

Original Article



Lactulose efficacy in reduction of nitrogen products, blood potassium and fluid overload in patients with end-stage renal failure

Open Access

Negin Aleagha¹, Farahnaz Pasha^{2*}, Maryam Shiehmorteza³

¹Department of Clinical Pharmacy, Islamic Azad University-Pharmaceutical Sciences Branch, (IAUPS), Tehran, Iran.

² Nephrology Department, Islamic Azad University, Tehran Medical Branch, Tehran, Iran.

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

Abstract

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

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.

Lactulose significantly decreased urea levels ($p=0.001$), blood potassium (0.001) and fluid overload (with due attention to patient's weight $p=0.001$) in patients with end-stage renal failure. The decrease in serum creatinine and uric acid were not significant.

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: +989123859038
Email address: farahnazpasha@yahoo.com

INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem that often goes unrecognized until late-stage disease (1). 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 (2). Hyperkalemia is a potential threat to patient safety in CKD and its occurrence increases the odds of mortality (3).lactulose is a hyper osmotic agent increases stool water contents, softens stool, promotes peristalsis and reduces blood ammonia concentration (5) andalso could promote fecal excretion of water, sodium, potassium, ammonium, urea, and protons (4). Lactulose, as a prebiotic, plays an important role in regulating nitrogen unwanted 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 overloadin 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 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 an12-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 mean \pm 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

Parameter	Before Treatment	After Treatment	P
Creatinine, mg/dl	9.26 \pm 3.47	7.47 \pm 3.41	0.07
Urea, mg/dl	118.02 \pm 24.57	105.39 \pm 39.41	0.001
Uric acid, mg/dl	6.05 \pm 1.17	5.44 \pm 1.57	0.7

Table 2: Mean change in Level of Blood potassium After Treatment With Lactulose in Patients With Chronic Kidney Disease

Parameter	Before Treatment	After Treatment	P
Blood Potassium	5.51±0.78	4.29±0.49	0.001

Table 3: Mean change in Patient's weight After Treatment With Lactulose in Patients With Chronic Kidney Disease

Parameter	Before Treatment	After Treatment	P
Patient's weight	75.54±6.30	74.69±6.20	0.001

Mean Changes in Levels of Blood Nitrogen Products after Treatment with Lactulose in Patients with Chronic Kidney Disease are shown in Table 1. Urea level was significantly reduced 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 is shown in Table 2. Potassium was also significantly lower after the treatment with lactulose (Table 2). And according to Table 3 the Fluid overload was significantly reduced after 3 month.

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, and secondary problems of metabolic acidosis, bone disease and insulin resistance become prominent (6). 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, level of kidney function, concomitant diseases that may affect potassium balance such as diabetes, and use of medications that influence potassium excretion (7). Lactulose is a non-absorbable disaccharide and plays an important role in regulating nitrogen unwanted products. Evidence suggests that metabolism by the enteric flora is 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 (8). Although lactulose adherence is relatively poor, in large part due to gastrointestinal adverse effects such as abdominal pain, bloating, and flatus(9-12). It is well tolerated in CKD patients (13). In this study we evaluated this possibility in patients with advanced CKD and observed a significant reduction in urea and potassium level

after 3 months of treatment with oral lactulose. As 1 month before and during the study period, all patients were on routine medical management with the same quantity and quality; these reductions could be attributed to lactulose administration. Urea reduction is possibly due to increased fecal excretion of nitrogen products and reduced urinary excretion (14). It is shown that lactulose causes a reduction in urea production in patients with hepatic encephalopathy (15) and increases nitrogen excretion into the fecal fractions in cirrhotic patients (16).

A study by TayebiKhosroshahishowed 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 (17). Like our findings, Yang and colleagues, DePreterobserved urea lowering effects of lactulose (18-19). Mathialahan reported a significant reduction in potassium level after treatment with lactulose (20). Limitation of our study is having no control group, short period of study and number of patients. As another limitation, 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 reduction of 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 receive better therapeutic results. More studies are needed to confirm these findings.

ACKNOWLEDGMENTS

The authors wish to thank the hemodialysis staff of Boooli Hospital, Tehran, for their continuing efforts.

REFERENCES

- Weiner DE. Causes and consequences of chronic kidney disease: implications for managed health care. *JManag Care Pharm.*2007 Apr,13,3, 1-9. DOI: <http://dx.doi.org/10.18553/jmcp.2007.13.s3.1>
- Vanholder R, Argiles A, Baurmeister U, et al. Uremic toxicity: present state of the art. *Int J Artif Organs.* 2001, 24,10,695-725. PMID: 11817319
- 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.
- Vogt B, Frey FJ. Lactulose and renal failure. *Scand J Gastroenterol Suppl.*1997;32, Supplement 222, 83-87.. DOI:10.1080/00365521.1997.11720726
- Weber FL Jr. Scand. Effects of Lactulose on Nitrogen Metabolism. *Scandy J Gastroenterol.*1997;32,Supplement 222,83-87. doi:10.1080/00365521.1997.11720726.
- SMandayam, WE Mitch. Dietary protein restriction benefits patients with chronic kidney disease (Review Article). *Nephrology.*February 2006. 11, 1, 53-57., DOI: 10.1111/j.1440-1797.2006.00528.x.
- I Lazich, GL Bakris. Prediction and management of hyperkalemia across the spectrum of chronic kidney disease. *Seminars in nephrology.*May 2014. 34, 3, 333-339. doi:10.1016/j.semnephrol.2014.04.008
- Weber, Jr. F.L. Lactulose and Combination Therapy of Hepatic Encephalopathy: The Role of the Intestinal Microflora. *Dig Dis,*1996. 14, Suppl.1,53-63. DOI:10.1159/000171583
- Watanabe A, Sakai T, Sato S, et al. Clinical efficacy of lactulose in cirrhotic patients with and without subclinical hepatic encephalopathy. *Hepatology.* 1997,26, 6,1410-1414. DOI: 10.1002/hep.510260606
- 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

Dhiman RK, Sawhney MS, Chawla YK, Das G, Ram S, Dilawari JB. Efficacy of lactulose in cirrhotic patients with subclinical hepatic encephalopathy. *Dig Dis Sci*. 2000; 45,8,1549-52. DOI:10.1023/A:1005556826152

Meng S, Pan Y, Deng Q, Wang L, Chang Q. Efficacy and safety of lactulose on the treatment of puerperal constipation. *Zhonghua Yi Xue Za Zhi*. 2015 Jul, 28,95,28,2288-90. PMID: 26710954

Cockram DB, Hensley MK, Rodriguez M, et al. Safety and tolerance of medical nutritional products as sole sources of nutrition in people on hemodialysis. *J Renal Nutr*. 1998,8,1, 25-33. doi:10.1016/S1051-2276(98)90034-6

De Preter V, Vanhoutr T, Huys G, Swings J, Rutgeerts P, Verbeke K. Effect of lactulose and *Saccharomyces boulardii* administration on the colonic urea-nitrogen metabolism and the bifidobacteria concentration in healthy human subjects. *Aliment Pharmacol Ther*. 2006,23, 7, 963-974. DOI: 10.1111/j.1365-2036.2006.02834.x

Weber FL Jr. Lactulose and combination therapy of hepatic encephalopathy: the role of the intestinal microflora. *Dig Dis*. 1996,14Suppl 1,53-63. DOI:10.1159/000171583

Clausen MR, Mortensen PB. Lactulose, disaccharides and colonic flora. *Clinical consequences*. *Drugs*. 1997, 53,6,930-942. DOI: 10.2165/00003495-199753060-00003

TayebiKhosroshahi H, Habibzadeh A, Khoshbaten M, Rahbari B, Chaichi P, Badiie AH. Lactulose for reduction of nitrogen products in patients with chronic kidney disease. *Iran J Kidney Dis*. 2014 sep,8,5,377-81.

Yang SF, Tseng HS, Huang HC, Hsin IF, Yao YH, Chen JY. A patient with hemodialysis-related hyperammonemic encephalopathy: a delayed presentation of congenital arterioportal fistulas. *Clin Nephrol*. 2013 Jun; 79,6,499-503. DOI: 10.5414/CN107048

De Preter V, Vanhoutte T, Huys G, Swings J, Rutgeerts P, Verbeke K. Effects of Lactulose and *Saccharomyces boulardii* administration on the colonic urea-nitrogen metabolism and bifidobacteria concentration in healthy human subjects. *Aliment Pharmacol Ther*. 2006 Apr 1,23,7,:963-74. DOI: 10.1111/j.1365-2036.2006.02834.x

Mathialahan T, Sandle GI. Dietary potassium and laxatives as regulators 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