REPORT

TO STUDY THE EFFICACY OF LOSARTAN ON URINARY URIC ACID EXCRETION IN THIAZIDE INDUCED HYPERURICEMIC AND HYPERTENSIVE PATIENTS

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ABSTRACT

The precise relationship of Hyperuricemia found in hypertensive patients is still obscure; this study is a urinary uric acid lowering intervention with Losartan in hypertensive patients induced by Thiazide diuretics. A number of pharmacological agents like loop diuretics, similarly low doses of aspirin (<3g daily) aggravate Hyperuricemia. The effect of Losartan on urinary uric acid excretion In Hypertensive patients with Thiazide induced Hyperuricemia were investigated in the Department of pharmacology and therapeutics, Basic Medical Sciences Institute Jinnah Postgraduate Medical Centre Karachi. It was randomized, open label, prospective, comparative study. Total 60 hypertensive Hyperuricemic patients were enrolled one by one in this study, selected from medical OPD and wards of Jinnah Postgraduate Medical Centre, Karachi. Patients were divided in three groups. Group-1 patients were treated with Thiazide 50 mg/day, Group-2 with Losartan + Thiazide 50 mg/day, and Group-3 with Losartan 50 mg/day. The effect on urinary uric acid level was measured, after every fortnightly.

Treatment with Thiazide + Losartan group and Losartan group showed significantly increase in urinary uric acid excretion. Whereas, Thiazide group decrease in urinary uric acid level. In contrast to Thiazide and Losartan alone Thiazide + Losartan led to a greater increased in urinary uric acid excretion. The average percentage increase in urinary uric acid excretion in Thiazide + Losartan group was -13.27% and the average percentage increased in urinary uric acid excretion was 6.7% in Losartan group. Thus it can be concluded from the present study that urinary uric acid excretion was more increased in combination therapies. Ultimately Losartan decrease serum uric acid level and uricosuric effect of Losartan might be particularly useful in Hyperuricemic patients those on Thiazide diuretic (for hypertension and heart failure).

Keywords: Hypertension, Hyperuricemia, thiazide diuretic, Losartan potassium, urinary uric acid level.

INTRODUCTION

A number of pharmacological agents, decrease serum uric acid levels, including Allopurinol, probenecid, benzbromarone, benziodarone, sulfinpyrazone, salicylate, fibric acid, and Losartan (Puig *et al*., 1999; Sorense *et al*., 1976).

The Angiotensin-II antagonist Losartan also produces a uricosuric effect in healthy volunteers, hypertensive patients, and CV transplant patients, typically decreasing serum uric acid levels by 20% to 25% (Johnson *et al.*, 2003; Libero Poulos *et al*., 2002). The parent molecule Losartan, not its active E-3174 metabolite, is the active agent blocking uric acid reabsorption. The uricosuric action of Losartan is not shared by other antihypertensive agents (Libero Poulos *et al* 2002; Campion *et al.*, 1987). ACE inhibitors and Calcium channel blockers increase uric acid excretion but the effect is modest and does not decrease serum uric acid levels (Johnson *et al*., 2003). Diuretics have a propensity to increase serum uric acid levels and may even, rarely, provoke attacks of gout (Chobanian *et al*., 2003). This has led some authorities to recommend that they should be avoided in patients with gout (Nikas *et al*., 2000). Losartan can offset the elevations in serum uric acid levels occurring with hydrochlorothiazide or indapamide (Soffer *et al*., 1995; Roch-Ramed *et al*., 1997). Increased uric acid secretion produced by Losartan appears to result from a reduction in the postsecretory reabsorption of uric acid in the proximal tubule of the kidney (Roch-Ramed *et al*., 1994). Studies using human proximal brush border membrane vesicles indicate that tubular secretion and reabsorption of urate are mediated via a urate/anion exchanger and a urate voltage-sensitive transporter (Shahinfar *et al*., 1999). Losartan appears to inhibit the urate/lactate exchanger and urate/chloride exchanger in the proximal convoluted tubule with an affinity greater than that seen with probenecid (Johnson *et al*., 2003).

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To date, the attenuating effect of Losartan on serum and urinary uric acid levels has not been associated with untoward adverse effects, including flank pain or renal stone formation. Because Losartan tends to increase urine pH, which increases the solubility of uric acid, the risk of supersaturation seems to be avoided. This is evidenced by study of the effect of Losartan on the risk of acute urate nephropathy in 63 hypertensive patients with Thiazide-induced asymptomatic Hyperuricemia (Doehner *et al*., 2002). Adverse events typically associated with acute urate nephropathy flank pain, hematuria, or increased blood urea (Doehner *et al*., 2002).

MATERIALS AND METHODS

This Randomized, open label, prospective, comparative study was conducted in the department of Pharmacology and Therapeutics; Basic Medical Sciences institute (BMSI), Jinnah Postgraduate Medical Centre, Karachi in collaboration with other ward/OPD.

60 hypertensive Hyperuricemic patients were enrolled in this study, selected from medical OPD & wards of Jinnah Postgraduate Medical Centre Karachi. 57 patients remained associated through out the study period .whereas 3 patients were dropped due to failure of the follow-up period among those 2 in Thiazide group and 1 in Losartan + Thiazide group.

AT1 receptor blocker Losartan 50 mg
Thiazide diuretic 50 mg (Hydrochlorothiazide)
Kit for uric acid (linear chemicals)
Disposable syringes

Patients were advised to bring 24 hours urine also to be collected in container in such a way that first portion of morning sample to be discarded and time noted and so on to complete24 hours urine collection but last sample was included this is used for the estimation of 24 hours urinary uric acid. Laboratory test were performed at screening and then fortnightly follow up visits. The uric acid was estimated by enzymatic colorimetric method.

Inclusion criteria
Thiazide induced Hyperuricemic hypertensive patients (serum uric acid level between 7.0 to 12.0 mg /dl of either sex, their ages ranging from 45 to 65 years.

Exclusion criteria
Secondary hypertension, history of gout and renal lithiasis with in the; last two years, history of malignant hypertension, history of cerebrovascular accidents with in last two years cardiac arrhythmia, clinically significant renal and hepatic impairment, pregnant and lactating women, history of neurological and mental disorder, patients using any drug that could affect serum uric acid level and urinary uric acid level.

Study design
The selected patients were divided into three groups.

Group 1-Twenty hypertensive Hyperuricemic patients with above mention inclusion criteria were given tab Thiazide 50 mg/ day for 12 weeks.

Group 2-Twenty hypertensive Hyperuricemic patients with the same criteria were given Tab. Losartan 50 mg + Thiazide 50 mg once daily for 12 weeks.

Group 3-Twenty hypertensive Hyperuricemic patients with same criteria were given Tab Losartan 50 mg/ day for 12 weeks.

STATISTICAL ANALYSIS

All the values are taken as Mean± SEM. The primary efficacy measurement was the mean change in urinary uric acid excretion throughout the study period from the baseline to end point. To compare mean and standard deviation 0f quantitative variable between three groups, Student t test was used.

RESULTS

Urinary uric acid
Out of 20 patients treated by Thiazide on day 0, 18 patients were treated till day 90. The mean urinary uric acid excretion was decreased from 443.50 ± 10.47 mg/dl at day 0 to 419.17 ± 11.28mg/dl at day 45 to 402.22 ± 10.25 mg/dl at day 90. The reduction was statistically highly significant with a p value of (<0.001) when compared between day 0 to day 45, between day 45 to day 90 and between day 0 to day 90. The average percentage decrease in urinary uric acid excretion was -9.30% from day 0 to day 90 as depicted in table 1, figs. 1 and 3.

Out of 20 patients on day 0 in Thiazide + Losartan group 19 patients were treated till day 90. The urinary uric acid excretion level was increased from 499.50 ± 18.15 mg/ dl at day 0 to 546.25 ± 18.25mg/dl on day 45 and to 565.79 ± 19.24mg/dl on day 90. The increase was statistically highly significant ($p<0.001$) when compared between day 0 to day 45 between day 45 to day 90 and between day 0 to day 90. The average percentage increase in urinary uric acid excretion was 13.27% from day 0 to day as depicted in table 1, figs. 1 and 3.

Out of patients on day 0 of Losartan group 19 patients were till day 90. The mean urinary uric acid excretion was increased from 472.75 ± 8.60mg/dl at day 0 to 495.75 ± 9.67mg/dl on day 45 and to 504.50 ± 8.47mg/dl at day 90. However the increase when evaluated statistically was highly significant when compared day 0 to day 45 to day ay 0 to day 90. The average percentage increase in urinary

Table 1: Changes in mean urinary uric acid level from day 0-day 45, day 90 and day 0-day 90 of treatment with thiazide, Losartan + thiazide and Losartan in Hyperuricemic and hypertensive patients.

Group		At day 0	At day 45	At day 90	P value			Percentage
					D0-D45	D45-D90	D0-D90	D0-D90
Thiazide	n	20	18	18				
	Mean	443.50	419.17	402.22				
	± SEM	10.47	11.28	10.25	0.001	0.001	0.001	-9.30%
Losartan+ Thiazide	n	20	20	19				
	Mean	499.50	546.25	565.79	0.001	0.001	0.001	13.27%
	±SEM	18.15	18.25	19.24				
Losartan	n	20	20	20				
	Mean	472.75	495.75	504.50	0.001	0.001	0.001	6.70%
	±SEM	8.60	9.67	8.47				

Key: All observations were measured in mg/dl figure in parentheses indicate number of patients. D = Day, n= Number of patients, Figure in (mean ± SEM), (-) Indicate decrease per percentage.

uric acid excretion was 6.70% from day 0 to day 90 as depicted in table 1, figs. 1 and 3.

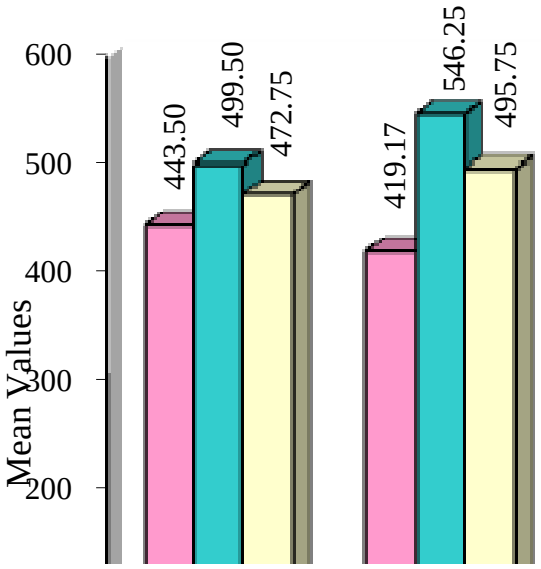

Fig. 1: Changes in mean urinary uric acid level from day 0, day 45 and day 90 of treatment with thiazide, Losartan thiazide and Losartan in Hyperuricemic and hypertensive patients

DISCUSSION

In current study, we conducted a comparative clinical trial to evaluate the uricosuric effect of Losartan in hypertensive patients with Thiazide induced Hyperuricemia in Pakistani population, the primary objective of this study was to study the uricosuric effect of Losartan with elevated levels of serum uric acid in Thiazide treated patients Losartan was first reported to decrease serum uric acid in a dose dependent manner with uricosuric properties and this study extends those finding in the Pakistani population. In one study Losartan was shown to decrease the Hyperuricemia in hypertensive experience Losartan attenuated the increase in serum uric acid by comparison to the Atenolol treated group over the entire duration of study of 4. 8 years (P<0.001) in life, baseline serum uric acid was significantly associated with increased cardiovascular risk (Johnson, 2003). 29% of the reduction in the composite outcome measure cardiovascular death was shown in the secondary analysis life study (Hoieggen, 2004). This study demonstrates significant change in urinary uric acid level. Basically this study was designed to assess the uricosuric effect of Losartan in hypertensive patients already taken Thiazide for hypertension and that Thiazide caused Hyperuricemia. The increase in urinary uric acid level with Losartan + Thiazide was significantly higher as compared to Thiazide and Losartan. When Thiazide compared with Thiazide + Losartan statistically, a highly significant difference observed with p<0.001 at day 90 of the study. In contrast when Thiazide compared with Losartan statistically a highly significant difference observed with p<0.001 at day 90 of study. When Thiazide + Losartan compared to Losartan a significant difference (p<0.005) was seen proving the more effect of Losartan +Thiazide. In contrast to Thiazide, Thiazide + Losartan and Losartan led to a greater increase in urinary uric acid level as depicted in table 1, figs. 1, 2. Our study is supported by the study of (Bardin, 2003) showing that Losartan increase urinary uric acid excretion up to 30% and was observed 15% reduction in mean serum uric acid level by Losartan. Our observation of Losartan+ Thiazide group and Losartan regarding urinary uric acid also supported by (Puig *et al*., 1999) observe that Losartan increase urinary uric acid level (25%) (Moore, 2002) concluded that Losartan is unique among the angiotensin II antagonist with a uricosuric effect. The serum uric acid lowering effect of Losartan prevents Thiazide induced Hyperuricemia when it is given in the combination with a Thiazide diuretic.

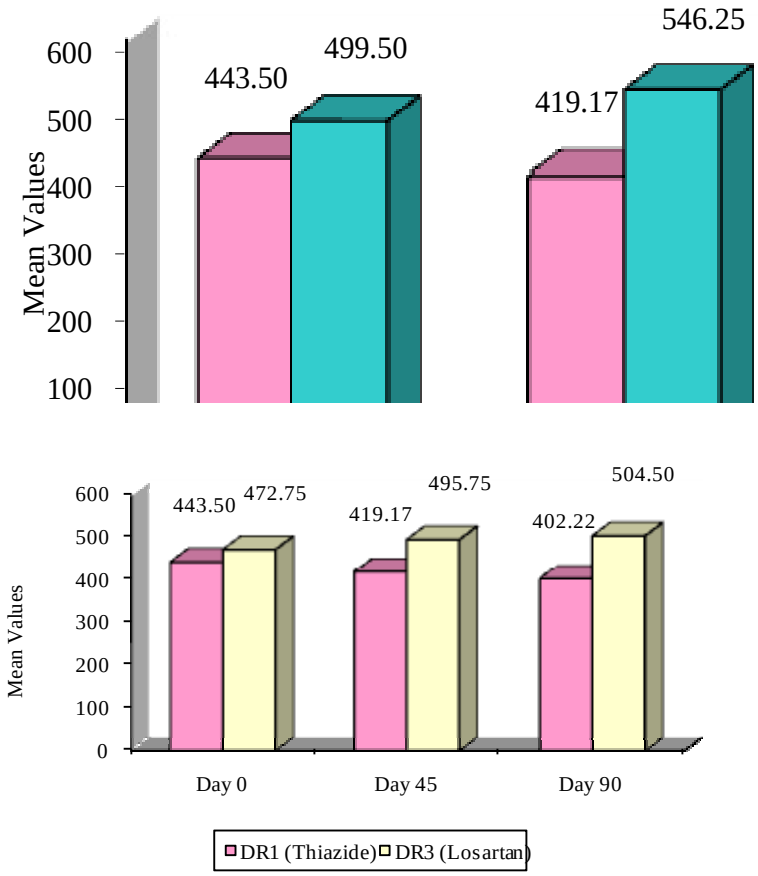

Fig. 2: Comparison between thiazide and Losartan +Thiazide, thiazide and Losartan and thiazide + Losartan and Losartan in mean urinary uric acid level from day 0, day 45 and day 90 in Hyperuricemic and hypertensive patients.

.CONCLUSION

There are many classes of potentially antihypertensive drugs based on the efficacy and tolerability, a number of considerations enter in to the selection of drugs for hypertensive patients who are also Hyperuricemic. Hence it can be concluded from the present study that the combination therapy Losartan the first member of Angiotensin II type I receptor blocker and Thiazide might be particularly useful in Hyperuricemic patients on Thiazide diuretics to control blood pressure. And we can prescribe Thiazide in combination with Losartan in patients having Hyperuricemia, hypertension and gout.

REFERENCES

Bardin T. Fenofibrate and Losartan (2003). *Ann. Rheum. Dis.*, **62**: 487-498.

Burnier M, Rutschmann B, Nussberger J, Versaggi J, Shahinfar S, Waeber B et al (all names of authors instead of et al.) (1993). Salt-dependent renal effects of an angiotensin II antagonist in healthy subjects. *Hypertension*, **22**: 339-347.

Campion EW, Glynn RJ and DeLabry LO (1987). Asymptomatic hyperuricemia: Risks and consequences in the Normative aging study. *Am.J. Med.*, **82**:421-426.

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr et al (all names of authors instead of et al.) (2003). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. *JAMA*, **289**: 2560-2572.

Doehner W, Schoene N, Rauchhaus M, Leyva-Leon F, Pavitt DV, Reaveley DA *et al* (all names of authors instead of et al.) (2002). Effects of xanthine oxidase inhibition with allopurinol on Endothelial function and peripheral blood flow in Hyperuricemic patients with Chronic heart failure: Results from 2 placebo-controlled studies. *Circulation*, **105**: 2619-2624.

Hoieggen (2004). The impact of serum uric acid on cardiovascular outcome. *Kidney International*, **65**: 1041-1049.

Johnson RJ, Kang DH, Feig D, Kirlighn S, Kanellis J, *et al* (all names of authors instead of et al.) (2003). Is there a Pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension*, **41**(6): 1183-1190.

Liberopoulos E, Christides D and Elisaf M (2002). Comparative effects of Losartan and irbesartan on serum uric acid in hypertensive patients with Hyperuricemia and gout. *J. Hypertens*, **20**: 347.

Moore MA (2002). Improving the managed care of hypertension with angiotensin II antagonists. *Am. J. Med. Sci.*, **323**(1): 25-33.

Nikas S, Rizos E, Milionis H, Bairaktari E, Kalaitzidis R, Siamopoulos K *et al* (all names of authors instead of et al.) (2000). The effects of the addition of Losartan on uric acid metabolism in patients receiving indapamide. *J. Renin Angiotensin Aldosterone Syst*., **1**: 289-291.

Puig JG, Mateos F, Buno A, Ortage R, Rodriguez F and Dal-Re R (1999). Effect of eprosartam and losartan on uric acid metabolism in patients with essential Hypertension. *J. Hypertens*, **17**(7): 1033-1039.

Roch-Ramel F, Guisan B and Diezi J (1997). Effects of uricosuric and antiuricosuric agents on urate transport in human brush-border membrane vesicles. *J. Pharmacol. Exp. Ther*, **280**: 839-845.

Roch-Ramel F, Werner D and Guisan B (1994). Urate transport in brush-border membrane of human kidney. *Am. J. Physiol.*, **266**: F797-F805.

Shahinfar S, Simpson RL, Carbides AD, Thiyagarajan B, Nakagawa Y, Umans JG *et al* (all names of authors instead of et al.) (1999). Safety of Losartan in hypertensive patients with Thiazide-induced hyperuricemia. *Kidney Into.*, **56**: 1879-85.

Sica DA and Schoolwerth AC (2002). Uric acid and losartan. *Curr. Opin. Nephrol. Hypertens*, **11**: 475-482.

Sorensen LB and Levinson DJ (1976). Clinical evaluation of benzbromarone: A new uricosuric drug. *Arthritis Rheum*., **19**: 183-190.

Sironi AM, Vichi S, Gastaldelli A, Pecori N, Anichini R, Foot E *et al* (all names of authors instead of et al.) (1997). Effects of troglitazone on insulin action and cardiovascular risk factors in patients with on-insulin-dependent diabetes. *Clin. Pharmacol. Ther.*, **62**: 194-202.

Soffer BA, Wright JT, Jr, Pratt JH, Wiens B, Goldberg AI and Sweet CS (1995). Effects of Losartan on a background of hydrochlorothiazide in patients with hypertension. *Hypertension*, **26**: 112-117.

Watanabe S, Kanellis J, Nakagawa T, Han L, Ohashi R, Lan H *et al* (all names of authors instead of et al.) (2002). Reducing uric acid as a means to prevent cardiovascular and renal disease. *Expert Opin. Ther. Patents*, **12**: 193-199.