

[ORIGINAL ARTICLE]

Efficacy of Switching from Kanamycin Sulfate to Rifaximin in Patients with Hepatic Cirrhosis

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Abstract:

Objective This study evaluated the efficacy associated with switching to rifaximin in patients with hepatic cirrhosis receiving kanamycin sulfate for the treatment of hepatic encephalopathy and hyperammonemia.

Methods We included 37 patients who switched from kanamycin sulfate to rifaximin at our institution from January 2017 to December 2018. The onset of hepatic encephalopathy and changes in blood ammonia values during a six-month period were retrospectively evaluated.

Results There were 4 (11%) patients with hepatic encephalopathy at the time of switching from kanamycin sulfate to rifaximin. The cumulative incidence of hepatic encephalopathy was 3% and 16% at 3 and 6 months later, respectively. The blood ammonia levels at the time of switching to rifaximin and at 3 and 6 months later were 94 (range, 20-243) $\mu\text{g/dL}$, 95 (range, 33-176) $\mu\text{g/dL}$, and 81 (range, 32-209) $\mu\text{g/dL}$, respectively, and no significant changes were observed. However, in the 11 patients receiving an oral dose of <1,500 mg/day of kanamycin sulfate, the blood ammonia levels at the time of switching and at 3 and 6 months later were 136 (range, 35-243) $\mu\text{g/dL}$, 95 (range, 33-150) $\mu\text{g/dL}$, and 63 (range, 43-124) $\mu\text{g/dL}$, respectively. Furthermore, the blood ammonia levels significantly decreased at the time of the switching to rifaximin and at three and six months later ($p=0.043$ and $p=0.011$, respectively).

Conclusion Switching to rifaximin in hepatic cirrhosis patients receiving kanamycin sulfate to treat hepatic encephalopathy and hyperammonemia showed effects that were equivalent to or greater than the original therapy, thereby demonstrating the clinical efficacy.

Key words: cirrhosis, hepatic encephalopathy, kanamycin sulfate, rifaximin

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Introduction

Hepatic encephalopathy is a brain dysfunction caused by hepatic failure and portosystemic shunts. The condition presents as a broad spectrum of neurological or psychiatric abnormalities, ranging from subclinical alterations to coma (1). Overt encephalopathy occurs in 30-41% of cirrhosis patients, and recurrence is common (2, 3). Hepatic encephalopathy is a poor prognosis factor (4), and an improvement in hepatic encephalopathy and the prevention of recurrence are important in the management of hepatic cirrhosis.

The efficacy of nonabsorbable disaccharides and poorly absorbed antibiotics, such as rifaximin, in treating hepatic

encephalopathy has been reported (5, 6). A meta-analysis has also shown that poorly absorbed antibiotics were superior to nonabsorbable disaccharides in reducing the risk of hepatic encephalopathy (7). After being approved in Italy in 1985 (8), rifaximin has received approval in more than 80 countries and territories to date. In Japan, kanamycin sulfate was used as a poorly absorbed antibiotic before approval to use rifaximin was obtained in 2016 (9). Since the approval of rifaximin, patients have been switched from kanamycin sulfate (10). However, the efficacy associated with switching from kanamycin sulfate to rifaximin has not been sufficiently analyzed. Furthermore, the association between the dose of kanamycin sulfate prior to the switch and the efficacy after the switch to rifaximin have not been clarified.

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Given the above, we evaluated the efficacy of switching to rifaximin in patients with hepatic cirrhosis receiving kanamycin sulfate for the treatment of hepatic encephalopathy and hyperammonemia.

Materials and Methods

Patients

This study included 37 patients with hepatic cirrhosis who had been treated with kanamycin sulfate for hepatic encephalopathy and hyperammonemia and who were switched to rifaximin at our institution from January 2017 to December 2018. The inclusion criteria were as follows: 1) patients who had been taking kanamycin sulfate for at least three months prior to switching, 2) patients who had received rifaximin at a dose of 1,200 mg/day, and 3) patients who continued taking rifaximin for at least 6 months.

Method

After switching to rifaximin, the onset of hepatic encephalopathy and changes in blood ammonia values during a six-month period were retrospectively evaluated. The degree of hepatic encephalopathy was determined on the basis of West Haven criteria (1). The onset of hepatic encephalopathy was defined as the appearance of overt encephalopathy. This study was approved by the institutional review board of our institution.

Statistical analyses

The Kaplan-Meier method was used to obtain the cumulative incidence of hepatic encephalopathy. Repeated analysis of variance tests were performed on blood ammonia levels at the time of switching to rifaximin and at three and six months later. Multiple comparisons were performed using Bonferroni tests. EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used for statistical analyses (11). Each value is presented as the median, and statistical significance was set at $p < 0.05$.

Results

Patient background characteristics

The patient background characteristics are shown in Table 1. There were 24 (66%) men with a median age of 68 years old. The background hepatic diseases were alcohol, hepatitis B virus (HBV), hepatitis C virus (HCV), HBV+HCV, nonalcoholic fatty liver disease, and others in 13 (35%), 7 (19%), 3 (8%), 1 (3%), 3 (8%), and 10 (27%) patients, respectively. Twenty-six patients (70%) had complications. Major complications were hypertension, diabetes, dyslipidemia, hyperuricemia, atrial fibrillation and others in 16 (43%), 15 (41%), 6 (16%), 6 (16%), 2 (5%), and 11 (30%) patients, respectively. At the time of switching from kanamycin sulfate to rifaximin, there were 7 (19%), 24

(65%), and 6 (16%) patients with Child-Pugh classifications of A, B, and C, respectively. Ascites, hepatic encephalopathy, hepatocellular carcinoma, esophageal varices, and portosystemic shunts with vessel diameters of ≥ 10 mm were found in 20 (54%), 4 (11%), 5 (13%), 18 (49%), and 26 (70%) patients, respectively. A combination of oral drugs including nonabsorbable disaccharides, branched-chain amino acids, L-carnitine, zincs and diuretics were given to 24 (65%), 31 (84%), 9 (24%), 5 (14%) and 22 (59%) patients, respectively. The dosage for the oral administration of kanamycin sulfate was $< 1,500$ mg/day and $\geq 1,500$ mg/day in 11 (30%) and 26 (70%) patients, respectively. The median duration for the oral administration of kanamycin sulfate was 20 months.

Cumulative incidence of hepatic encephalopathy after switching to rifaximin

Hepatic encephalopathy was reported in 6 patients (16%) after switching to rifaximin. The cumulative incidence of hepatic encephalopathy was 3% and 16% at three and six months later, respectively (Fig. 1). The course of the onset of hepatic encephalopathy for those six patients at six months before and after switching to rifaximin is shown in Fig. 2. Three patients (50%) had no hepatic encephalopathy prior to the rifaximin switch, and their Child-Pugh Scores increased 6 months after the rifaximin switch compared to before the rifaximin switch (Table 2).

Blood ammonia levels after switching to rifaximin

The blood ammonia levels at the time of switching to rifaximin and at three and six months later were 94 (range, 20-243) $\mu\text{g/dL}$, 95 (range, 33-176) $\mu\text{g/dL}$, and 81 (range, 32-209) $\mu\text{g/dL}$, respectively. No significant changes were observed in the blood ammonia levels at the time of switching to rifaximin or at three or six months later (Fig. 3a).

The dosage for the oral administration of kanamycin sulfate was 500 mg/day, 750 mg/day, 1,500 mg/day, 2,000 mg/day, and 2,250 mg/day in 1 (3%), 10 (27%), 21 (57%), 2 (5%) and 3 (8%) patients, respectively. The daily dose of 1,500 mg was the most frequently administered dose. We thus divided the patients into 2 groups according to the dose of kanamycin sulfate: the low dose ($< 1,500$ mg/day) group and the high dose ($\geq 1,500$ mg/day) group. We then checked whether or not blood ammonia levels would change in the high and low kanamycin dose groups when we switched from kanamycin to rifaximin.

The blood ammonia levels for the 11 patients who received an oral dose of $< 1,500$ mg/day of kanamycin sulfate at the time of switching to rifaximin and at 3 and 6 months later were 136 (range, 35-243) $\mu\text{g/dL}$, 95 (range, 33-150) $\mu\text{g/dL}$, and 63 (range, 43-124) $\mu\text{g/dL}$, respectively. Thus, the blood ammonia levels significantly decreased at the time of switching to rifaximin and at three and six months after switching to rifaximin ($p = 0.043$, $p = 0.011$) (Fig. 3b). The blood ammonia levels for the 26 patients receiving an oral dose of $\geq 1,500$ mg/day of kanamycin sulfate at the time of

Table 1. Characteristics of Hepatic Cirrhosis Patients Who Switched from Kanamycin Sulfate to Rifaximin.

Variables	n=37, median (range) or n (%)
Age, year	68 (29-84)
Sex, male/female	24 (66)/13 (34)
Etiology	
Alcohol	13 (35)
Hepatitis B virus	7 (19)
Hepatitis C virus	3 (8)
Hepatitis B virus+Hepatitis C virus	1 (3)
Non-Alcoholic fatty liver disease	3 (8)
Others	10 (27)
Complications	
Hypertension	16 (43)
Diabetes	15 (41)
Dyslipidemia	6 (16)
Hyperuricemia	6 (16)
Atrial fibrillation	2 (5)
Others	11 (30)
Child-Pugh classification, A/B/C	7 (19)/24 (65)/6 (16)
Ascites	20 (54)
Overt encephalopathy	4 (11)
Hepatocellular carcinoma	5 (13)
Esophageal varices	18 (49)
Portosystemic shunts*	26 (70)
Concomitant oral medication	
Nonabsorbable disaccharides	24 (65)
Branched-chain amino acids	31 (84)
L-carnitine	9 (24)
Zincs	5 (14)
Diuretics	22 (59)
Dose of kanamycin sulfate, <1,500 mg/day/≥1,500 mg/day	11 (30)/26 (70)
Kanamycin sulfate administration period, months	20 (4.7-118.1)
Aspartate amino transferase, IU/L	40 (16-84)
Alanine aminotransferase, IU/L	24 (7-53)
Platelet, ×10 ⁴ /μL	7.3 (2.4-21.3)
Albumin, g/dL	3.2 (1.7-4.6)
Total bilirubin, mg/dL	1.5 (0.3-5.0)
Prothrombin activity, %	61 (32-89)
Ammonia, μg/dL	94 (20-243)
Creatinine, mg/dL	0.82 (0.36-1.61)
Estimated glomerular filtration rate, mL/min/1.73 m ²	67.3 (34.5-139.5)

*Patients with a maximum shunt vessel diameter of 10 mm.

switching to rifaximin and at three and six months later were 93 (range, 23-177) μg/dL, 96 (range, 33-176) μg/dL, and 94 (range, 28-209) μg/dL, respectively. No significant changes in the blood ammonia levels were observed at the time of switching to rifaximin or at three or six months later (Fig. 3c).

Child-Pugh class after switching to rifaximin

The changes in the Child-Pugh classes distribution after switching to rifaximin are shown in Fig. 4. On comparing the state at the time of switching to rifaximin with that at 6 months later, the Child-Pugh class had improved in 3 pa-

tients (8%). The contributing factors to an improved Child-Pugh class were an improvement in hepatic encephalopathy (0/3, 0%), albumin levels (1/3, 33%), total bilirubin levels (2/3, 66%), prothrombin activity (1/3, 33%) and ascites (0/3, 0%). In contrast, the Child-Pugh class had worsened in 7 patients (19%). The contributing factors to a worsened Child-Pugh class were worsening of hepatic encephalopathy (0/7, 0%), albumin levels (4/7, 57%), total bilirubin levels (2/7, 29%), prothrombin activity (1/7, 14%) and ascites (3/7, 43%).

Concomitant oral medication after switching to rifaximin

Oral concomitant medications affect hepatic encephalopathy and blood ammonia levels. Therefore, we investigated the transition of oral concomitant medications after switching to rifaximin. The transition of oral concomitant medications is shown in Fig. 5. There were 5 patients (14%) who changed oral concomitant drugs due to hepatic encephalopathy or hyperammonemia. We added nonabsorbable disaccharides to 2 patients (5%) and L-carnitine to 3 patients (8%).

Adverse events

The main adverse events were gastrointestinal disorders

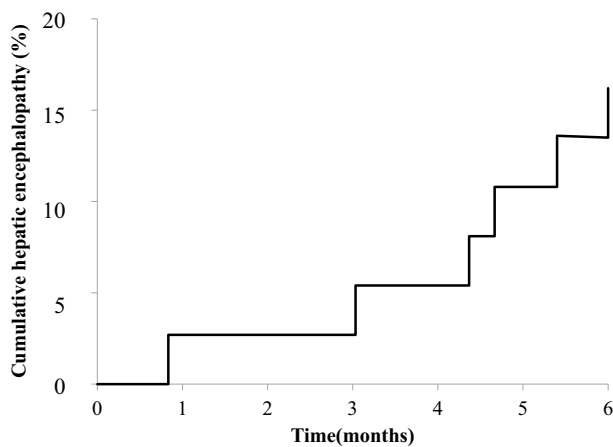


Figure 1. The cumulative incidence of hepatic encephalopathy after switching from kanamycin sulfate to rifaximin was 3% and 16% after three and six months, respectively.

(14%, 5 of 37 patients) and itching (14%, 5 of 37 patients). The details of gastrointestinal disorders were diarrhea (8%, 3 of 37 patients), constipation (3%, 1 of 37 patients), and abdominal pain (3%, 1 of 37 patients). No patients needed to discontinue rifaximin because these adverse events were not serious.

Discussion

In Japan, kanamycin sulfate has been used in the clinical setting as a poorly absorbed antibiotic for hepatic encephalopathy. Kanamycin sulfate is an aminoglycoside antibiotic effective against Gram-positive and Gram-negative bacteria discovered in Japan in 1957 (12). However, kanamycin sulfate has not been approved for the treatment of hepatic encephalopathy or hyperammonemia. Furthermore, no clear evidence has been found proving its safety or efficacy in long-term administration. Although serum concentrations of kanamycin sulfate after oral administration at a 6 g/day dose were reported to be $\leq 2 \mu\text{g/mL}$ (13), its safety, including long-term nephrotoxicity, has not been adequately reported. Conversely, the serum concentrations of rifaximin after oral administration at a 1,200 mg/day dose were reported to be $\leq 58 \text{ ng/mL}$ (14), and the onset of renal impairment caused by long-term oral administration has been ruled out (6). Regarding the aminoglycoside antibiotics neomycin and rifaximin, no differences in the efficacy were reported between the two groups in the treatment of hepatic encephalopathy in a double-blind, randomized comparative clinical study (15). In Japan, the long-term administration of rifaximin was reported to be effective in preventing the recurrence of hepatic encephalopathy in patients with cirrhosis and a history of

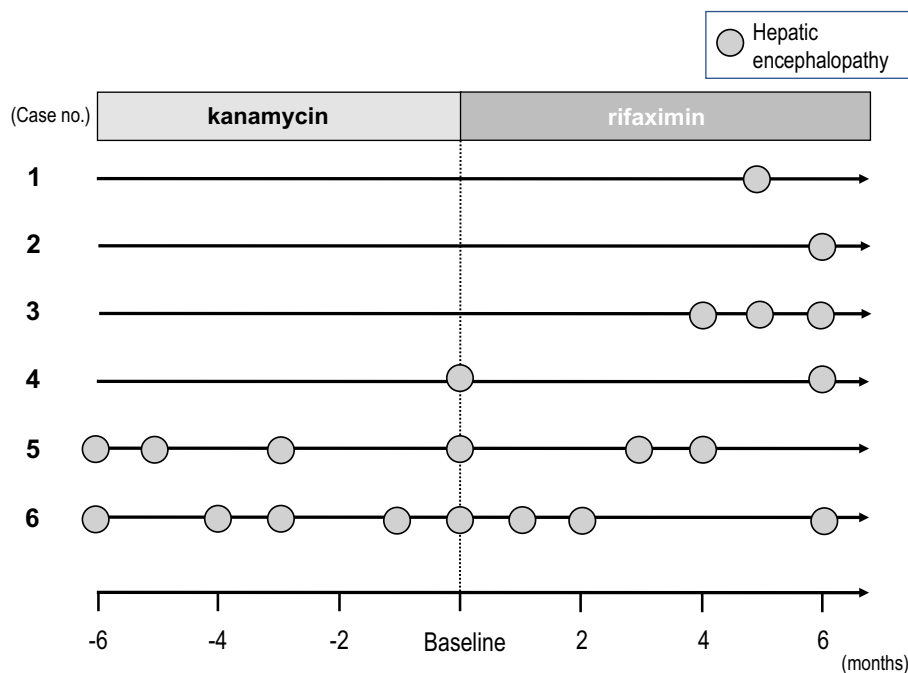


Figure 2. The onset of hepatic encephalopathy six months before and after switching to rifaximin. Circles indicate that patients developed hepatic encephalopathy at least once a month.

Table 2. Characteristics of Patients with Hepatic Encephalopathy after Switching from Kanamycin Sulfate to Rifaximin.

Case no.	1	2	3	4	5	6
Age	44	67	78	84	78	68
Sex	Male	Female	Female	Female	Female	Male
Etiology	Alcohol	HBV	HBV	HCV	Cryptogenic	HCV
Child-Pugh score	10	7	10	10	7	9
Ascites	Yes	No	Yes	No	No	Yes
Overt encephalopathy	No	No	No	Yes	Yes	Yes
Hepatocellular carcinoma	Yes	No	No	No	No	Yes
Esophageal varices	Yes	No	Yes	Yes	No	Yes
Portosystemic shunts*	Yes	Yes	Yes	Yes	Yes	No
Concomitant oral medication						
Nonabsorbable disaccharides	Yes	No	No	Yes	No	Yes
Branched-chain amino acids	Yes	Yes	Yes	Yes	Yes	No
L-carnitine	No	Yes	No	No	No	Yes
Zincs	No	No	No	Yes	No	No
Diuretics	Yes	Yes	Yes	Yes	Yes	Yes
Dose of kanamycin sulfate, mg	750	1,500	1,500	1,500	2,000	2,000
Kanamycin sulfate administration period, months	12.8	11.0	8.8	12.2	43.8	34.5
Time to onset of overt encephalopathy, months	4.7	6.0	4.4	5.4	3.0	0.8
Child-Pugh score 6 months after switching kanamycin sulfate to rifaximin	11	9	12	9	8	8

* Patients with a maximum shunt vessel diameter of ≥ 10 mm.

HBV: hepatitis B virus, HCV: hepatitis C virus

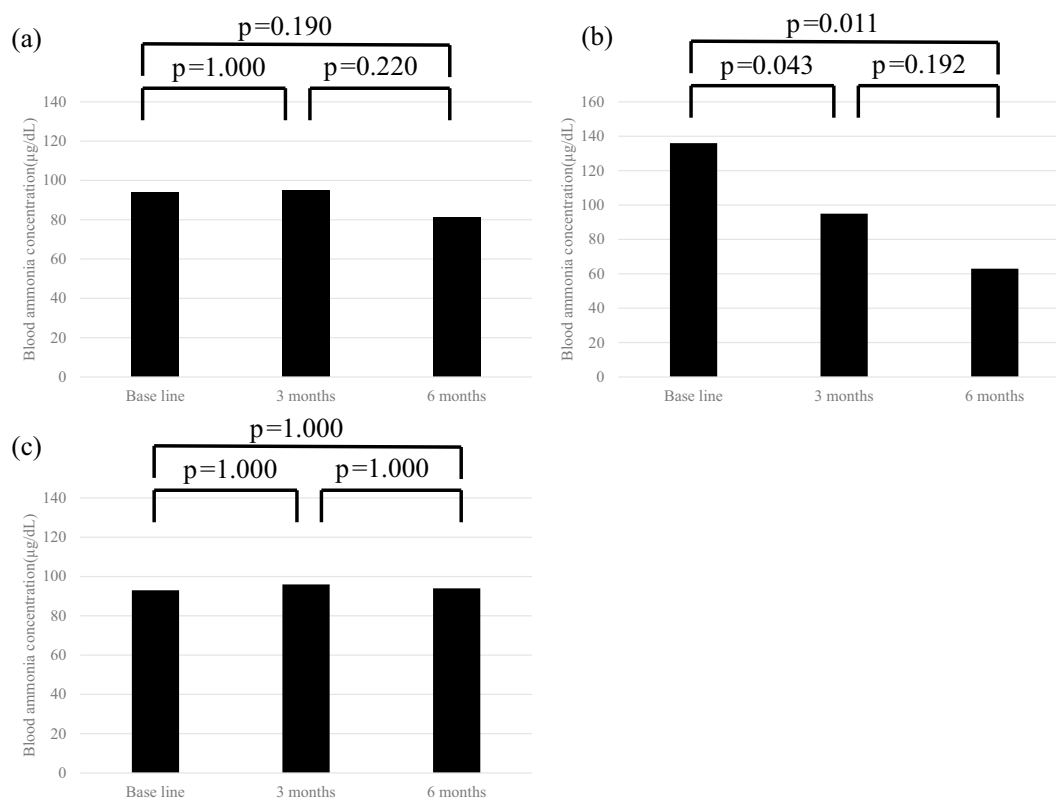


Figure 3. Changes in blood ammonia levels after switching from kanamycin sulfate to rifaximin. (a) All patients who switched from kanamycin sulfate to rifaximin. (b) Patients who switched from kanamycin sulfate to rifaximin who were receiving an oral dose of $<1,500$ mg/day of kanamycin sulfate. (c) Patients who switched from kanamycin sulfate to rifaximin who were receiving an oral dose of $\geq 1,500$ mg/day of kanamycin sulfate.

hepatic encephalopathy (10). While that study also included patients who switched from kanamycin sulfate to rifaximin, detailed assessments were not performed on the patients who switched from kanamycin sulfate to rifaximin.

Thirty-seven patients with hepatic cirrhosis receiving oral kanamycin sulfate as prophylaxis for hepatic encephalopathy in this study switched to rifaximin, and 6 patients (16%) developed hepatic encephalopathy during a six-month period, while the remaining majority of patients had controlled disease. Among the patients in whom the onset of hepatic encephalopathy was observed, 3 (50%) did not present with hepatic encephalopathy at the time of switching to rifaximin. These patients were those in whom the Child-Pugh score increased during the course of treatment after switching, and the aggravation of hepatic cirrhosis was thought to have affected the onset of hepatic encephalopathy.

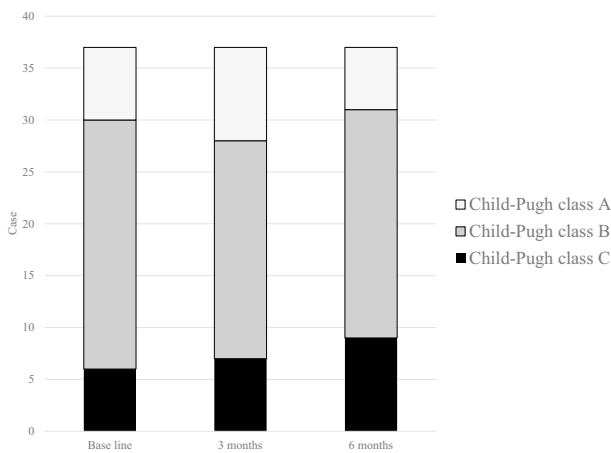


Figure 4. Patients with Child-Pugh class A, B, and C after switching to rifaximin. On comparing the status at the time of switching to rifaximin with that at six months later, the Child-Pugh class had improved in 3 patients (8%) but worsened in 7 patients (19%).

As blood ammonia concentrations did not show an increasing trend over the course of six months following the switch to rifaximin, rifaximin appeared to be at least as effective as (if not more than) kanamycin sulfate. The dosage of kanamycin sulfate and the changes in blood ammonia levels after switching to rifaximin were also evaluated. The changes in the ammonia levels after switching were compared with a daily kanamycin sulfate dose in two groups. No significant changes in the ammonia level were found after switching in the group that received an oral dose of $\geq 1,500$ mg/day of kanamycin sulfate, but a significant decrease in the serum ammonia level was observed after switching to rifaximin in the group that received an oral dose of $<1,500$ mg/day. These results suggest that 1,200 mg/day of rifaximin may have a stronger blood ammonia-lowering effect than $<1,500$ mg/day of kanamycin sulfate, so switching may have a greater effect, particularly in patients receiving a lower dose of kanamycin sulfate. The difference observed in the daily dose of kanamycin sulfate in this study may have been due to the unclear optimal dose for hepatic encephalopathy and the large number of orally administered capsules. Kanamycin sulfate comes in 250-mg capsules and is administered orally at a dose of 2,000-4,000 mg/day for infectious enteritis. Since patients with hepatic cirrhosis have to take kanamycin sulfate for a long period of time and since these patients may be taking more than one oral drug, the use of kanamycin sulfate at a low dose has been increased in many patients.

It was reported that the Child-Pugh score improved after 12 weeks of rifaximin administration in patients with liver cirrhosis who had a history of hepatic encephalopathy (10). Improvements in the blood albumin levels, bilirubin levels, and prothrombin activity also contributed to the improvement of the Child-Pugh score, just as did the improvement of hepatic encephalopathy. In our study, on comparing the status at the time of switching to rifaximin and that at six

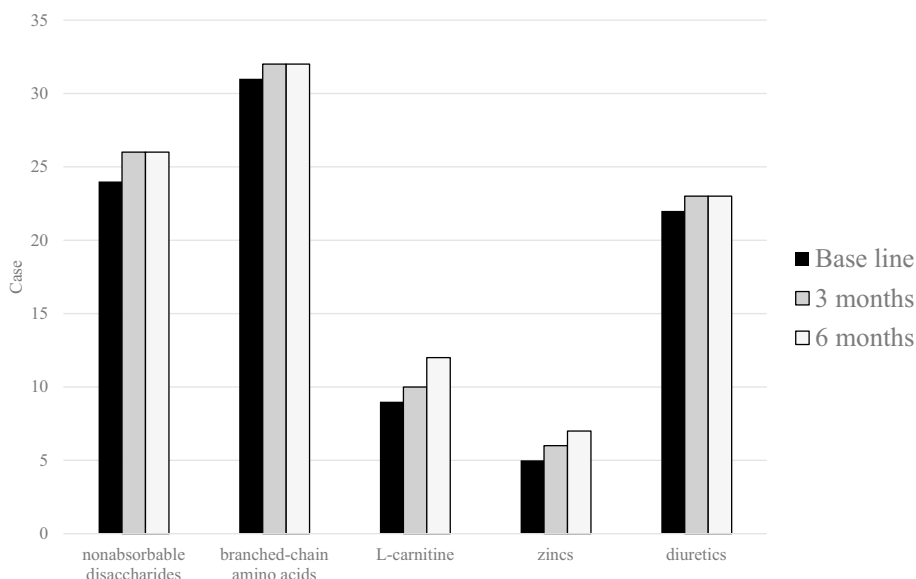


Figure 5. Concomitant oral medication after switching to rifaximin.

months later, the number of patients with a worsened Child-Pugh score was greater than the number of patients with an improved score. These results suggested that the long-term administration of rifaximin might not improve the liver function.

One limitation of this study was the fact that it was a retrospective study targeting a small number of patients at a single site, which may have resulted in biases. We selected patients who could be treated with both kanamycin sulfate and rifaximin for a certain period of time and attempted to evaluate the efficacy in relatively stable cirrhosis patients.

In conclusion, the clinical utility of switching to rifaximin in hepatic cirrhosis patients receiving kanamycin sulfate for the treatment of hepatic encephalopathy and hyperammonemia was demonstrated, as it exhibited equivalent or greater effects than the original treatment.

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

References

- Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology* **60**: 715-735, 2014.
- Amodio P, Del Piccolo F, Pettendò E, et al. Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients. *J Hepatol* **35**: 37-45, 2014.
- Romero-Gómez M, Boza F, García-Valdecasas MS, García E, Aguilar-Reina J. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. *Am J Gastroenterol* **96**: 2718-2723, 2001.
- D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* **44**: 217-231, 2006.
- Sharma BC, Sharma P, Agrawal A, Sarin SK. Secondary prophylaxis of hepatic encephalopathy: an open-label randomized controlled trial of lactulose versus placebo. *Gastroenterology* **137**: 885-891, 2009.
- Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* **362**: 1071-1081, 2010.
- Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. *BMJ* **328**: 1046, 2004.
- De Marco F, Santamaria A, D'ariento A. Rifaximin in collateral treatment of portal-systemic encephalopathy: a preliminary report. *Curr Ther Res* **36**: 668-674, 1984.
- Suzuki K, Endo R, Takikawa Y, et al. Efficacy and safety of rifaximin in Japanese patients with hepatic encephalopathy: a phase II/III, multicenter, randomized, evaluator-blinded, active-controlled trial and a phase III, multicenter, open trial. *Hepatol Res* **48**: 411-423, 2018.
- Suzuki H, Sezaki H, Suzuki F, et al. Real-world effects of long-term rifaximin treatment for Japanese patients with hepatic encephalopathy. *Hepatol Res* **49**: 1406-1413, 2019.
- Kanda Y. Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant* **48**: 452-458, 2013.
- Umezawa H, Ueda M, Maeda K, et al. Production and isolation of a new antibiotic: kanamycin. *J Antibiot (Tokyo)* **10**: 181-188, 1957.
- Hewitt WL, Finegold SM. Laboratory studies with kanamycin. *Ann N Y Acad Sci* **76**: 122-128, 1958.
- Williams R, James OF, Warnes TW, Morgan MY. Evaluation of the efficacy and safety of rifaximin in the treatment of hepatic encephalopathy: a double-blind, randomized, dose-finding multicentre study. *Eur J Gastroenterol Hepatol* **12**: 203-208, 2000.
- Pedretti G, Calzetti C, Missale G, Fiaccadori F. Rifaximin versus neomycin on hyperammonemia in chronic portal systemic encephalopathy of cirrhotics. A double-blind, randomized trial. *Italian J Gastroenterol* **23**: 175-178, 1991.

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