Austin Hypertension

Open Access

Austin Publishing Group

Research Article

Comparison of the Effect of Angiotensin II Type I Receptor Blockers on Serum Uric Acid in Hypertensive Patients in Mosul City

Dawood KH[1]*, Saeed AA[2] and Khudhur GA[3]

[1]Diploma of Family Medicine, Al-Quds Health Center, Mosul, Iraq

[2]F.I.C.MS Path, Nineva Rehabilitation Center, Mosul, Iraq

[3]Diploma of Family Medicine, Al-Quds Health Center, Mosul, Iraq

***Corresponding author:** Kasim Hazim Dawood, Diploma of Family Medicine, Al-Quds Health Center, Mosul, Iraq

Received: July 18, 2022; **Accepted:** August 16, 2022; **Published:** August 23, 2022

Abstract

Background: Angiotensin II type I Receptor Blockers (ARB) are a frequently used class of antihypertensive drugs. The ARB losartan is known to decrease the serum uric acid (S_{UA}) level. However, there are very few clinical data comparing the effects of other ARBs on S_{UA} level under the conditions of clinical practice. This study evaluated and compared the long-term effects of monotherapy with five ARBs on S_{UA} level in hypertensive patients in Mosul city.

Methods: We identified hypertensive patients who had been treated with monotherapy with losartan (n = 30), valsartan (n = 32), telmisartan (n = 29), candesartan (n = 31), or irbemesartan (n = 28), in whom laboratory data of S_{UA} between December 1 2019 and February 1 2021 were available and compared the S_{UA} level. The mean exposure of losartan was 245 days, valsartan 240 days, telmisartan 238 days, candesartan 242 days, and irbesartan 239 days.

Results: In losartan users, mean S_{UA} level was significantly decreased from baseline, while it was conversely increased in users of other ARBs; valsartan, telmisartan, candesartan, and irbemesartan. The mean reduction of S_{UA} level from baseline was significantly greater in losartan users compared with that in other ARB users. Comparison of ARBs other than losartan showed no significant difference in mean change in S_{UA} level from baseline.

Conclusions: Our study showed that losartan had the most beneficial effect on S_{UA} level among five ARBs, and that there was no significant difference in the unfavorable effects on S_{UA} level among four ARBs other than losartan, at least during one year. These findings provide evidence of an effect of ARBs on S_{UA} level.

Keywords: ARB monotherapy; Losartan; Valsartan; Telmisartan; Candesartan; Irbesartan; Serum Uric Acid; Hypertension

Abbreviations

ARB: Angiotensin type II Receptor Blocker; CCB: Calcium Channel Blockers; NSAID: Non-Steroidal Anti- Inflammatory Drug; S_{UA}: Serum Uric Acid; URAT1: Urate Transporter 1

Introduction

The main cause of gout is high concentration of serum uric acid (S_{UA}), and is also associated with the metabolic syndrome, including hypertension [1-4]. In the report of the US National Health and Nutrition Examination Survey, among patients with gout, 74% had hypertension [5]. Many patients with hyperuricemia are using antihypertensive agents because hypertension and hyperuricemia are conditions that frequently coexist. Antihypertensive drugs have different effects on uric acid. Beta blockers and thiazide diuretics increase the S_{UA} level whereas alpha-blockers and Calcium-Channel Blockers (CCB) decrease the S_{UA} level [6-8]. The effect of Angiotensin II type I Receptor Blockers (ARBs) on the S_{UA} level differs among drugs. Of ARBs, losartan decreases the S_{UA} level [9-17] via its influence on Urate Transporter 1 (URAT1) [18-20]. Differing from losartan, valsartan and candesartan have been reported to increase the S_{UA} level in patients with hypertension [21,22]. Several studies have compared the effect of losartan on S_{UA} with that of another drug or placebo. Few studies have performed a multiple comparison of the effects on S_{UA} level among various ARBs in clinical practice. The aim of this study was to evaluate and compare the long-term effect of five ARB monotherapies; losartan, valsartan, candesartan, telmisartan, and irbesartan, on S_{UA} in hypertensive patients in Mosul city.

Study Populations

We identified patients with mild to moderate hypertension aged over 20 years, who had been newly treated with ARB monotherapy for at least two months between December 1, 2019 and February 1, 2021. The five ARBs used in this study were losartan potassium, valsartan, telmisartan, candesartan cilexetil, and irbesartan (Table 1). The numbers of monotherapy patients in this study were; losartan (n = 30), valsartan (n = 32), telmisartan (n = 29), candesartan (n = 31), and irbesartan (n = 28) (Table 2). The experimental protocol was approved by the Ethical Committee of Al-Quds health center and was conducted in compliance with the ethical guidelines for epidemiological research of the Ministry of Health Iraq.

Citation: Dawood KH, Saeed AA and Khudhur GA. Comparison of the Effect of Angiotensin II Type I Receptor Blockers on Serum Uric Acid in Hypertensive Patients in Mosul City. Austin Hypertens. 2022; 3(1): 1013.

Exposure and Measurements

The baseline measurement period (non-exposure period) was defined as within 12 months before the start of ARB monotherapy. The exposure period (outcome measurement period) was defined as between 2 and 12 months after the start of ARB monotherapy. Laboratory data of the level of S_{UA} for each subject were collected at the date nearest the start of ARB monotherapy in the baseline period, and at the date nearest 12 months after the start of ARB monotherapy in the exposure period. The mean exposure of losartan was 245 days, valsartan 240 days, telmisartan 238 days, candesartan 242 days, and irbesartan 239 days.

Data Elements

For each patient, we collected information of patient demographics (age and sex), medical history, use of medication, and laboratory results as baseline covariates. Medical history included cerebrovascular disease, ischemic heart disease, other heart disease, thyroid gland disorder, rheumatoid disease and hyperlipidemia. Drugs used during the 60 days before the start of ARB monotherapy included, lipid- lowering drugs (including statins, fibrates, and other lipid-lowering drugs), thyroids drugs, antipsychotics, antithrombotic drugs, drugs, steroids, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), proton pump inhibitors, and histamine H2 receptor blockers.

Statistical Analysis

All statistical analyses were performed with Microsoft Office Excel 2013 software. This is a retrospective observational study. We compared the mean change from the baseline value to the exposure value among ARB users. A result was considered statistically significant if the p value was less than 0.05.

Results

Tables 2 shows the characteristics of the patients who had been treated with ARB monotherapy. Table 3 shows the results of laboratory tests at baseline and during the exposure period. In losartan users, the mean level of S_{UA} was significantly decreased in the exposure period compared with the baseline level. In users of other ARBs, valsartan, telmisartan candesartan, and irbesartan, the mean levels of S_{UA} were significantly increased in the exposure period compared with those in the baseline. There was no significant difference in the increase of S_{UA} level among the users of ARBs other than losartan; valsartan, telmisartan, candesartan, and irbesartan.

Discussion

In this study, we evaluated and compared the effect of long-term monotherapy, up to one year, among five ARBs on S_{UA} in hypertensive patients. The mean level of S_{UA} after treatment with losartan significantly decreased compared with the baseline. The mean level of S_{UA} after treatment with other ARBs (valsartan, telmisartan, candesartan, and irbesartan) significantly increased compared with baseline. The reduction of S_{UA} level from baseline in losartan users was significantly greater than that in other ARB users. This study suggests that, among the five ARBs, losartan had the most beneficial effect on S_{UA} in hypertensive patients. It is known that losartan decreases the level of S_{UA} in clinical practice and in animals. In clinical practice, some studies have reported a lowering effect of losartan on S_{UA} level. It was reported that losartan significantly lowered S_{UA} compared to placebo in patients with type 2 diabetes and nephropathy [16]. In patients with hypertension, 12-week treatment with losartan decreased the mean level of S_{UA} compared with baseline [21]. In patients with mild to moderate hypertension, the mean level of S_{UA} was significantly decreased from baseline after 12 weeks of treatment with losartan [26]. A study using xenopus oocytes, an in vitro study, and administration in hypertensive patients have revealed that losartan decreases S_{UA} level via inhibition of URAT 1, which is the transporter of uric acid reabsorption in the proximal renal tubule [18-20]. Supporting these previous reports, our study indicated that long-term monotherapy with losartan has a beneficial effect on S_{UA} level in mildly to moderately hypertensive patients. Because hypertension and hyperuricemia often coexist, therapy with losartan is suitable for hypertensive patients. In a comparison of ARBs, it has been shown that the reduction of S_{UA} level by losartan is stronger than that by other ARBs. In patients with hypertension and serum uric acid ≥ 7 mg/dL, the mean level of S_{UA} was significantly decreased after 24 weeks of losartan treatment compared with candesartan treatment [22]. In one study, losartan but not irbesartan significantly lowered S_{UA} level compared to placebo in patients with type 2 diabetes and nephropathy [14]. The risk of onset of gout, which is strongly related to S_{UA} level, has been reported to be lower in losartan users than in other ARB or CCB users [26,27]. In this multiple comparison study, we showed that losartan had the most beneficial effect on S_{UA} level among five ARBs in hypertensive patients. Based on these clinical findings, losartan should be preferentially used in patients with hypertension, especially in those with comorbid disease of hyperuricemia or gout, over other ARBs. Some in vitro studies have investigated the different effects of ARBs on URAT1, which may explain the variable effects of ARBs on S_{UA} level. Candesartan, irbesartan and valsartan did not show a cis-inhibitory effect but showed a trans-stimulatory effect on URAT1, potentially leading to an increase of S_{UA} level [19]. Corresponding with these in vitro studies, several clinical studies have reported that some ARBs increased S_{UA} level. In patients with hypertension, 12-week treatment with valsartan increased the mean level of S_{UA} compared with baseline [22]. In patients with coronary artery disease, the mean S_{UA} level in valsartan users was increased compared with the baseline [28]. In patients with mild to moderate hypertension, the mean level of S_{UA} was significantly increased after 12 weeks of treatment with candesartan [26]. In this study, the mean S_{UA} level in candesartan, irbesartan and valsartan users was increased in comparison with baseline, and there was no significant difference in the mean change of S_{UA} level in the exposure period from baseline among these ARBs. On the other hand, in the study using xenopus oocytes, losartan and telmisartan exhibited a cisinhibitory effect on uric acid transport via URTA1, which means a reduction of

Table 1: Angiotensin II type I receptor blockers.

Generic name	Trade name	Number of cases of monotherapy
Losartan	Losartess	30
Valsartan	Diovan	32
Candesartan	Atacand	31
Telmisartan	Micardis	29
Irbisartan	Aprovel	28

Table 2: Baseline characteristics.

Characteristics	Number of patients				
	Losartan	Valsartan	Candesartan	Telmisartan	Irbesartan
Total No of Patients	30	32	31	29	28
Men	17	16	19	13	15
Medical History	4	3	8	3	2
Cerebrovascular disease	5	4	3	2	1
Ischemic heart disease	1	0	2	3	3
Other heart disease	6	5	4	2	3
Thyroid disease	4	1	0	2	3
Rheumatoid disease	5	9	9	8	9
Hyperlipidemia	4	1	0	2	3
Current medication	5	9	9	8	9
Immunosuppressive drugs	2	0	3	2	2
Lipid lowering drugs	6	9	9	9	11
Statins	5	8	9	6	8
Fibrate	1	3	8	6	7
Other drugs lipid lowering	0	5	3	4	7
Thyroid drugs	6	5	4	2	2
Antithrombotic drugs	19	17	20	23	19
Steroids	2	3	2	0	1
NSAIDs	11	15	17	19	20
Proton pump inhibitors	6	12	13	17	10
H2 receptor blockers	4	5	6	8	4

Table 3: Adjusted mean level of S_{UA} at baseline and during exposure period.

ARB	Baseline		Exposure		P value
	Mean	95% CL	Mean	95% CL	
Losartan	5.18	(5.03, 5.32)	5.04	(4.90, 5.19)	0.0194
Valsartan	5.30	(5.15, 5.45)	5.49	(5.34, 5.63)	0.0012
Candesartan	5.54	(5.43, 5.65)	5.68	(5.57, 5.79)	0.0011
Telmisartan	5.35	(5.18, 5.49)	5.47	(5.32, 5.63)	0.0253
Irbesartan	5.39	(5.22, 5.56)	5.58	(5.41, 5.75)	0.0013

reabsorption of uric acid [19]. To our knowledge, however, there is no clinical report that telmisartan may decrease S_{UA} level, whereas some clinical studies have shown a lowering effect of losartan on S_{UA} level. In patients with hypertension, high- dose treatment with telmisartan for three months significantly increased S_{UA} level [29]. In this study, we showed that long-term monotherapy with telmisartan increased S_{UA} level. The reason for this discrepancy between in vitro and clinical study outcomes is unclear. The contribution of other mechanisms, e.g., disturbance of urinary excretion, which may be predominant over the inhibitory effect on URTA1 in telmisartan users, cannot be excluded. Concerning ARBs other than losartan, our findings suggest that regular checks of S_{UA} level are recommended in patients treated with candesartan, irbesartan, valsartan or telmisartan. Our study has several limitations. First, the retrospective and non-randomized nature of the design entailed inherent issues of selection bias and confounding. Other potential confounding factors that could not be considered in this database study are alcohol intake, smoking, Body Mass Index (BMI) and Muscle Mass Index (MMI). Furthermore, the possibility that the findings of comparison of the baseline and exposure period in each treatment group may be confounded by other variables should be considered when interpreting the results. Therefore, the findings of our study, based on a nonrandomized design, call for further studies, such as similar analyses of larger databases, prospective population-based studies, and randomized clinical trials, for confirmation. Second, we did not fix the daily dosage of ARBs, because the achievement of BP goal requires various doses of an agent across different individuals or even in the same individual in clinical practice. This study was not designed to assess the effects of ARBs at each dosage, because it is difficult to determine whether or not pharmaco dynamics are dose-dependent in clinical settings. However, we consider that the findings of our study, in a real-world setting, are reliable and will be informative for clinicians.

Conclusion

The results of the present study suggested that losartan had the most beneficial effect on S_{UA} level among five ARBs; losartan, valsartan, candesartan, telmisartan, and irbesartan, at least up to one year. Our study provides evidence of the long-term effect of various ARBs on S_{UA} level in hypertensive patients.

Competing Interests

The authors declare that they have no competing interests.

References

1. Gustafsson D, Unwin R. The pathophysiology of hyperuricaemia and its possible relationship to cardiovascular disease, morbidity and mortality. BMC Nephrology. 2013; 14: 164-164.
2. Wen CP, Cheng TD, Chan HT, Tsai MK, Chung WI, Tsai SP, et al. Is high serum uric acid a risk marker or a target for treatment? Examination of its independent effect in a large cohort with low cardiovascular risk. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2010; 56: 273-288.
3. Oliveira EPD, Burini RC. High plasma uric acid concentration: causes and consequences. Diabetology & Metabolic Syndrome. 2012; 4: 12-12.
4. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA. 1991; 266: 3008.
5. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. The American journal of medicine. 2012; 125: 679-687.e1.
6. Li C, Hsieh M, Chang S. Metabolic syndrome, diabetes, and hyperuricemia. Current Opinion in Rheumatology. 2013; 25: 210-216.
7. Reyes AJ. Cardiovascular Drugs and Serum Uric Acid. Cardiovascular Drugs and Therapy. 2004; 17: 397-414.
8. Smith SM, Gong Y, Turner ST, Cooper-DeHoff RM, Beitelshees AL, Chapman AB, et al. Blood pressure responses and metabolic effects of hydrochlorothiazide and atenolol. American journal of hypertension. 2012; 25: 359-365.
9. Kim EJ, Song W, Lee JU, Shin M, Lee S, Kim B, et al. Efficacy of losartan and carvedilol on central hemodynamics in hypertensives: a prospective, randomized, open, blinded end point, multicenter study. Hypertension Research. 2014; 37: 50-56.
10. Puddu PE, Lanti M, Menotti A, Mancini M, Zanchetti A, Cirillo M, et al. Serum uric acid for short-term prediction of cardiovascular disease incidence in the Gubbio population Study. Acta Cardiologica. 2001; 56: 243-251.
11. Moriarity JT, Folsom AR, Iribarren C, Nieto FJ, Rosamond WD. Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) Study. Annals of epidemiology. 2000; 10: 136-143.
12. Lindholm LH, Ibsen H, Dahlöf B, Devereux RB, Beevers G, de Faire U, et al. LIFE Study Group: Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE). Lancet. 2002; 359: 1004–1010.
13. Chobanian A, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee: The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report. J Am Med Assoc. 2003; 289: 2560–2582.
14. Nakamura M, Anzai N, Jutabha P, Sato H, Sakurai H, Ichida K. Concentration-dependent inhibitory effect of irbesartan on renal uric acid transporters. Journal of pharmacological sciences. 2010; 114: 115-118.
15. E J Lewis, L G Hunsicker, W R Clarke, T Berl, M A Pohl, J B Lewis. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001; 345: 851–860.
16. Smink PA, Bakker SJL, Laverman GD, Berl T, Cooper ME, Zeeuw DD, et al. An initial reduction in serum uric acid during angiotensin receptor blocker treatment is associated with cardiovascular protection: a post-hoc analysis of the RENAAL and IDNT trials. Journal of Hypertension. 2012; 30: 1022-1028.
17. Miao Y, Ottenbros SA, Laverman GD, Brenner BM, Cooper ME, Parving H, et al. Effect of a Reduction in Uric Acid on Renal Outcomes During Losartan Treatment: A Post Hoc Analysis of the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan Trial. Hypertension. 2011; 58: 2-7.
18. Enomoto A, Kimura H, Chairoungdua A, Shigeta Y, Jutabha P, Cha SH, et al. Molecular identification of a renal urate–anion exchanger that regulates blood urate levels. Nature. 2002; 417: 447-452.
19. Iwanaga T, Sato M, Maeda T, Ogihara T, Tamai I. Concentration-Dependent Mode of Interaction of Angiotensin II Receptor Blockers with Uric Acid Transporter. Journal of Pharmacology and Experimental Therapeutics. 2007; 320: 211-217.
20. 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. American journal of hypertension. 2008; 21: 1157-1162.
21. Elliott WJ, Calhoun DA, DeLucca PT, Gazdick LP, Kerns DE, Zeldin RK. Losartan versus valsartan in the treatment of patients with mild to moderate essential hypertension: data from a multicenter, randomized, double-blind, 12-week trial. Clinical therapeutics. 2001; 23: 1166-1179.
22. Rayner BL, Trinder YA, Baines D, Isaacs S, Opie LH. Effect of losartan versus candesartan on uric acid, renal function, and fibrinogen in patients with hypertension and hyperuricemia associated with diuretics. American journal of hypertension. 2006; 19: 208-213.
23. Nishida Y, Takahashi Y, Nakayama T, Soma M, Asai S. Comparative effect of olmesartan and candesartan on lipid metabolism and renal function in patients with hypertension: a retrospective observational study. Cardiovascular Diabetology. 2011; 10: 74-74.
24. Takahashi Y, Nishida Y, Nakayama T, Asai S. Adverse effect profile of trichlormethiazide: a retrospective observational study. Cardiovascular Diabetology. 2011; 10: 45-45.
25. Nishida Y, Takahashi Y, Nakayama T, Asai S. Comparative effect of angiotensin II type I receptor blockers and calcium channel blockers on laboratory parameters in hypertensive patients with type 2 diabetes. Cardiovascular Diabetology. 2012; 11: 53-53.
26. Manolis AJ, Grossman E, Jelakovic B, Jacovides A, Bernhardi DC, Cabrera WJ, et al. Effects of losartan and candesartan monotherapy and losartan/hydrochlorothiazide combination therapy in patients with mild to moderate hypertension. Losartan Trial Investigators. Clinical therapeutics. 2000; 22: 1186-1203.
27. Choi HK, Soriano LC, Zhang Y, Rodríguez LAG. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. The BMJ. 2012; 344: d8190-d8190.
28. Sugihara M, Miura S, Takamiya Y, Kiya Y, Arimura T, Iwata A, et al. Safety and efficacy of antihypertensive therapy with add-on angiotensin II type 1 receptor blocker after successful coronary stent implantation. Hypertension Research. 2009; 32: 625-630.
29. Shiga Y, Miura S, Mitsutake R, Norimatsu K, Nagata I, Arimura T, et al. Efficacy and safety of a single-pill fixed-dose combination of high-dose telmisartan/hydrochlorothiazide in patients with uncontrolled hypertension. Journal of the Renin-Angiotensin-Aldosterone System. 2012; 13: 394-400.