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Research Article
Concurrent Administration of Date Palm Fruits with Lisinopril Increases Serum Potassium Level in Male Rabbits

[1]Kazeem Babatunde Yusuff, [2]Promise Madu Emeka and [3]Mahesh Attimarad

[1]Department of Pharmacy Practice, College of Clinical Pharmacy, King Faisal University, Hofuf Al-Ahsa, Kingdom of Saudi Arabia
[2]Department of Pharmaceutical Sciences, Pharmacology Section, College of Clinical Pharmacy, King Faisal University, Hofuf Al-Ahsa, Kingdom of Saudi Arabia
[3]Department of Pharmaceutical Sciences, Pharmaceutical Chemistry Section, College of Clinical Pharmacy, King Faisal University, Hofuf Al-Ahsa, Kingdom of Saudi Arabia

Abstract

Background and Objective: Date palm fruit is potassium-rich and widely consumed in the Middle East in general and Saudi Arabia in particular. Hence, the possibility for food-drug interaction exists when concurrently used with a potassium-sparing medicine such as lisinopril. The objective was to investigate the effect of concurrent administration of date palm fruits with lisinopril on serum potassium levels in male rabbits. **Materials and Methods:** A non-randomized controlled study with 12 male rabbits divided into 3 groups (dates only-I), (lisinopril plus dates-II) and (lisinopril plus normal feed-III). The rabbits in group I and II were each fed on 25 g of dried dates daily, while group III was fed *ad libitum* on feed for 6 days. About 2 mg kg^{-1} day^{-1} of lisinopril was administered to group II and III daily for 6 days. Blood samples were analyzed for serum potassium with atomic absorption spectroscopy. **Results:** Serum potassium increased from the baseline to day 3 in all the three experimental groups, but this increase reached statistical significance in only the lisinopril+date group (group II) ($p<0.05$). The serum potassium level declined from day 3 to day 6 in all the three experimental groups. **Conclusion:** Co-administration of date fruits with lisinopril in male rabbits significantly increase the serum level of potassium and may be potentially harmful in kidney-related co-morbidities.

Key words: Date palm fruit, lisinopril, food-drug interaction, serum potassium, hypertension

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Corresponding Author: Kazeem B. Yusuff, Department of Pharmacy Practice, College of Clinical Pharmacy, King Faisal University, P.O. Box 400, 31982 Al-Ahsa, Kingdom of Saudi Arabia Tel: +966531263569

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Date palm (*Phoenix dactylifera* L.) is a major indigenous fruit that is widely consumed in the Middle East in general and Saudi Arabia in particular[1]. The use of date palm fruits as food and snacks is age-old, widespread and deeply rooted in the cultural ethos of Arabs especially Saudis living in Al-Hassa, the most important date-growing region in Saudi Arabia[2-3]. Date palm fruits contain several minerals including potassium. The percentage content of minerals in dried dates varies from 0.1-916 mg/100 g with the potassium concentration as high as 0.9% in the flesh of date fruits[4-5]. Data from the United States, Department of Agriculture (USDA) National Nutrient Database showed that the average potassium concentration in 100 g of date palm fruits (6-7 date fruits) is 656 mg[6].

The extensive consumption of date palm fruits in Saudi Arabia suggests that an investigation of any potential food-drug interaction with potassium-sparing medicines is warranted. This is particularly important for medicines that are used for the long-term or life-long management of chronic disease such hypertension. Hypertension is an endemic chronic disease in Saudi Arabia with an increasing prevalence especially in the Eastern region where the consumption of date palm fruits is widespread[7]. Continuous intensive management with appropriately prescribed antihypertensive medicines, in addition to relevant lifestyle modification, is a major therapeutic intervention used to achieve normotension and prevent the on-set of end organ damage in Saudi Arabia and worldwide[8]. Angiotensin-converting enzyme inhibitors (ACEIs) are one of the most frequently prescribed anti-hypertensive medicine classes among Saudis. The ACEIs are widely known to conserve potassium through their secondary effect on the reduction of the release of Aldosterone from the adrenal cortex[9-12]. Hence, the potential for food-drug interaction that may result in an unintended increase in potassium level exists when ACEIs are used concurrently with potassium-rich fruits like a date.

Several studies have characterized the morphological and physical parameters and the biochemical and nutritional contents of date palms[4,13]. However, literature search did not reveal any study that investigates the probability of an interaction that could lead to an increase in serum potassium level when date palm fruits are co-administered with potassium-conserving pharmacological agents such as ACEIs. The potential negative clinical consequence of the probable existence of such drug-food interaction could be dire and contributory to the morbidity and mortality among hypertensive patients prescribed such a combination in Saudi Arabia. Hence, a preliminary investigation of the effect of the co-administration of date palm fruits and ACEIs on serum potassium level using animal models is warranted. The results of the investigation provide the first initial insight into the research area which significantly adds to knowledge and upon which future studies involving human subjects can be premised. The findings of this preliminary study opens up a new lead that requires further studies and subsequent research with human subjects to explore the clinical consequences of concurrent administration of date palm fruits with lisinopril especially in hypertension with chronic kidney co-morbidities. The objective of this preliminary pre-clinical study was to investigate the effect of concurrent administration of date palm fruits with lisinopril on serum potassium level in an animal model.

MATERIALS AND METHODS

Experimental design: A non-randomized controlled pre-clinical study was conducted between 1st and 30th June, 2016. All the solutions and chemicals used for the study were of analytical grade. Twelve male rabbits obtained from the College of Veterinary Medicine, King Faisal University (KFU), Hofuf, Saudi Arabia were acclimatized for five days in separate well-ventilated cages and divided into three groups of four including group I (date palm fruit only), group II (lisinopril plus date palm fruit) and group III (lisinopril plus normal feed). All the rabbits were given access to clean water and treated in accordance with the International protocol and KFU scientific rules for the care and use of laboratory animals for experimental purposes. Institutional review of the study protocols was done by the Deanship of Scientific Research at KFU and approval was granted before the commencement of the study. The rabbits were all subjected to temperature and humidity control in a 12 h light-dark cycle. The rabbits in group I and II were each fed on 25 g of dried date palm fruit daily, while group III rabbits were fed *ad libitum* on feed for 6 days. The baseline weight and serum potassium levels of all the rabbits were determined before daily feeding with dates (groups I and II) and feed (group III). About 2 mg kg^{-1}/day of freshly prepared solution of lisinopril (Sigma Aldrich-L277-IG) was administered daily for 6 days to all the rabbits in groups II and III. The choice of the dose was based on its documented evidence of inhibition of renin-angiotensin-aldosterone system[14]. Weight was determined with the use of digital balance, while blood samples were collected at baseline, day 1, 3 and 7.

Sample collection: The rabbits were all fasted overnight before blood sampling to minimize interference by food consumption. During sample collection, the rabbits were restrained and their ears were shaved and cleaned with 95% v/v alcohol. Thereafter, blood was sampled via the marginal ear vein using a 26 g needle. After collection, a clean sterile cotton wool was used to clean the site and finger pressure was applied to stop bleeding. The collected blood samples were stored in plain Eppendorf tubes and allowed to clot by standing for about 30 min. The blood samples were then centrifuged at 6000 rpm for 20 min at 4°C to separate the serum and stored at -80°C until the determination of the serum potassium concentration with Atomic absorption spectroscopy[15].

Determination of serum potassium in rabbit serum: Atomic absorption spectrophotometer (AA 6300, Shimadzu Corporation, Japan) equipped with potassium hallow cathode lamp, high sensitivity nebulizer and the air-acetylene flame was used for the determination of the concentration of potassium in rabbit plasma/serum. The wavelength of the Cathode lamp was set at 766.5 nm for measurement of absorption. Double distilled water prepared on the daily basis was used for the experiment. The standard potassium solutions (0.1-2.0 ppm) were prepared by diluting the 1000 mg L^{-1} potassium solution (Scharlaur, Spain) with 1 mL of 1 N nitric acid and the calibration curve was constructed by least square regression analysis of absorption against the concentration of calibration standards. One milliliter of 1N nitric acid was added to the serum (0.2 mL) and diluted with double distilled water to get the concentration in the range of calibration curve. The atomic absorption was determined for the serum samples and concentration was calculated with the linear equation.

Statistical analysis: Data analysis was done with the Statistical Package for Social Sciences (SPSS) version 23 for Windows[16]. Results were presented as means (standard deviations) and percentages. One-way analysis of variance (ANOVA) was used to assess the difference in serum potassium between the three groups, while paired t-test was used to analyze the difference in weight between the baseline and day7 [17]. An a priori level of statistical significance of $p \leq 0.05$ was used for all comparisons.

RESULTS

The change in body weight at the baseline and after 6 days of treatment with dates, lisinopril and feeds is as shown in Table 1. There was a significant loss of weight in rabbits fed with dates only (group I) ($p>0.05$). The rabbits in group II (lisinopril plus dates) also experienced a decrease in weight which however did not reach statistical significance. On the contrary, there was a noticeable increase in the weight of the rabbits in group III (lisinopril+normal feed), but this was not statistically significant.

The effect of the co-administration of a daily dose of 2 mg kg^{-1}/day of lisinopril with date palm fruits and feeds for 6 days on serum potassium level in rabbits fed on dates and on feed is as shown in Table 2 and Fig. 1. There was an increase in serum level of potassium from the baseline to day 3, with the increase reaching the peak on day 3 in all the three experimental groups. However, increase in serum potassium level was statistically significant in only the lisinopril+date palm fruit group (group II) ($p<0.05$). In addition, there was an increase in serum potassium level from the baseline up to day 3 in the rabbits fed with date palm fruit only (group I), but this increase did not reach statistical

Table 1: Lisinopril dosing, food consumption and body weight changes in male rabbit over a six-day experimental period

Groups	Rabbits (n)	Lisinopril dose (mg kg^{-1}/day) SC for 6 days	Food	Food consumption (g/day/rabbit)	Body weight (g) Day 1, Mean±SD	Body weight (g) Day 6, Mean±SD	Body weight gain (%)	p-values (change in body weight)
I-Dates only	4	0	Dates	25	472±96	433±80	-8.3	0.019*
II-Lisinopril+dates	4	2	Dates	25	560±89	529±30	-5.5	0.596
III-Lisinopril+feed	4	2	Feed	*ad lib.*	540±78	665±90	18.8	0.002*

SC: Subcutaneous, *$p<0.05$: Significant

Table 2: Effect of co-administration of lisinopril with date palm fruits on serum potassium levels in rabbits

Days	Dates only Mean±SD	Lisinopril+dates (Mean±SD)	Lisinopril+feeds (Mean±SD)	ANOVA p-values
Baseline	3.6±0.44	3.5±0.29	3.5±0.42	0.757
Day 1	3.8±0.29	4.5±1.2	3.6±0.29	0.235
Day 3	4.2±0.25	*5.6±0.99	4.1±0.67	0.023*
Day 7	3.2±0.47	3.5±0.55	3.0±0.38	0.362

ANOVA: Analysis of variance, Tukey's HSD test (*post hoc*) reveals mean accounting for significance, *Reveals mean that accounted for the statistical significance, $p<0.05$: Significant

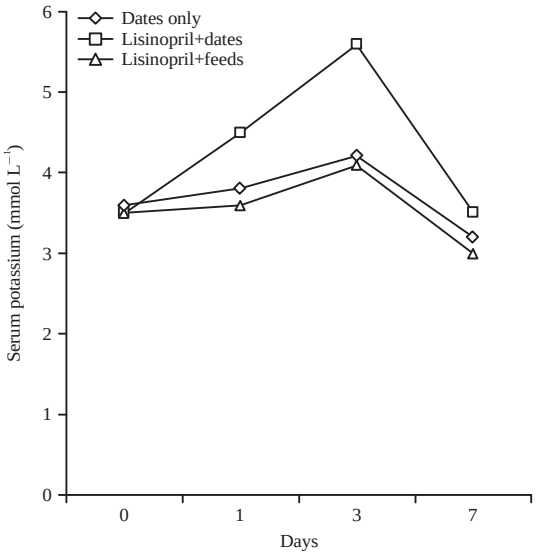

Fig. 1: Effect of daily co-administration of lisinopril (2 mg kg^{-1}/day) and date palm fruits (25 g/day) on serum potassium levels of rabbits

significance ($p>0.05$). Furthermore, these findings showed that there was a decline in serum potassium level from day 3 to day 7 in all the three experimental groups (Fig. 1).

DISCUSSION

The study findings suggest that the consumption of date palm fruit alone resulted in an increase in serum potassium level from the baseline to the 3rd day when it reached the peak, but this was not statistically significant ($p>0.05$). The same trend was observed in the serum potassium of the rabbits in group III (lisinopril+feed). On the other hand, co-administration of date palm fruit with lisinopril resulted in a statistically significant increase in serum potassium level from the baseline to the peak on the day 3 of the 6 days experimental treatment ($p<0.05$). This increase was however, not sustained till the end of the experiment. Lisinopril-associated increase in serum potassium level is well documented by several pre-clinical and clinical researches. The inhibition of aldosterone in the renin-angiotensin aldosterone system by ACEIs including lisinopril is strongly linked to the observed increase in serum potassium[9,11,14,18]. However, the current preliminary study appeared to be first to report a significant ($p<0.05$) increase in serum potassium due to co-administration of lisinopril with date palm fruits. This is an important finding with a potentially significant clinical implication due to the possibility of the risk of occurrence of hyperkalemia-associated cardiac toxicity in patients who are hypertensive and on chronic management with lisinopril or other ACEIs in Saudi Arabia and other Middle Eastern countries[19-21]. This is because date palm fruit is a staple snack which is widely consumed by the majority of the populace including hypertensive patients on treatment with ACEIs in this part of the world. Furthermore, the observed decrease in serum potassium level in all the three groups from day 3 to day 6 (end of the study) suggests that in the absence of an organic problem in the kidney, the serum potassium level returned to pre-treatment (baseline) level. Hence, it appears that the risk of a rise in serum potassium level due to co-administration of date palm fruit with lisinopril may be higher in hypertensive patients with co-morbidities such as chronic kidney disease, type-2 diabetes mellitus and/or diabetic kidney disease[12,22-24]. This is an important preliminary finding that requires further studies and subsequent research with human subjects to explore the clinical consequences of this probable food-drug interaction especially in hypertension with chronic kidney co-morbidities.

The negative but insignificant difference in weight between the baseline and day 6 in rabbits treated with lisinopril+dates and the significantly ($p<0.05$) increased weight observed in the lisinopril+feed group appears to suggest that neither lisinopril nor date palm fruit is contributory to weight loss or gain. Food types and amount consumed appeared to be a major contributory factor. The rabbits in the lisinopril+feed group had *ad libitum* access to feed over the 6 days experimental period and this may have contributed to the weight increase, while those in the dates-only group were restricted to 25 g/day/animal. Hence, the weight loss observed in the dates-only and lisinopril+date palm fruit group is probably due to the restriction of feeding. This restriction was necessitated by concerns for the protection of the animals from any potentially harmful consequences due to the probable occurrence of hyperkalemia. This is because the data from the USDA's National nutrient database showed that 100 g of date palm fruit contains 656 mg of potassium and this translates to about 37 mmol.

The finding with regards to the probable weight-neutral effect of lisinopril in the rabbit is consistent with that of Hajj-Ali and Zimmerman[14], who reported that the administration of 2 mg kg^{-1}/day for 6 days did not result in any significant change in weight in rabbits. This finding is also consistent with that of Dodiya *et al.*[25], who reported that there was no significant impact on the weight of rats administered with two different doses of 20 and 50 mg kg^{-1}/day of lisinopril for 21 days. This weight-neutral effect may potentially

prove beneficial in contributing to the reported clinical improvement in insulin sensitivity, glucose uptake and glycemic control associated with lisinopril[26-28]. The study is limited by the fact that this is a pre-clinical study done over a period 6 days using limited number of male rabbits. However, the study provides the first report of an increase in serum potassium level that is associated with the concurrent use of date palm fruits with a potassium-sparring pharmacological agent such as lisinopril. Further studies are warranted to explore the potential negative consequences of this probable food-drug interaction especially in hypertension with chronic kidney co-morbidities.

CONCLUSION

The co-administration of date palm fruits with lisinopril in male rabbits appears to significantly increase the serum level of potassium and this may be a food-drug interaction with a potentially harmful negative clinical consequence especially in hypertensive patients with co-morbidities such as chronic disease, type-2 diabetes mellitus and diabetic kidney disease. Further research with human subjects is required to assess the potential clinical consequence of this probable food-drug interaction

SIGNIFICANCE STATEMENT

This study discovers an increased serum potassium level when date palm fruits were co-administered with lisinopril in a rabbit model. This preliminary finding helps to uncover the critical areas of co-administration of date palm fruits with lisinopril that have not been reported before and on which future studies in the research area can be premised.

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REFERENCES

1. Vayalil, P.K., 2012. Date fruits (*Phoenix dactylifera* Linn): An emerging medicinal food. Crit. Rev. Food Sci. Nutr., 52: 249-271.
2. Habib, H.M. and W.H. Ibrahim, 2011. Nutritional quality of 18 date fruit varieties. Int. J. Food Sci. Nutr., 62: 544-551.
3. USDA., 2016. USDA national nutrient database for standard reference, release 28. United States Department of Agriculture (USDA), Agricultural Research Service, USA., May 2016.
4. El-Sohaimy, S.A. and E.E. Hafez, 2010. Biochemical and nutritional characterizations of date palm fruits (*Phoenix dactylifera* L.). J. Applied Sci. Res., 6: 1060-1067.
5. Al-Farsi, M.A. and C.Y. Lee, 2008. Nutritional and functional properties of dates: A review. Crit. Rev. Food Sci. Nutr., 48: 877-887.
6. Al-Nozha, M.M., M. Abdullah, M.R. Arafah, M.Z. Khalil and N.B. Khan *et al*., 2007. Hypertension in Saudi Arabia. Saudi Med. J., 28: 77-84.
7. Saeed, A.A., N.A. Al-Hamdan, A.A. Bahnassy, A.M. Abdalla, M.A. Abbas and L.Z. Abuzaid, 2011. Prevalence, awareness, treatment and control of hypertension among Saudi adult population: A national survey. Int. J. Hypertens. 10.4061/2011/174135.
8. Epstein, M., 2016. Hyperkalemia constitutes a constraint for implementing renin-angiotensin-aldosterone inhibition: The widening gap between mandated treatment guidelines and the real-world clinical arena. Kidney Int. Suppl., 6: 20-28.
9. Weir, M.R. and M. Rolfe, 2010. Potassium homeostasis and renin-angiotensin-aldosterone system inhibitors. Clin. J. Am. Soc. Nephrol., 5: 531-548.
10. Raebel, M.A., 2012. Hyperkalemia associated with use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Cardiovasc. Therapeut., 30: e156-e166.
11. Shearer, F., C.C. Lang and A.D. Struthers, 2013. Renin-angiotensin-aldosterone system inhibitors in heart failure. Clin. Pharmacol. Therapeut., 94: 459-467.
12. Farag, K.M., A.S El-Sabagh and H.A. El-Ashry, 2012. Fruit characteristics of Zaghloul date palm in relation to metaxenic influences of used pollinator. Am.-Eurasian J. Agric. Environ. Sci., 12: 842-855.
13. Hajj-Ali, A.F. and B.G. Zimmerman, 1992. Enhanced blood pressure and renal hemodynamic effect of chronic versus acute lisinopril administration in the rabbit. J. Pharmacol. Exp. Therapeut., 263: 158-162.
14. Nielsen, S.S., 2015. Sodium and Potassium Determinations by Atomic Absorption Spectroscopy and Inductively Coupled Plasma-Atomic Emission Spectroscopy. In: Food Analysis Laboratory Manual (Food Science Text Series), Nielsen, S.S. (Ed.). 2nd Edn., Chapter 11, Springer, New York, USA., ISBN-13: 978-1441914620, pp: 87-93.
15. IBM., 2015. IBM SPSS Statistics for Windows, Version 23.0. IBM Corporation, Armonk, NY., USA.
16. Norman, G.R. and D. Streiner, 2008. Biostatistics: The Bare Essentials. 3rd Edn., B.C. Decker Inc., Hamilton, Ontario, Canada, ISBN-13: 9781550093476, pp: 70-72.

17. Maddirala, S., A. Khan, A. Vincent and K. Lau, 2008. Effect of angiotensin converting enzyme inhibitors and angiotensin receptor blockers on serum potassium levels and renal function in ambulatory outpatients: Risk factors analysis. Am. J. Med. Sci., 336: 330-335.
18. Parham, W.A., A.A. Mehdirad, K.M. Biermann and C.S. Fredman, 2006. Hyperkalemia revisited. Texas Heart Inst. J., 33: 40-47.
19. Jain, N., S. Kotla, B.B. Little, R.A. Weideman, E.S. Brilakis, R.F. Reilly and S. Banerjee, 2012. Predictors of hyperkalemia and death in patients with cardiac and renal disease. Am. J. Cardiol., 109: 1510-1513.
20. Kovesdy, C.P., 2014. Management of hyperkalaemia in chronic kidney disease. Nat. Rev. Nephrol., 10: 653-662.
21. Johnson, E.S., J.R. Weinstein, M.L. Thorp, R.W. Platt and A.F. Petrik *et al*., 2010. Predicting the risk of hyperkalemia in patients with chronic kidney disease starting lisinopril. Pharmacoepidemiol. Drug Saf., 19: 266-272.
22. Einhorn, L.M., M. Zhan, L.D. Walker, M.F. Moen, S.L. Seliger, M.R. Weir and J.C. Fink, 2009. The frequency of hyperkalemia and its significance in chronic kidney disease. Arch. Internal Med., 169: 1156-1162.
23. Weinberg, J.M., L.J. Appel, G. Bakris, J.J. Gassman and T. Greene *et al*., 2009. Risk of hyperkalemia in nondiabetic patients with chronic kidney disease receiving antihypertensive therapy. Arch. Internal Med., 169: 1587-1594.
24. Dodiya, H., V. Kale, S. Goswami, R. Sundar and M. Jain, 2013. Evaluation of adverse effects of lisinopril and rosuvastatin on hematological and biochemical analytes in Wistar rats. Toxicol. Int., 20: 170-176.
25. Ogino, K., M. Kato, Y. Furuse, Y. Kinugasa and Y. Kaetsu *et al*., 2010. Addition of losartan to angiotensin-converting enzyme inhibitors improves insulin resistance in patients with chronic heart failure treated without β-blockers. Circ. J., 74: 2346-2352.
26. Aksnes, T.A., H.M. Reims, S. Guptha, A. Moan, I. Os and S.E. Kjeldsen, 2006. Improved insulin sensitivity with the angiotensin II-receptor blocker losartan in patients with hypertension and other cardiovascular risk factors. J. Hum. Hypertens., 20: 860-866.
27. Jin, H.M. and Y. Pan, 2007. Angiotensin type-1 receptor blockade with losartan increases insulin sensitivity and improves glucose homeostasis in subjects with type 2 diabetes and nephropathy. Nephrol. Dial. Transplant., 22: 1943-1949.