg/dL)           | 0.92 (0.5-1.2)   |                            |                          |                          |
| B-NH₃ (μg/mL)          | 140 (30-86)      |                            |                          |                          |

Biochemical examination was performed in April, 2017.

*Baseline ranges are shown in Ninohe Prefectural Hospital.

WBC: white blood cells, RBC: red blood cells, Hb: hemoglobin, Ht: hematocrit, T-Bil.: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γGT: γ-glutamyl transpeptidase, T-Protein: total protein, CRP: C-reactive protein, BUN: blood urea nitrogen, CRNN: creatinine, B-NH₃: plasma ammonia concentration, BTR: serum branched-chain amino acids to tyrosine ratio, PT-INR: prothrombin time-international ratio, anti-mitochondrial antibody, AFP: α-fetoprotein, PIVKA-II: prothrombin-induced vitamin K absent-II

Discussion

A systemic evaluation, including an assessment of the severity of liver damage, the existence of PSS, participating factors, exacerbating factors and other complications [e.g., spontaneous bacterial peritonitis (SBP)], should be performed prior to the management of HE in LC patients. (1, 2, 11) In particular, an evaluation of the disease type according to the severity of liver damage is very important; for example, hepatocellular injury-dominant type (in-
including acute-on-chronic type) usually shows hyperbilirubinemia and low prothrombin time activity, while shunt-dominant type shows slight or mild hepatocellular damage. These disease types directly affect the prognosis and quality of life (11). Our case showed Child-Pugh grade B liver damage before the administration of rifaximin, which was maintained at grade B throughout the administration of rifaximin. However, regarding PSS, although only esophageal varices were observed at the first admission (2015), dilation of the inferior mesenteric vein from the superior mesenteric vein and veins of retzius from the inferior vena cava was newly observed at the fifth admission (2017). No other shunts, including splenorenal shunt, were observed during the course of illness.
The treatment of hepatic encephalopathy (HE) in patients with liver cirrhosis (LC) is crucial for maintaining cognitive function and improving quality of life.

**Table 2. History of Admission and Medications for Hepatic Encephalopathy before and after Administration of Rifaximin.**

| Before administration of rifaximin (2015.5-2017.4) | After administration of rifaximin (2017.4-2020.5) |
|---------------------------------------------------|---------------------------------------------------|
| History of admission/maximal coma grade of HE     | History of admission/maximal coma grade of HE     |
| First admission: 2015.5/III                       | No newly admission.                               |
| Second admission: 2015.7/II                       |                                                   |
| Third admission: 2016.4/II                        |                                                   |
| Fourth admission: 2017.2/II                       |                                                   |
| Fifth admission: 2017.4/III (involves the period of administration of rifaximin) |                                                   |

| Medications for HE (including ammonia-lowering agents) | Medications (including ammonia-lowering agents) |
|-------------------------------------------------------|-------------------------------------------------|
| Lactulose (60 mL→90 mL/day) changes to lactitol (18 g/day→36 g/day) | Lactitol (36 g/day→18 g/day)                     |
| Kanamycin sul fate (500 mg/day, only 2 weeks in first admission only) | Rifaximin (1,200 mg/day)                         |
| BCAA enriched nutrient (Aminoleban EN®) 50 g/day→100 g/day→150 g/day→100 g/day | BCAA enriched nutrient (Aminoleban EN®) (100 g/day→50 g/day) |
| BCAA granules (LIVACT® granules) (12 g/day→9 g/day) | BCAA granules (LIVACT® granules) (8 g/day→stopped→12 g/day) |
| L-carnitine (300 mg/day→600 mg/day→900 mg/day) | L-carnitine (300 mg/day→600 mg/day→300 mg/day→stopped→300 mg/day→600 mg/day) |
| Zinc (polaprezinc) (34 mg/day) | Zinc (polaprezinc) (34 mg/day)                   |
| Other medications | Other medications |
| Proton pump inhibitor (esomeprazole magnesium hydrate) 20 mg/day | Proton pump inhibitor (esomeprazole magnesium hydrate) 20 mg/day |
| Magnesium oxide (1.5 g/day) with other laxatives | Magnesium oxide (0.7-15 g/day) with other laxatives |
| Clostridium butyricum (Miya BM®) 3.0 (g/day) | Clostridium butyricum (Miya BM®) (3.0 g/day) |
| Diuretics (furosemide 20 mg/day and spiranolactone 50 mg/day) | Diuretics (stopped→spiranolactone 25 mg/day) |

**Precipitating factors of HE in LC include dietary protein overload, gastrointestinal bleeding (rupture of gastroesophageal varices), bowel movement abnormality (mainly constipation), infection, excessive administration of sedative/analgesic agents, electrolyte abnormality due to overdose of diuretic agent, dehydration, and surgery, including transjugular intrahepatic portosystemic shunt. Furthermore, hypoxemia, systemic circulatory disturbance, hypoglycemia, hypotension, serum electrolyte abnormality (particularly sodium, potassium and magnesium), and hypoalbuminemia have been also known to exacerbate HE (11). In the present case, constipation and/or the over-intake of protein might have had an important impact on the patient’s condition, despite the administration of lactitol and magnesium oxide, lubiprostone and semisodium A-B calcium. In addition, dehydration due to the overdose of furosemide might have precipitated the onset of overt HE at the fifth admission before the administration of rifaximin.**

Lactulose or lactitol is a first-line therapy in LC patients with overt HE and/or hyperammonemia. In Japan, BCAA-enriched formulas, including infusion solutions, enteral nutritional supplement, and BCAA granules, have been also widely used, depending on both the clinical stage (coma or recovery stage) and the presence or absence of protein-energy malnutrition (PEM) (11-14). Infusion therapy with BCAA-enriched amino acid solution has generally been used during the overt coma stage, although its use has not been adopted worldwide (11, 12). Enteral nutritional supplement (Aminoleban EN®) and BCAA granules have been used in the recovery stage of HE and/or with PEM (11, 13, 14). In particular, it is necessary to adjust the amount of enteral nutritional supplement according to the dietary protein dosage. Furthermore, L-carnitine (L-CA) and zinc have been used as ammonia-lowering agents. Carnitine (CA) plays an important role in fat metabolism and energy production in the mitochondria and is also closely associated with the detoxification of ammonia via the urea cycle (15). LC is a disease that shows a secondary state of CA deficiency (16), although our recent study showed that the prevalence of secondary CA deficiency is low in LC, as evaluated by the serum CA level (17). At present, although the administration of L-CA and/or acetyl-L-CA (ALC) has also been used as an optional therapy for LC patients with overt or covert HE (18), this drug is still not covered by the Japanese National Insurance System when used to treat overt HE (19). Zinc is an essential trace element with various biological effects (20). As a previous report suggests that zinc deficiency is closely associated with hyperammonemia (21), zinc supplementation has been evaluated in LC patients with hyperammonemia and/or HE (22). Our recent study of Japanese LC patients with hyperammonemia also showed that zinc (zinc acetate) supplementation for three months seemed effective and safe (23). Furthermore, we clearly indicated that the serum zinc level in LC patients showed a negative correlation with the serum albumin level (24). Although these data suggest that zinc supplementation may be effective for managing hyperammonemia, zinc acetate and other drugs containing zinc (e.g., polaprezinc used in this case), the use of these drugs in the treatment of overt HE, is not currently approved for insurance coverage. **Table 2 summarizes the history of admissions and medications in our case before and after the administration of rifaximin. The B-NH3 level stabilized after the initiation of rifaximin treatment, which was effective for reducing the**
doses of other drugs in the long-term management of HE.

Rifaximin is a second-line drug for the treatment of HE, and its indications—according to the guidelines of the American Association for the Study of Liver Diseases and European Association for the Study of the Liver—include HE (covert HE and overt HE), idiopathic PSS, and a hyperammonemic state in chronic liver disease (1-3). Rifaximin is also recommended for use in LC patients with overt HE and/or hyperammonemia by the Japanese Society of Liver Diseases (19). However, because data on Japanese LC patients with HE (coma grade I) and/or hyperammonemia are limited to within three months, the efficacy and safety of long-term rifaximin treatment have remained unclear (6). Recently, Nishida et al. reported that long-term rifaximin treatment (median follow-up period: 62 weeks) was effective and safe in decompensated LC patients with overt HE (7). During long-term treatment in LC patients, it is important for patients with at risk for the development of recurrent HE to consider the ideal dosage and duration of rifaximin treatment for cirrhotic patients with ameliorated HE.

In conclusion, we experienced a cirrhotic patient with recurrent and recurrent overt HE that was complicated with early gastric cancer and HCC. It was considered that the long-term control of overt HE by treatments involving rifaximin therapy could allow these complications to be smoothly treated.

Several intrahepatic and extrahepatic complications appear during long-term treatment in LC patients. Indeed, the present case was complicated with early gastric cancer and HCC. It was considered that the long-term control of overt HE by treatments involving rifaximin therapy could allow these complications to be smoothly treated.

In conclusion, we experienced a cirrhotic patient with recurrent and recurrent overt HE that was considered to be well controlled by the administration of rifaximin for more than three years. Although no apparent adverse drug reactions were observed in this case, in the near future, further studies and discussions concerning the efficacy and safety of the long-term administration of rifaximin are needed to confirm the ideal dosage and duration of rifaximin treatment for cirrhotic patients with ameliorated HE.

Informed consent was obtained from the patient included in this study.

The authors state that they have no Conflict of Interest (COI).

Yudai Fujiwara and Kazuyuki Suzuki contributed equally to this work.

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