Short Communication

Cross-over study in hyperammonemia patients for efficacy, safety, and acceptability of a new lactulose preparation (SK-1202) compared to approved drug

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Aim: A novel jelly lactulose preparation (SK-1202) has been developed to improve compliance and reduce the elevation of blood glucose levels in diabetic patients. To compare the equivalence in the efficacy and safety of SK-1202 and an approved commercially available syrup preparation, we undertook a randomized multicenter cross-over study in hyperammonemia patients with liver cirrhosis who were taking lactulose.

Methods: Forty-four patients were enrolled and took each preparation for 2 weeks. Efficacy was evaluated using the Number Connection Test, blood ammonia concentration, coma grade, and the flapping tremor grade. Safety was evaluated by the number of adverse events observed, vital signs, and laboratory tests. We also examined the acceptability of each preparation using questionnaires evaluating sweetness, aftertaste, ease of use, and preference of the preparations.

Results: There were no differences in efficacy or safety between SK-1202 and the approved syrup preparation. With regard to the acceptability evaluation, given over 80% of the participants chose the SK-1202 preparation, it appears to be preferred by patients.

Conclusions: It is expected that SK-1202 could represent a useful agent for patients with hepatic encephalopathy.

Key words: hyperammonemia, lactulose, liver cirrhosis, new preparation, SK-1202, taste

INTRODUCTION

LACTULOSE SYRUP HAS been used for hyperammonemia and constipation for many years in many countries around the world.1–3 According to the Japanese guidelines for hepatic cirrhosis, disaccharides such as a lactulose are recommended for patients with hepatic encephalopathy (evidence level, high; strength, strong recommendation).4 However, one important issue associated with lactulose syrup is its excessively sweet taste, which ultimately influences patient compliance with treatment. An additional issue to consider is that the lactulose syrup, formulated in accordance with the Japanese Pharmacopoeia, US Pharmacopoeia, or European Pharmacopoeia, contains some free lactose and galactose, and thus, should be used with caution in patients with diabetes mellitus. In order to overcome the aforementioned concerns, we developed a novel lactulose preparation (SK-1202) that has appropriate palatability and contains less free sugar. We compared the efficacy, safety, and acceptability of SK-1202 with an approved currently available lactulose syrup by a cross-over study.

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METHODS

Study design

The study schedule is shown in Figure 1. Patients were screened on visits 1 and 2 during the observation period. Eligible subjects were randomized to either of two groups in turn according to an assignment list for each study site. The assignment lists were created using the SAS software program (SAS Institute, Cary, NC, USA.). In the first phase of the study, the patients in group A received the new preparation (SK-1202) and patients in group B received the approved lactulose syrup for 2 weeks, and in the subsequent step, the patients were crossed over to the alternative preparation for an additional 2 weeks of treatment.

Patients

This multicenter study enrolled patients from five hospitals in Japan: Sapporo-Kosei General Hospital, Toranomon Hospital, Toranomon Hospital Kajigaya, Nara Medical University Hospital, and Hiroshima University Hospital. Based on the previous clinical study of lactulose\(^5\) and the number of subjects in which an adverse event with 10% incidence is detectable with a probability of 95%, a sample size of 40 subjects was planned. The main inclusion criteria were: (i) stable hyperammonemia with compensated liver cirrhosis; (ii) treatment with an approved lactulose product of 19.5–39 g t.i.d. for >4 weeks before the observation period; (iii) Inuyama coma score of 1 or no coma; and (iv) values of no more than 200% of blood ammonia measurements in two separate samples during the observation period, calculated by the normal upper limit value of the testing site (100%). The main exclusion criteria were: (i) changes in dosage of lactulose during the observation period and/or 4 weeks before the observation period; (ii) fulminant hepatitis and/or higher than grade C of the Child-Pugh classification; (iii) plan for endoscopic injection sclerotherapy or endoscopic variceal ligation for esophageal varix during the study period; (iv) plan to undergo new treatment for malignant tumor during the observation period or 4 weeks prior, and/or planned new treatment during the study period; (v) severe renal impairment or serum creatinine $\geq 1.7$ mg/dL (men) or $\geq 1.3$ mg/dL (women) at the start of the observation period; (vi) dementia; (vii) severe heart disease or heart attack 26 weeks before the observation period; (viii) severe gastrointestinal disorders; (ix) galactosemia; and (x) hyperammonemia with inborn errors of metabolism. Informed written consent to participate in this study was obtained from all patients. This study was approved by the ethics committee of each institution and was carried out in compliance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Preparation and dosage

SK-1202 is produced by Sanwa Kagaku Kenkyusho Co., Ltd. (Nagoya, Japan). The active pharmaceutical ingredient in this preparation is crystal lactulose with a purity of $>97%$. This preparation is in gel form and contains 6.5 g lactulose in a sachet. Lactulose syrup (Monilac; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) containing 6.5 g/10 mL lactulose in a sachet was launched in Japan in 1975.

The patients took SK-1202 or lactulose syrup three times daily containing the same amount of lactulose taken in the observation period.

Efficacy and safety evaluation

Efficacy was evaluated by the number connection test (NCT), concentration of blood ammonia, coma grade, and flapping tremor grade at visits 3, 4, and 5. The NCT was measured using Neuro-Psychological Tests provided by The Japan Society of Hepatology.\(^6\) Fasting blood ammonia levels were measured at the participating sites and

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**Figure 1** Design of a randomized, multicenter, cross-over study to compare SK-1202 and an approved commercially available lactulose syrup in hyperammonemia patients with liver cirrhosis.
the values were adjusted according to the upper limit values of each site. Data were calculated to a percent value against the upper limit value of each institution. The coma grade was evaluated using the six levels of the Inuyama coma scale (no coma and grades I–V). The flapping tremor grade was evaluated according to four levels: 0, no tremor; 1, unclear; 2, present; and 3, clearly present. Safety was determined based on the presence of adverse events, changes in vital signs, and laboratory tests, which included hematological tests, biochemical blood tests, coagulation tests, and urine tests.

**Acceptability evaluation**

The acceptability of the preparation was evaluated at visits 4 and 5 by questionnaire on the sweetness, aftertaste, ease of administration, and preference of the preparation. The questions consisted of four levels of sweetness (good, slightly sweet, very sweet, too sweet), aftertaste (not unpleasant, slightly unpleasant, unpleasant, very unpleasant), and ease of administration (excellent, easy, difficult, very difficult). The question regarding preference involved selection of the preferred preparation.

**Statistical analysis**

Continuous data were evaluated using ANOVA, and the ordered data were evaluated using the Wilcoxon rank sum test, Wilcoxon signed-rank test, or sign test.

**RESULTS**

**Patients**

Forty-six subjects were screened; of which two subjects were ineligible because of conflicts with the inclusion or exclusion criteria. Overall, 44 subjects were registered in this study. Demographic data are shown in Table 1. Twenty-six subjects were men (59.1%) and the mean age was 65.4 years. The main cause of hyperammonemia was alcohol consumption, with a ratio of >50%. The coma grade for all subjects was <1. Forty-four subjects were randomized to two groups, group A or B. Twenty-four subjects in group A were dosed with lactulose syrup and 20 subjects in group B were dosed with SK-1202 for the first 2 weeks, and then they were crossed over to the alternative preparation for another 2 weeks. Only one subject in group A withdrew at the end of the first treatment period (lactulose syrup) at the subject’s request. The remaining subjects completed the study. The number of subjects for the evaluation of SK-1202 or lactulose syrup was 43 and 44, respectively.

**Efficacy**

The NCT results are shown in Figure 2(a). The changes in NCT were $-3.72 \pm 8.96$ (mean ± standard deviation [SD]) during the SK-1202 treatment period and $-2.63 \pm 9.96$ during the lactulose syrup treatment period. The results of the ANOVA indicated there was no difference between the preparations (difference of conditioned mean, $-1.15$;...
Figure 2 Changes in number connection test and blood ammonia levels among hyperammonemia patients with liver cirrhosis treated with SK-1202 or lactulose syrup for 2 weeks each. (a) Number connection test (NCT). (b) Serum ammonia level. Values are reported as mean ± standard deviation.

Figure 3 Acceptability evaluation of SK-1202 and lactulose syrup in hyperammonemia patients with liver cirrhosis after subjects were treated with each preparation separately for 2 weeks (4 weeks in total). Subjects evaluated each product for sweetness (a), aftertaste (b), ease of use (c), and preference (d). The question evaluating preference was “Which medicine would you like to continue taking in the future?”
95% confidence interval [CI]. −5.84, 3.54). The changes in blood ammonia (%) levels were −12.49 ± 54.78 (mean ± SD) during the SK-1202 treatment period and 8.13 ± 54.47 (mean ± SD) during the lactulose syrup treatment period, as shown in Figure 2(b). The results of ANOVA showed there was no difference between the preparations (differences of conditioned mean, −22.18; 95% CI, −51.76, 7.39).

Only one subject in group B had grade I coma at visit 3 and the coma grade of this subject changed from I to no coma following SK-1202 treatment.

Only two subjects in group B had grade 1 (unclear) flapping tremor at visit 3 and the tremor grade of these subjects changed from 1 to 0 (no tremor) after SK-1202 treatment.

Safety

Eight adverse events were observed in six patients (14.0%) during the SK-1202 treatment period and included four cases of diarrhea in two patients (4.7%). Nine adverse events were observed in six patients (13.6%) during the lactulose syrup treatment period and included five cases of diarrhea in three patients (6.8%). Diarrhea was considered an adverse reaction. No other adverse events were considered adverse reactions. Among all the adverse events observed, one case of mycoplasma pneumonia in the lactulose syrup treatment period was the only serious adverse event. No significant changes were observed in vital signs or laboratory tests.

Acceptability

The results of the questionnaires are shown in Figure 3. The number of subjects who responded “good” for sweetness, “not unpleasant” for aftertaste, and “excellent” for ease of administration were 41 (95.3%), 31 (72.1%), and 23 (53.5%) for the SK-1202 preparation, and 10 (22.7%), 12 (27.3%), and 7 (15.9%) for the lactulose syrup. Each result of the questionnaire was statistically significant between the preparations (P < 0.001, Wilcoxon rank sum test). With regard to preference of the preparation, 37 subjects (86.0%) selected SK-1202 whereas 6 (14.0%) selected the lactulose syrup (P < 0.001, sign test).

DISCUSSION

An issue affecting patient compliance with lactulose therapy is the excessively sweet taste of the currently available lactulose formulation. The National Health System reports on its website that “Some people do not like the sweet taste of lactulose.”2 Another important issue is that many lactulose preparations contain some free lactose and galactose, and thus, should be used with caution in patients with diabetes mellitus. Therefore, we developed a new jelly lactulose preparation (SK-1202) in order to improve compliance and reduce free sugar. SK-1202 is composed of lactulose crystals, which contain lower amounts of free sugar, with the addition of other inactive ingredients to adjust for taste.

To evaluate the equivalency in efficacy, safety, and acceptability of SK-1202 compared to the currently approved lactulose syrup (Monilac; Chugai Pharmaceutical Co., Ltd.), we carried out a randomized multicenter cross-over study in hyperammonemia patients with liver cirrhosis who had been taking lactulose. The results showed equivalency of each preparation with regard to efficacy and safety. In this study, four episodes of diarrhea in two patients (4.7%) occurred during the SK-1202 treatment period and five in three patients (6.8%) occurred during the lactulose syrup treatment; these were considered adverse reactions to lactulose. Indeed, diarrhea is the most frequent adverse reaction observed with lactulose; the package insert of Monilac shows that the incidence of diarrhea is >5%. The present study indicates that SK-1202 has the same efficacy and safety profile as the approved lactulose syrup preparation. Conversely, SK-1202 has better taste and more acceptability than the approved lactulose syrup, suggesting that the SK-1202 preparation would likely improve patient compliance for lactulose treatment. In addition, because of the reduced levels of free sugar, SK-1202 could be better suited to treat patients with diabetes mellitus. Given this formulation design and the results presented herein, it is expected that SK-1202 could represent a useful agent for patients with hepatic encephalopathy.

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