Lactulose Efficacy in Reduction of Nitrogen Products, Blood Potassium, and Fluid Overload in Patients with End-Stage Renal Failure

Negin Aleagha¹, Farahnaz Pasha²*, Maryam Shiehmorteza³

¹Department of Clinical Pharmacy, Islamic Azad University-Pharmaceutical Sciences Branch, (IAUPS), Tehran, Iran.
²Nephrology Department, Islamic Azad University, Tehran Medical Branch, Tehran, Iran.
³Department of Clinical Pharmacy, Faculty of Pharmacy, Islamic Azad University-Pharmaceutical Sciences Branch, (IAUPS), Tehran, Iran.

Abstract

Introduction: Chronic kidney disease (CKD) is a major public health problem that often goes unrecognized until its late-stage. Patients with chronic kidney disease face uremic toxins and hyperkalemia. Also, fluid overload in CKD patients is associated with rapid decline in kidney function. Lactulose is a hyperosmotic agent and as a prebiotic, it plays an important role in regulating serum urea and potassium levels and has some effects on fluid overload. The aim of this study was to evaluate the effect of lactulose on serum levels of biochemical products in patients with CKD.

Materials and Methods: In this interventional study, 17 patients with end stage of CKD (76.47 % men; mean age 65.88 ± 13.4) were evaluated. All patients received lactulose, 10 ml, 3 times per day for 3 months. Blood samples from all participants were collected before and at the end of intervention to examine changes in biochemical parameters, including potassium, urea, creatinine and uric acid.

Results: Lactulose significantly decreased urea levels (p=0.001), blood potassium (0.001) and fluid overload (considering the patient’s weight p=0.001) in patients with end-stage renal failure. The decrease in serum creatinine and uric acid were not significant.

Conclusion: Lactulose administration in CKD patients could decrease levels of various deleterious elements, especially urea and blood potassium and its daily use can be recommended in these patients.

Keywords: Lactulose, chronic kidney disease, blood urea, creatinine, fluid overload

*Corresponding author: Farahnaz Pasha, Nephrology Department, Islamic Azad University, Tehran Medical Branch, Tehran, Iran.
Tel:
Email address:
INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem that often goes unrecognized until late-stage disease (Weiner, 2007). In patients with chronic kidney disease, potentially toxic compounds are accumulated in the body, called uremic toxins. All efforts are due to reduce these products (Vanholder, 2001). Hyperkalemia is a potential threat to patient safety in CKD and its occurrence increases the odds of mortality (Lisa, 2009). Lactulose is a hyperosmotic agent which increases stool water contents, softens stool, promotes peristalsis and reduces blood ammonia concentration (Weber, 1997). Also, it could promote fecal excretion of water, sodium, potassium, ammonium, urea, and protons (Vogt and Frey, 1997). Lactulose, as a prebiotic, plays an important role in regulating unwanted nitrogen products and biochemical parameters in healthy individuals, but there is little information about these effects on patients with kidney failure. In this study, we aimed to evaluate lactulose efficacy in reduction of nitrogen products, blood potassium, and fluid overload in patients with end-stage renal failure.

MATERIALS AND METHODS

In this prospective before-after intervention study, 17 patients with end-stage renal disease (ESRD) were evaluated. Patients older than 45 years were included in the study. The exclusion criteria were a history of the gastrointestinal or metabolic disease. Participants were advised to maintain their usual diet during the study period. Those who could not keep up with the study protocol or tolerate study medications were excluded. The Ethics Committee of Islamic Azad University of Pharmaceutical Sciences approved the study, and all patients gave informed consent. The study was conducted over the 12-week period. The participants received 10 ml of lactulose syrup, 3 times a day. The doses administered were chosen based on therapeutic recommendations for CKD patients in a way that they would not suffer from negative effects or discomfort. Before and at the end of the study, blood samples were collected. Concentrations of nitrogen waste products were measured before and after lactulose treatment, including urea, creatinine and uric acid. Blood potassium and fluid overload were also evaluated. Statistical analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 18.0). Continuous variables were expressed as a mean ± standard deviation. Differences in the means before and after treatment were evaluated by the repeated measure ANOVA test. A P value less than 0.05 was considered significant.

RESULTS

17 CKD patients including 76.47 % men and 23.53 % women with the mean age of 65.88 were evaluated.

Table 1: Mean changes in levels of blood nitrogen products after treatment with lactulose in patients with chronic kidney disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine, mg/dl</td>
<td>9.26±3.47</td>
<td>7.47±3.41</td>
<td>0.07</td>
</tr>
<tr>
<td>Urea, mg/dl</td>
<td>118.02±24.57</td>
<td>105.39±39.41</td>
<td>0.001</td>
</tr>
<tr>
<td>Uric acid, mg/dl</td>
<td>6.05±1.17</td>
<td>5.44±1.57</td>
<td>0.7</td>
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</table>
Mean changes in the level of blood nitrogen products after treatment with lactulose in Patients with Chronic Kidney Disease were shown in Table 1. Urea level was reduced significantly, after the treatment with lactulose. Although there was a decrease in creatinine and uric acid levels, the difference was not significant (Table 1).

Mean change in Level of Blood potassium was shown in Table 2. Potassium was also significantly lower after the treatment with lactulose (Table 2). According to Table 3, the fluid overload was significantly reduced after 3 months.

### DISCUSSION

Most CKD symptoms or uremia are caused by protein intolerance; symptoms arise because the patient is unable to excrete metabolic products of dietary protein and the ions contained in protein-rich foods. Consequently, CKD patients accumulate salt, phosphates, uric acid and many nitrogen-containing metabolic products. Therefore, secondary problems of metabolic acidosis, bone disease, and insulin resistance become prominent (Mandayam and Mitch, 2006). Hyperkalemia commonly limits optimizing treatment to slow stage 3 or higher chronic kidney disease (CKD) progression. The risk of hyperkalemia is linked to dietary potassium intake, the level of kidney function, concomitant diseases that may affect potassium balance such as diabetes, and use of medications that influence potassium excretion (Lazich and Bakris, 2014).

Lactulose is a non-absorbable disaccharide and plays an important role in regulating unwanted nitrogen products. Evidence has suggested that metabolism by the enteric flora was necessary for its mechanism of action. When the intestinal flora metabolizes lactulose, bacterial incorporation of nitrogen increases, as does the bacterial mass. The presence of a carbohydrate and the acidic environment, caused by the production of organic acids, also act to reduce the breakdown of other nitrogen-containing compounds to ammonia and other potential cerebral toxins. The administration of lactulose to humans causes an increase in fecal nitrogen. Lactulose administration causes a reduction in the urea production rate consistent with a reduced entry of ammonia into portal blood (Weber, 2008). Although lactulose adherence is relatively poor, in large part due to gastrointestinal adverse effects such as abdominal pain, bloating, and flatus (Watanabe, 1997; Prasad et al, 2007; Dhiman et al, 2000; Meng et al, 2015), it is well tolerated in CKD patients (Cockram et al, 1998). In this study, we evaluated this possibility in patients with advanced CKD and observed a sig-

### Table 2: Mean change in level of blood potassium after treatment with lactulose in patients with chronic kidney disease

<table>
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<tr>
<th>Parameter</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Potassium</td>
<td>5.51±0.78</td>
<td>4.29±0.49</td>
<td>0.001</td>
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</tbody>
</table>

### Table 3: Mean change in patient’s weight after treatment with lactulose in patients with chronic kidney disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s weight</td>
<td>75.54±6.30</td>
<td>74.69±6.20</td>
<td>0.001</td>
</tr>
</tbody>
</table>
significant reduction in urea and potassium levels after 3 months of treatment with oral lactulose. As 1 month before and during the study period, all patients were on the routine medical management of the same quantity and quality; these reductions could be attributed to lactulose administration. Urea reduction was possibly due to increased fecal excretion of nitrogen products and reduced urinary excretion (De Preter et al, 2006). It was shown that lactulose caused a reduction in urea production in patients with hepatic encephalopathy (Weber, 1997) and increased nitrogen excretion into the fecal fractions in cirrhotic patients (Clausen and Mortensen, 1997). A study by TayebiKhosroshahi showed that using lactulose could reduce nitrogen products including urea and creatinine. However, in our study, we found no significant reduction in creatinine level after treatment with lactulose but we found a significant reduction in blood urea nitrogen (TayebiKhosroshahi et al, 2014). Like our findings, Yang and colleagues, DePreter observed urea lowering effects of lactulose (Yang et al, 2013; De Preter et al, 2006). Mathialahan reported a significant reduction in potassium level after treatment with lactulose (Mathialahan, 2003). Limitation of our study were having no control group, short period of study and number of patients. Another limitation was that we could not control patients’ food and life style during the study, which could affect the blood urea nitrogen levels. The longer treatment with lactulose would show better results.

CONCLUSIONS

Lactulose administration in CKD patients along with other treatments has beneficiary effects of a reduction in some nitrogen products. In addition, there is a positive effect on blood potassium and fluid overload. The use of lactulose in CKD patients can be suggested in order to get better therapeutic results. More studies are needed to confirm these findings.

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REFERENCES


Lisa M. Einhorn, BS; Min Zhan, PhD; Van Doren Hsu, PharmD; Lori D. Walker, BS; Maureen F. Moen, BS; Stephen L. Seliger, MD, MS; Matthew R. Weir, MD; Jeffrey C. Fink, MD, MS. The Frequency of Hyperkalemia and Its Significance in Chronic Kidney Disease.-ArchIntern Med.2009,169,12,1156-1162. doi:10.1001/archinternmed.2009.132.

Mathialahan T, Sandle GI. Dietary potassium and laxatives as legurators of colonic potassium secretion in end-stage renal disease.Nephrol Dial Transplant.2003 Feb;18,2,341-7.DOI: 10.1093/ndt/18.2.341

Meng S, Pan Y, Deng Q, Wang L, Chang Q.Efficacy and safety of lactulose on the treatment of puerper
Prasad S, Dhiman RK, Duseja A, Chawla YK, Sharma A, Agarwal R. Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy. Hepatology. 2007; 45,3,549-59.DOI: 10.1002/hep.21533


