[Downloaded free from http://www.thejhs.org on Tuesday, August 09, 2016, IP: 41.128.165.40]

Original Article

# The hypotensive and uricosuric effect of valsartan compared to losartan in gout patients

**Anas Bahnassi[1], Amjad Abuirmeileh[2], Ayman Abuirmeileh[3]**

[1]Department of Clinical and Hospital Pharmacy, College of Pharmacy, Taibah University, Madinah, Saudi Arabia, [2]Department of Applied Pharmaceutical Sciences, College of Pharmacy, Isra University, Amman, Jordan, [3]Department of Internal Medicine, St. Vincent Charity Medical Center, Cleveland, OH, USA

## ABSTRACT

**Objective:** Our objective was to investigate the possible relationship between previous or concurrent use of losartan or valsartan and gout in newly diagnosed patients.

**Materials and Methods:** Thirty-two newly-diagnosed gout patients, whose blood pressure was controlled using losartan for at least 3 months were included. The study was divided into 3 stages; stage I where patients were controlled for 3 months using losartan (50 mg/day), stage II - where patients were switched from losartan to valsartan (80 mg/day) with their blood pressure controlled and maintained for another 3 months using valsartan instead of losartan and stage III - where patients were switched back to losartan (50 mg/day). All changes in clinical and biochemical parameters were reported.

**Results:** There were no significant changes in biochemical parameters such as liver enzymes, serum levels of creatinine, sodium and bicarbonate. Serum levels of potassium and uric acid were elevated. Valsartan significantly increased potassium and uric acid levels at the end of stage II ($P$ = 0.024). Since these adverse effects did not disappear after changing back to losartan at the end of stage III, we performed an additional 3-month follow-up stage. The subjects required a period of 6 months to return to levels seen at the end of stage I.

**Conclusion:** Losartan showed a slightly higher hypotensive effect than valsartan in patients newly diagnosed with gout. It also resulted in lower uric acid levels.

**Keywords:** Gout, hypertension, losartan, uric acid, valsartan

## INTRODUCTION

There have been many reports linking hypertension to gout.[1,2] This comorbidity can be attributed to changes in the renal pathology in hypertensive patients resulting in decreased uric acid (UA) excretion.[3] The occurrence of hypertension is independently associated with the risk of gout occurrence[4] through reduced renal blood flow due to increased renal and peripheral vascular resistance and decreased rate of renal excretion of UA.[5-7] Valsartan is a competitive angiotensin II receptor blocker (ARB), selective for its AT1 subtype. In addition to selective blockade of AT1 receptors, valsartan blocks other components of the renin-angiotensin-aldosterone system, all of which attribute to its pharmacodynamics and therapeutic effects.[8] Although losartan, the prototype of this therapeutic group, was found to lower serum UA levels,[9,10] valsartan showed either a slight decrease in blood UA levels[11] or neutral effect on these levels.[12] The aim of this study is to investigate any possible relationship between patients newly diagnosed with gout and their previous or concurrent use of losartan and valsartan.

**Address for correspondence:**
Prof. Anas Bahnassi, Department of Clinical and Hospital Pharmacy, College of Pharmacy, Taibah University, P. O. Box 30117, Madinah 41477, Saudi Arabia.
E-mail: abahnassi@gmail.com

**Access this article online**

Quick Response Code:

Website: www.thejhs.org

DOI: 10.4103/1658-600X.173833

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Bahnassi A, Abuirmeileh A, Abuirmeileh A. The hypotensive and uricosuric effect of valsartan compared to losartan in gout patients. J Health Spec 2016;4:52-5.



© 2016 Journal of Health Specialties | Published by Wolters Kluwer - Medknow

[Downloaded free from http://www.thejhs.org on Tuesday, August 09, 2016, IP: 41.128.165.40]



## METHODOLOGY

Thirty-two newly-diagnosed gout patients from the medical unit of Isra University in Amman, Jordan, with age range of 52 ± 6 years, who were controlled for hypertension using losartan over a period of at least 3 months, were selected for the study. All other patients with secondary hypertension, heart failure of New York Heart Association grade III or IV, liver dysfunction, kidney dysfunction (serum creatinine level of more than 2.0 mg/dL), pregnancy or a history of allergy to losartan or valsartan were excluded. The protocol was approved by the Ethical Clinical Committee of the College of Pharmacy (1435/1/a), and all subjects provided their informed written consent to participate in the study.

Our study was divided into three stages, which included stage I - where patients were controlled for 3 months using losartan (50 mg/day), stage II - where patients were switched from losartan to valsartan (80 mg/day) with their blood pressure [BP] controlled and maintained for another 3 months using valsartan instead of losartan and stage III - where patients were switched back to losartan (50 mg/day). All changes in clinical and biochemical parameters were reported and documented.

### Evaluation of clinical parameter

Clinical and biochemical parameters of each patient were analysed at the end of each stage and it included mean arterial pressure (MAP), pulse rate (PR), body weight, height and various serum and urinary levels. BP was determined as the mean of two measurements obtained in the setting position using a mercury sphygmomanometer after at least 5 min of rest. All measurements were made by the same investigator on the patient's dominant arm. MAP was calculated as,[13,14]

$$\frac{\text{Systolic blood pressure} + (2 \times \text{diastolic pressure})}{3}$$

All blood and urinary samples were collected after overnight fasting in the morning. Data of serum levels of high sensitive C-reactive protein, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), triglycerides (TG), UA, creatinine (Cr), fasting glucose and haemoglobin A1c, sodium (Na) and potassium (K) and Cr and albumin (Alb) were collected for all tested patients. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. All other characteristics with regard to patients' history of diabetes mellitus (DM), dyslipidaemia (DL), hyperuricaemia (HU), smoking status and medication use were obtained from medical records. DM was defined according to the Canadian Diabetes Association criteria or the use of a glucose-lowering drug. Patients with LDL-C ≥ 3.6 mmol/L, TG ≥1.7 mmol/L and/or HDL-C < 1 mmol/L, or who were receiving lipid-lowering therapy, were considered having DL. HU was defined as a serum UA level of ≥ 415 μmol/L or the use of UA-lowering agents.

### Statistical analysis

Statistical analysis was performed using the analysis of variance (ANOVA) function (one-way, repeated measurement) to test for changes within the study group over time. The significance of differences between mean values was evaluated by the paired *t*-test or one-way ANOVA followed by the Fisher's protected-least-significant-difference test as appropriate. Relationships between variables were tested by Pearson and Spearman correlations. A value of $P < 0.05$ was considered statistically significant.[15] Data are shown as the mean ± standard deviation.

## RESULTS

### Baseline clinical characteristics

Clinical characteristics of the 32 patients studied are shown in Table 1 (20 [62.5%] men and 12 [37.5%] women). The prevalence of DM, DL and HU was 15.6%, 47% and 90%, respectively. The mean age was 52 ± 6 years, BMI was 24 ± 3 $kg/m^2$, MAP was at 112 ± 8 and PR was 70 ± 10 beats/min. In addition, the present use of calcium channel blocker, β-blocker and 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors was 46%, 22% and 42%, respectively; none of the patients received α-blockers.

Table 2 shows no significant changes in biochemical parameters such as liver enzymes, serum levels of Cr, Na and bicarbonate. Serum levels of UA and K were elevated. Valsartan significantly increased serum UA and K at the end of stage II ($P = 0.024$). Since these adverse effects did not disappear after changing back to losartan at the end of stage III, we performed an additional 3-month follow-up stage.

The subjects required a period of 6 months to return to the levels seen at the end of stage I. Losartan may have a more positive effect on decreasing UA compared to valsartan.

## DISCUSSION

We have noticed that both losartan and valsartan were effective in lowering MAP. Losartan was slightly more effective. Switching the patient from losartan to valsartan resulted in increase in UA and K serum levels. Recent clinical studies have demonstrated that not all ARBs have the same effects; certain effects may be molecular rather than class - related.[16] Losartan has a molecular effect as uricosuric action through the

[Downloaded free from http://www.thejhs.org on Tuesday, August 09, 2016, IP: 41.128.165.40]



**Table 1: Baseline clinical characteristics of the study subjects (*n*=32)**

| Clinical characteristic | Prevalence | Percentage of patients' medication use (%) |
|---|---|---|
| Age mean+/- SD | 52 ± 6 years | |
| Gender (male %) | 62.5 | HMG-CoA reductase inhibitors (42) |
| BMI (kg/m$^2$) | 24 ± 3 | |
| Smoking (%) | 56.3 | Ezetimibe (6) |
| DM (%) | 15.6 | |
| Fasting glucose (mmol/L) | 5.88 ± 0.6 | Fibrates (22) |
| HbA1c (%) | 5.3 ± 0.4 | Diuretics (52) |
| DL (%) | 47 | Calcium channel blockers (46) |
| TG (mmol/L) | 1.49 ± 0.12 | |
| HDL-C (mmol/L) | 0.9 ± 0.04 | β-blockers (22) |
| LDL-C (mmol/L) | 3.13 ± 0.7 | Metformin (6) |
| HU (%) | 70 | Sulfonylurea (4) |
| UA (μmol/L) | 401.6 ± 38 | Allopurinol (18) |

BMI: Body mass index, DM: Diabetes mellitus, DL: Dyslipidaemia, HU: Hyperuricaemia, HbA1c: Haemoglobin A1c, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, TG: Triglycerides, UA: Uric acid, HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A

**Table 2: Changes in biochemical parameters at the end of each stage of the study**

| Biochemical parameter | Stage I | Stage II | Stage III |
|---|---|---|---|
| Liver enzymes | | | |
| AST (IU/L) | 26 ± 16 | 28 ± 19 | 27 ± 14 |
| ALT (IU/L) | 27 ± 25 | 24 ± 19 | 22 ± 14 |
| ALP (IU/L) | 219 ± 67 | 228 ± 59 | 231 ± 68 |
| GGT (IU/L) | 50 ± 49 | 52 ± 60 | 48 ± 51 |
| LDH (IU/L) | 198 ± 37 | 209 ± 45 | 201 ± 53 |
| Haematology | | | |
| RBC ($10^{12}$/L) | 3.4 ± 0.4 | 3.9 ± 0.2 | 3.5 ± 0.3 |
| Hb (g/dL) | 10.5 ± 1 | 11.6 ± 1.0 | 10.4 ± 1.0 |
| Haematocrit (%) | 34.6 ± 2.4 | 31.1 ± 3 | 34.7 ± 2.1 |
| Platelets ($10^9$/L) | 230 ± 32 | 244 ± 52 | 224 ± 42 |
| WBC ($10^9$/L) | 6.0 ± 2.5 | 5.1 ± 1.7 | 6.3 ± 2.1 |
| Serum biochemistry | | | |
| Sodium (mmol/L) | 140 ± 3.0 | 142 ± 1.9 | 141 ± 2.4 |
| Potassium (mmol/L) | 3.8 ± 0.4 | 4.2 ± 0.7 | 3.7 ± 0.5 |
| Bicarbonate (mmol/L) | 22 ± 3 | 25 ± 2 | 23 ± 3 |
| HbA1c (%) | 5.5 ± 0.4 | 5.2 ± 0.3 | 5.4 ± 0.4 |
| Creatinine (μmol/L) | 79.3 ± 26.4 | 79.6 ± 24.1 | 80.1 ± 22.5 |
| Urea (mmol/L) | 22.3 ± 72 | 16.7 ± 5.3 | 17.2 ± 4.5 |
| UA (μmol/L) | 450 ± 101 | 519 ± 99 | 479 ± 78 |

AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase, GGT: Gamma glutamyl transferase, RBC: Red blood cells, WBC: White blood cells, HbA1c: Haemoglobin A1c, UA: Uric acid, Hb: Haemoglobin

inhibition of uric acid transporter 1 in hypertensive patients.[17] Valsartan, however, does not have this effect. Some studies showed a significant increase in UA serum levels.[18] In the present study, valsartan again showed a statistically significant increase ($P > 0.05$) in serum UA levels compared to losartan. Thus, the results of this study were consistent with previous reports.[16-18]

In general, ARBs work by directly dilating peripheral arterioles in addition to their hypotenisve effects; thus, ARBs reduce intraglomerular pressure resulting in decrease in urinary protein excretion, preventing progression of renal dysfunction. Losartan is superior to valsartan in that manner due to its significant shift to renal tissue compared to valsartan.[19]

### Study limitation

Our study included two important limitations. The first limitation was that the studied sample size was relatively small, which limits our ability to determine the significance of the results. The second limitation is related to the study design that included the carried-over effect of switching patients from losartan to valsartan and vice versa.

## CONCLUSION

Losartan showed a slightly more hypotensive effect compared to valsartan in newly diagnosed gout patients. It is also preferred due to its uricosuric structural action, which results in lower UA serum levels.

### Financial support and sponsorship

This research was part of the research budget of the College of Pharmacy in Taibah University (a publicly funded university).

### Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Pillinger MH, Goldfarb DS, Keenan RT. Gout and its comorbidities. Bull NYU Hosp Jt Dis 2010;68:199-203.
2. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. Am J Med 2012;125:679-87.e1.
3. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, *et al.* Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 2003;41:1183-90.
4. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: The health professionals follow-up study. Arch Intern Med 2005;165:742-8.
5. Prebis JW, Gruskin AB, Polinsky MS, Baluarte HJ. Uric acid in childhood essential hypertension. J Pediatr 1981;98:702-7.
6. Puig JG, Ruilope LM. Uric acid as a cardiovascular risk factor in arterial hypertension. J Hypertens 1999;17:869-72.
7. Baker JF, Krishnan E, Chen L, Schumacher HR. Serum uric acid and cardiovascular disease: Recent developments, and where do they leave us? Am J Med 2005;118:816-26.
8. Alajbegovic S, Sukalo A, Alajbegovic A, Vranic JD, Ambeskovic M, Deljo D, *et al.* Valsartan in the treatment of hypertension. Med Arch 2013;67:174-7.
9. Shahinfar S, Simpson RL, Carides AD, Thiyagarajan B,

[Downloaded free from http://www.thejhs.org on Tuesday, August 09, 2016, IP: 41.128.165.40]



Nakagawa Y, Umans JG, *et al.* Safety of losartan in hypertensive patients with thiazide-induced hyperuricemia. Kidney Int 1999;56:1879-85.

10. Høieggen A, Alderman MH, Kjeldsen SE, Julius S, Devereux RB, De Faire U, *et al.* The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int 2004;65:1041-9.
11. Plum J, Bünten B, Németh R, Grabensee B. Effects of the angiotensin II antagonist valsartan on blood pressure, proteinuria, and renal hemodynamics in patients with chronic renal failure and hypertension. J Am Soc Nephrol 1998;9:2223-34.
12. Sayin T, Döven O, Akyürek O, Dinçer I. Neutral effect of valsartan on serum uric acid and renal function tests. J Hum Hypertens 2001;15:435-6.
13. Zanchetti A, Mancia G. The centenary of blood pressure measurement: A tribute to Scipione Riva-Rocci. J Hypertens 1996;14:1-12.
14. Meaney E, Alva F, Moguel R, Meaney A, Alva J, Webel R. Formula and nomogram for the sphygmomanometric calculation of the mean arterial pressure. Heart 2000;84:64.
15. Sutradhar BC. Dynamic Mixed Models for Familial Longitudinal Data. New York, NY, USA: Springer; 2011.
16. Miura S, Karnik SS, Saku K. Review: Angiotensin II type 1 receptor blockers: Class effects versus molecular effects. J Renin Angiotensin Aldosterone Syst 2011;12:1-7.
17. Hamada T, Ichida K, Hosoyamada M, Mizuta E, Yanagihara K, Sonoyama K, *et al.* Uricosuric action of losartan via the inhibition of urate transporter 1 (URAT 1) in hypertensive patients. Am J Hypertens 2008;21:1157-62.
18. Reyes AJ. Cardiovascular drugs and serum uric acid. Cardiovasc Drugs Ther 2003;17:397-414.
19. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, *et al.* Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004;351:1285-95.