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Original Article

Assessment of the pharmacokinetics, removal rate of hemodialysis, and safety of lactulose in hemodialysis patients

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ABSTRACT

Lactulose is often used to treat hepatic encephalopathy or constipation, and also exhibits benefits to chronic renal insufficiency due to reduce nitrogen-related products in serum. The present study investigated the pharmacokinetics of lactulose, its removal rate through dialysis, and safety by administering lactulose 6.5 g (Lagnos Jelly Divided Pack 16.05 g) orally to six hemodialysis patients who resided in Taiwan. As a result, the means of maximum plasma concentrations (C_{max}) and Time to reach C_{max} (T_{max}) were 3090 ± 970 ng/mL and 6.5 ± 2.3 hours, respectively. The mean plasma concentration was 2220 ± 986 ng/mL after administration for 24 hours. Sequentially, the mean plasma concentration reduced to 307 ± 117 ng/mL after the application of 4-hour dialysis. Area under the plasma concentration-time curve from zero to 24 h post-dose (AUC_{0-24h}) were $56,200 \pm 21,300$ ng h/mL and the AUC_{0-28h} was $61,200 \pm 23,300$ ng h/mL. The rate of lactulose removal by dialysis was $83.6 \pm 8.9\%$. In addition, the multiple doses of lactulose using a simulated model suggested that no plasma accumulation would be expected while coordinating with dialysis. Good tolerability was confirmed, while the mild adverse effect of diarrhea was observed in one case during the study period. No death or serious adverse effect was reported. Based on the present study, we demonstrated the pharmacokinetic transition with respect to plasma levels of lactulose in patients with impaired renal excretion treated with hemodialysis.

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1. Introduction

Lactulose is a synthetic disaccharide composed of fructose and galactose. There are no enzymes that degrade lactulose into monosaccharides in the human gastrointestinal tract. In

the human body, most of the lactulose reaches the lower gastrointestinal tract and converts to organic acids (lactic acid, acetic acid, etc.) by bacterial decomposition, thereby lowering the pH [1]. Due to acidification of the intestinal tract, the number of fully-grown lactic acid bacteria increases, whereas

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the number of bacteroides and *Escherichia coli* decreases [2,3]. In agreement, it was also reported that lactulose has prebiotic-like effects against inflammatory bowel disease [4]. By increasing the amount of H^+ in the intestinal tract, the NH_3 would preferentially convert to nonabsorbable NH_4^+ , thus lowering the ammonia concentration in blood [5], for which can treat hepatic encephalopathy or related seizures [6]. It has also been shown that a laxative effect is induced in the lower gastrointestinal tract by osmotic regulation.

Due to toxic compounds that are accumulated in patients with chronic renal failure (CRF) [7], some treatments are able to assist with the excretion of unwanted wastes from bodies. In 1971, lactulose therapy was first applied to treat uremic toxins in patients with CRF [8]. Based on a published study conducted with healthy men, lactulose was poorly absorbed and could be found in urinary excretion relative to its oral amount by only 0.65% [9]. However, given that CRF is usually altered the pharmacokinetic profile of medicines, it is necessary to understand the plasma transition of lactulose in patients with impaired renal function and on dialysis.

For this study, our purpose was to investigate the pharmacokinetics of lactulose including the removal rate of dialysis by administering a single oral dose of lactulose (6.5 g) in hemodialysis patients.

2. Materials and methods

2.1. Drug information

The investigational drug was a jelly containing 6.5-g lactulose (Lagnos Jelly Divided Pack 16.05 g, Sanwa Kagaku Kenkyusho Co., Ltd., Nagoya, Japan).

2.2. Study population and design

A total of six hemodialysis patients were proposed to enroll into the study. This study followed the Taiwan Law of Pharmaceutical Affairs, Good Clinical Practices, local regulatory requirements, and was according to the Revised Declaration of Helsinki [10]. Before screening started, participants were verified to be fully aware of the purpose, content, and possible side effects of this study which were described in the informed consent. Signed informed consent was obtained from all individual participants enrolled in the study. Ethical approval for the study was received from Mackay Memorial Hospital Institutional Review Board, Taipei, Taiwan. Six Taiwanese patients including two men and four women with chronic renal failure who required regular hemodialysis 3 times/wk participated in this study. Their mean age was 48.5 ± 4.9 years (mean $\pm$ standard deviation) with mean weight of 56.4 ± 16.4 kg and a mean body mass index of 22.4 ± 4.3 kg/m². All patients had to satisfy inclusion/exclusion criteria throughout the study. Exclusion criteria were diabetes (the last 2 glycated hemoglobin measurements >8% with at least 1 measure within 3 months of enrollment), anemia (hemoglobin < 10.5 g/dL), severe heart (such as heart failure or with pacemaker) or liver disease (such as nonmetabolic cirrhosis or liver failure), medical histories of galactosemia, kidney transplant, gastrointestinal surgery, drug allergy or sensitivity

to analogous drugs, and on any medication that might interfere with drug absorption or metabolism.

This pharmacokinetic study was conducted by a single dose and open-labeled design with 6.5-g lactulose in hemodialysis patients. Prior to dosing, patients were hospitalized and fasted overnight for at least 10 hours. The study drug was administered orally with 50 mL of room temperature water. The oral cavities of the patients were inspected after administration to ensure they swallowed the jelly. Hemodialysis would be performed after dosing for 24 hours. All patients were served with the same standardized meals provided by study site staff during the hospitalization. No other food was allowed until 5 hours after administration. Water was available upon request. Alcohol, coffee, tea, cocoa, or cola were forbidden before 48 hours.

2.3. Pharmacokinetic measurement and analysis

Blood samples were obtained from the patient's forearm cutaneous vein into evacuated tubes containing sodium heparin prior to dosing and 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 10 hours, 12 hours, and 24 hours after dosing as well as the next day at the end of dialysis (28 hours after dosing) and stored in ice. Within 1 hour, plasma was separated by centrifugation at 1900 *g* for 10 minutes at 4°C. After that, plasma specimens were stored frozen at –80°C before further liquid chromatography-tandem mass spectrometry analysis for lactulose concentration. Vital signs including blood pressure, heart rate, and body temperature were recorded on the day before dosing, just prior to dosing and 24-hours postdosing.

WinNonlin 6.3 (Pharsight Corporation, Saint Louis, MO, USA) was used to analyze pharmacokinetic parameters (C_{max} , T_{max} , AUC_{0-24h} , and AUC_{0-28h}) based on lactulose plasma concentration of each time point using noncompartmental models. The peak plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) were individually measured. Meanwhile, the plasma concentration–area under the concentration–time curves (AUC_{0-24h} and AUC_{0-28h}) were calculated from measured values using the trapezoidal method. The removal rate (%) of drugs by dialysis was calculated using the plasma concentration before (24 hours after administration) and after dialysis (28 hours after administration) and Eq. (1). For simulation of repeated administrations, method of residuals was applied and calculated based on pharmacokinetic parameters to simulate the variations of plasma concentrations.

$$\text{Rate of drug removal (\%)} = \frac{[(\text{concentration before dialysis} - \text{concentration after dialysis}) / \text{concentration before dialysis}] \times 100}{(1)}$$

3. Results

3.1. Pharmacokinetics

The transition of the plasma concentration at each time point after lactulose administration, calculated pharmacokinetic parameters, and removal rate of drugs by dialysis are shown in Table 1. The mean plasma concentration 24 hours after administration was 2220 ± 986 ng/mL. A decreased concentration of 307 ± 117 ng/mL was found after dialysis. C_{max} was

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