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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.

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

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

3090 ± 970 ng/mL, T_{max} was at 6.5 ± 2.3 hours, and AUC_{0-24h} was 56,200 ± 21,300 ng h/mL. AUC_{0-28h} was 61,200 ± 23,300 ng h/mL including dialysis which was carried out during 24–28 hours. The rate of lactulose removal by dialysis was 69.5–93.5% (mean: 83.6 ± 8.9%). In addition, the mean plasma concentration–time curve of lactulose is shown in Figure 1. The mean lactulose levels were markedly decreased after hemodialysis. Figures 2 and 3 showed the prediction of repeated oral lactulose administration with different frequencies—one sachet daily and one sachet every 12 hours, respectively. The solid line shows the mean plasma concentration–time profile when 6.5-g lactulose was administered immediately after the end of dialysis. Based on the above plasma concentration–time profile shown in Figure 1, the dotted lines in Figures 2 and 3 show the plasma concentration–time profile.

3.2. The assessment of safety and tolerability

The adverse event of mild diarrhea was reported in one of six cases during the study. Considering the pharmacological effects of lactulose, there is a high possibility that diarrhea occurred after administration. Except for the former mention, no adverse events occurred during the study. With regard to clinical testing, no particular changes were observed during screening or follow-up inspection. Neither of vital signs nor electrocardiograms showed significant changes. Overall, lactulose was well tolerated in the present study when a single dose of lactulose was administered to hemodialysis patients.

4. Discussion

Chronic kidney disease is a global public health problem and the prevalence of end-stage renal disease is persistently

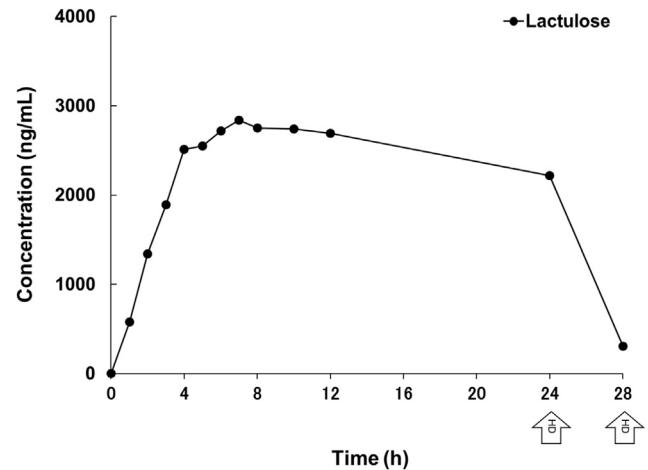


Figure 1 – The mean plasma concentration–time profile of lactulose. The arrows marked with “HD” indicate the hemodialysis start (24 hours) and end (28 hours).

increasing [11]. The use of lactulose is not uncommon in hemodialysis patients [12]. In this study, we demonstrated the pharmacokinetic transition of lactulose concentration in patients with maintenance hemodialysis.

In an earlier study reported by Hinohara and Suzuki [9], a maximum plasma concentration of 56.8 ± 25.2 µg/mL was observed after five healthy adults orally received 19.5 g lactulose syrup for 4 hours. However, a similar study design applied in Takimoto et al's [13] research showed a maximum plasma concentration of 10.7 ± 15.2 µg/mL. In comparison with the aforementioned results, the slight absorption of lactulose was observed corresponding to the dosage which had been given. Also, considering that the incomparable values of C_{max} may be attributed to individual differences, it

Table 1 – Plasma concentrations and pharmacokinetic parameters of lactulose (6.5 g) after oral administration in hemodialysis patients.

Time after administration (h)	Concentration (ng/mL)						Mean	SD
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6		
Pre	0	0	0	0	0	24.7	4.12	10.08
1	462	502	201	673	882	766	581	244
2	888	1260	990	1790	2150	962	1340	517
3	1000	3140	1050	2380	2730	1030	1890	974
4	1690	3840	1180	3260	3940	1170	2510	1312
5	1490	3410	1840	3500	3860	1200	2550	1167
6	1570	3690	2450	3560	3460	1580	2720	989
7	2240	3220	2630	3620	3760	1560	2840	853
8	2590	2750	2460	3470	3840	1400	2750	853
10	1730	3310	2240	3940	3850	1370	2740	1109
12	2050	3290	2440	3490	3630	1220	2690	950
24 ^a	1240	2850	1690	2990	3430	1140	2220	986
28 ^b	247	374	516	256	222	225	307	117
C_{max} (ng/mL)	2590	3840	2630	3940	3940	1580	3087	975
T_{max} (h)	8.0	4.0	7.0	10.0	4.0	6.0	6.50	2.35
AUC_{0-24h} (ng·h/mL)	38,475	69,937	45,731	74,238	80,232	28,500	56,186	21,300
AUC_{0-28h} (ng·h/mL)	41,449	76,385	50,143	80,730	87,536	31,230	61,246	23,307
R.r. (%)	80.1	86.9	69.5	91.4	93.5	80.3	83.6	8.9

AUC = area under the curve; C_{max} = maximum plasma concentration; R.r. = removal rate; SD = standard deviation; T_{max} = time to reach C_{max} .

^a Hemodialysis start.

^b Hemodialysis end.

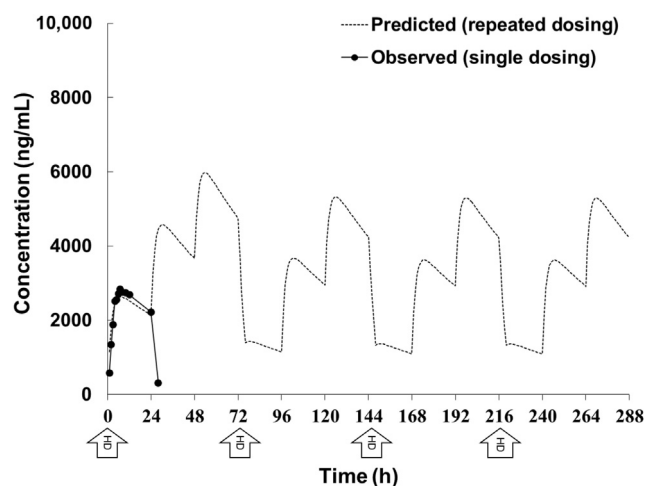


Figure 2 – Prediction of repeated oral lactulose administration (one sachet daily). The solid line shows the mean plasma concentration–time profile when lactulose 6.5 g was administered immediately after the end of dialysis. Based on the plasma concentration–time profile shown in Figure 1, the dotted line shows the plasma concentration–time profile (dialysis is performed 72 hours after the 1st administration) by administration in 24-hour intervals for 3 consecutive days. The arrows marked with “HD” indicate when hemodialysis was carried out.

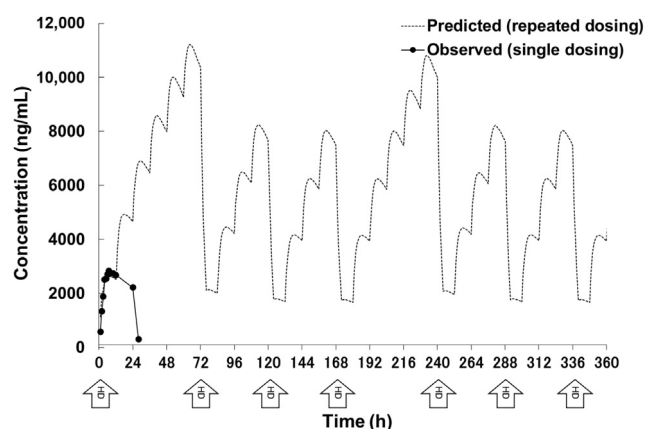


Figure 3 – Prediction of repeated oral lactulose administration (one sachet every 12 hours). The solid line shows the mean plasma concentration–time profile when lactulose 6.5 g was administered immediately after the end of dialysis. Based on the plasma concentration–time profile shown in Figure 1, the dotted line shows the plasma concentration–time profile after repeated administrations in 12-hour intervals. Dialysis is performed after 3 days, then 2 days later, then 2 days later (3 times/wk; administration performed immediately after dialysis). The arrows marked with “HD” indicate when hemodialysis was carried out.

seemed that there was no substantial difference in the plasma concentration. Furthermore, another report revealed that the plasma concentration of lactulose was only detectable in one

of the two cases who received the highest dosage of 53 g (maximum plasma concentration of 12.1 $\mu\text{g}/\text{mL}$ will be expected when dosage converted to 19.5 g) [14]. Based on the data obtained from the present study, the results showed that the plasma level of lactulose was low, and comparable to healthy adults. It is expected that the mean maximum plasma concentration will be 9.27 $\mu\text{g}/\text{mL}$ if a single dose of lactulose 19.5 g is administered to dialysis patients. Taken together, our observations confirmed that a slight amount of lactulose was absorbed in dialysis patients, which was also comparable with previous findings.

Absorbed lactulose is not metabolized in the human body and is excreted as a parental form in urine [1]. A previous study indicated that unchanged lactulose in urinary excretion has been determined to be 0.65% of the administered lactulose after a healthy adult received lactulose orally for 12 hours [9]. Out of the six cases with lactulose treatments, only one excreted 2.8% of the parental drug into urine, while the others had an unchanged excretion of <1% of the dosage [14]. It also confirmed the observation associated with marginal lactulose absorption in terms of the small amount of urinal excretion. In contrast to healthy adults whose absorbed lactulose was removed through excretion into urine, the plasma concentration of lactulose remained unchanged in dialysis patients due to their inability to excrete urine. Furthermore, an issue that needs to be addressed is that repeated dosing may cause elevated plasma levels of lactulose.

Based on pharmacokinetic parameters and dialysis removal rate obtained from this study, method of residuals was applied to simulate the plasma concentration of dialysis patients who were administered repeatedly. Two simulations were made. In the first simulation, lactulose 6.5 g was administered once a day in 24-hour intervals, while dialysis was carried out once every 72 hours (administration is done before dialysis; Simulation 1; Figure 2). In the second simulation, a dose of lactulose 6.5 g was administered in 12-hour intervals (dialysis was 3 times/wk in intervals of 3 days, 2 days, and 2 days; Simulation 2; Figure 3). In Simulation 1, after the first administration for 54 hours, the maximum plasma concentration was near 6000 ng/mL, but did not increase thereafter, and showed a tendency to decrease even with continued administration. In the same way, Simulation 2 using the 3-day interval, the maximum plasma concentration reached about 11,000 ng/mL before dialysis (64 hours after the first administration), then showed a downward trend. Based on our finding, it is unlikely that the plasma concentration will increase by repeated administration. The maximum plasma concentration is estimated to be about 6000 ng/mL when administered once a day, and about 11,000 ng/mL when administered twice a day.

In conclusion, the present study is the first to demonstrate the pharmacokinetics, removal rate of hemodialysis, and safety of lactulose in Taiwanese patients with CRF, even though the small sample size may affect the clinical representative. Certainly, multiple-dose administration will be conducted to investigate the long-term pharmacokinetics profile of lactulose in hemodialysis patients and the fidelity of simulation for repeated doses will be addressed.

Conflicts of interest

The authors have declared that no conflicts of interest exist.

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