Original Article

The Role of Allopurinol and Angiotensin Receptor Blockers in Serum Uric Acid Reduction in Gouty and Hypertensive Patients

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ABSTRACT

0bjective: To evaluate the effect of Allopurinol in combination with angiotensin receptor blockers on hyperuricemia in gouty and hypertensive patients.

Study design: Randomized, open label, prospective, comparative trial.

Place and Duration of Study: This study was conducted in the Department of Pharmacology. &Therapeutics; BMSI/JPMC, Karachi from April 2010 to November 2010.

Materials and Methods: 80 hypertensive and hyperuricemic patients were enrolled from OPD and medical wards and were divided into two groups. group DR-1(40 Patients) were given allopurinol 300mg plus candisartan 8mg daily and group DR-2 (40 patients) were given allopurinol 200mg Plus Losartan 50mg, daily four 4 months. 6 patients were unable to continue the follow-up 3 patients in each group.

Results: DR-1combination therapy decreased serum uric acid level from 8.92 ± 0.19mg/dl at day 0 to 5.33 ± 0.11mg/dl at day120. DR-2 group also showed a significant reduction in serum uric acid level from 9.14. ± 0.19mg/dl at day 0 to 4.74 ± 0.09mg/dl at day 120 ($p < 0.001$). when effects were compared in both treatment groups, the effect of group 2 regimens on serum uric acid level was more marked due to Losartan combination which also have uricosuric effects than in group 1 regimen, with average percentage decrease in serum uric acid -40.35% in group DR-1 and -48.24% in group DR-2.

Conclusion: The allopurinol 200mg and Losartan 50mg is more effective than allopurinol 300mg+ candesartan 8mg, to decrease serum uric acid level and group DR-2 drugs combination useful in those hyperuricemic patients who cannot tolerate high doses of uric acid lowering drugs.

Key Words: Hyperuricemia, allopurinol, Losartan Potassium, Serum uric Acid.

INTRODUCTION

Hyperuricemia is a metabolic disease that has become quite common over the past several decades. Hyperuricemia causes gouty tophi, gouty arthritis, nephropathy caused by uric acid and uric acid kidney stones .[7] Hyperuricemia with or without gout is associated with cardiovascular disease including stroke, peripheral vascular disease and coronary diseases .[1]

Hyperuricemia is commonly found in 25% untreated hypertensive patients, 50% patients on diuretic therapy and in >75% malignant hypertensive patients .[2] Various mechanisms suggested the importance of increase serum uric acid levels in cardiovascular diseases as a direct causative agent. Hyperuricemia cause endothelial dysfunction and impaired oxidative metabolism. It also causes platelet adhesiveness and aggregation .[3]

Increased serum uric acid is a causative agent to predict stroke and excess mortality in patients of non insulin-dependent diabetes mellitus.[5] In elderly population there is independent association between hyperuricemia and increased incidence of fatal stroke. Hyperuricemia in diabetic patients, along with obesity, insulin resistance and blood pressure plays a crucial role in the metabolic syndrome which in turn causes endothelial dysfunction.[6]

Allopurionl is the main drug which inhibit xanthine oxidase the enzyme convert xanthine into uric acid.[9] In human proximal brush border membrane tubular secretion and reabsorption of urate are mediated by urate/anion exchanger and urate voltage-sensitive transporter.[10] Losartan inhibits the urate/ anion exchanger and urate/chloride exchanger in the renal proximal brush border membrane .[12] Losartan potassium prevent renal stone formation by increase urinary PH , which intern prevent supersaturation and increase the solubility of uric acid.[11]

MATERIALS AND METHODS

This study was conducted at the Department of Pharmacology and Therapeutics, Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate Medical Centre (JPMC) Karachi from April 2010 to November 2010**;** eighty gouty and hypertensive patients with hyperuricemia were enrolled in the study, selected from Orthopedic and Medical OPDs of Jinnah Postgraduate Medical Centre (JPMC) Karachi and divided into two groups. The 74 patients remained associated through out the study period, Whereas 6 patients were dropped due to failure of the follow-up period among those 3 patients in Allopurinol 300mg + Candesartan 8mg group(DR-1) and 3 patients in

Allopurinol 200mg + Losartan 50mg group (DR-2). Gouty patients of either sex ages from 35 to 65 years having hyperuricemia and hypertension with serum uric acid level between 7.0 mg/dl to 12.0 mg/dl where included in the study. Lactating and pregnant women, subjects with cerebrovascular accidents or transients ischemic attacks within past three years, Secondary hypertension, Cardiac arrhythmia, Renal urolithiasis, Angina pectoris, hepatic and renal impairment and drugs which can affect serum uric acid level and urinary uric were excluded. . Combination therapies were given for 120 days daily and routine diet was advised. To estimate serum uric acid blood sample (3 ml) of each patient were drawn on day-0 and at every month follow up visits. Uric acid was estimated by the enzymatic colorimetric method.

Statistical software SPSS version 13 was used for data feeding and analysis, t. test was used to compare mean and standard deviation of quantitative variable between the two groups. The statistical significance of difference between the mean values of the two groups was evaluated by student t test.

Comparison of the effect of the two treatments groups was evaluated by paired t test. $P < 0.05$ and $P < 0.001$ were considered as statistically as significant and highly significant. At the end of study the percentage variation in serum uric acid level 0 to day 120 was calculated in both treatment groups separately by the following formula

$$\frac{\text{Day 0} - \text{Day 120}}{\text{Day 0}} \times 100$$

RESULTS

The enrolled patients were 67% male and 33% female. The Mean age of male patients were 52 years and the mean age of female patients were 49 years.

Patients given allopurinol 300 mg and candesartan 8 mg for 120 days revealed overall decrease in mean serum uric acid levels. The decrease in serum uric acid level was highly significant on day 30 i.e. 6.87± 0.12 mg/dl, as compared to 8.92 ± 0.19 mg/dl on day 0.

Mean serum uric acid levels further decrease to 6.18 ± 0.09 and 5.75 ± 0.11 mg/dl on day 60 and day 90 respectively, which were also highly significant. The serum uric acid levels were decreased to 5.33 ± 0.11 mg/dl on day 120. When compared from day 0 to day 120 the total reduction in serum uric acid level was 3.56 ± 0.13mg/dl which was highly significant, with overall reduction of 40.24%.

Patients given allopurinol 200 mg and losartan 50 mg for 120 days revealed overall decrease in mean serum uric acid levels. The decrease in serum uric acid level was highly significant on day 30 i.e. 6.54 ± 0.10 mg/dl, as compared to 9.14 ± 0.19 mg/dl on day 0.

Mean serum uric acid levels further decreased to 5.82 ± 0.09 and 5.27± 0.09mg/dl on day 60 and day 90 respectively, which were also highly significant. The serum uric acid levels were decreased to 4.74 ± 0.09 mg/dl on day 120. When compared from day 0 to day 120 the total reduction in serum uric acid level was 4.41 ± 0.14mg/dl which was highly significant, with overall reduction of 48.14 %.

Table No.1: Changes in Mean Serum Uric Acid level following Treatment with Drugs in Group Dr -1 and Dr- 2

Groups	Serum uric acid concentration mg/dl from days 0 to 120					% Decrease
	0	30	60	90	120	
DR-1	8.92± 0.19	6.87±0.12**	6.18±0.09**	5.75±0.11**	5.33±0.11**	40.32
DR-2	9.14± 0.19	6.54± 0.10**	5.82± 0.09**	5.27± 0.09**	4.74± 0.09**	48.14

DR-1 = Allopurinol 300 mg + Candesartan 8 mg

DR-2 = Allopurinol 200 mg + Losartan 50 mg

**P < 0.001 highly significant as compared to day 0

Figures are in (Mean ± SEM), n=40 (day 0), n=37 (day 30 to 120)

DISCUSSION

This study demonstrates significant change in serum uric acid as a result of administration of allopurinol 300mg in combination of candesartan 8mg (DR-1), and Allopurinol 200mg in combination with Losartan 50mg (DR-2) daily for four months. In our study drugs of both groups were well tolerated and effectively reduce serum uric acid but DR-2 drugs was more effective. Warzner and his colleague have evaluated the effect of Losartan on serum uric acid in hypertensive patients with hyperuricemia and gout, it was shown that Losartan significant decrease in serum uric acid level (p <0.01) in patients with hypertension, elevated levels of serum uric acid and gout. They found that increasing the dose of Losartan from 50mg once daily to twice a day did not further reduce serum uric acid level .[14] Where as in our study the combination therapies were given which were more effective to decrease serum uric acid level. Allopurinol after 24 month treatment in hyperuricemic patients was significantly decreased serum uric acid level (P= 0.001)[8].Where as in our study we add in DR-1 candesartan and losartan in DR-2 to allopurinol. The reduction in serum uric acid levels by

both combination therapies were more pronunced as compare to marium study may be due to allopurinol block uric acid synthesis and losartan increase its renal excretion. The administered dose of allopurinol was more 300mg/day in DR-1 as compare to 200mg/day in DR-2 but due to addition of losartan 50mg/day in DR-2 the serum uric acid reduction efficacy were equal in both groups. Losartan and benzbromazone 11% decrease in serum uric acid level in combination therapy.[4]

Losartan decreases serum uric acid level by 20-25% if used alone.[12],[14] In our study Allopurinol 300mg + Candisartan 8mg combination therapy decreases serum uric acid level by 40.35% and Allopurinol 200mg + Losartan 50mg combination therapy decreased serum uric acid by 48.24%. The use of low dose combination therapy is associated with a fewer side effects than higher doses of single agent required to achieve same levels. However patients on combination therapies showed more pronounced reduction in serum uric acid level and the tolerance generally good with no side effects.[13]

CONCLUSION

In present study allopurinol 200 mg + Losartan 50 mg was found to be more effective than allopurinol 300 mg + Candesartan 8 mg in reducing serum uric acid level.

REFERENCES

1. Baker JF, Krishnan E, Chen L,Schumaker HR. Serum uric acid and cardiovascular disease: recent developments, and where do they leave us? Am J Med 2005; 118:816-26.
2. Cannon PJ, Stson WB, Demartini FE, Sommers SC, Laragh JH. Hyperuricemia in primary and renal hypertension. N Eng J Med 2002;275: 457-464.
3. Hoieggen A, Alderman MH, Kjeldsen SE, Julius S, Devereux RB, Faire U et al. The impact of serum uric acid on cardiovascular outcomes in the life study. Kidney Intern 2004; 65: 1041 – 1049.
4. Takahashi S, Moriwaki Y, Yamamoto T, Tsutsumi Z, Ka T, Fukuchi M. Effects of combination treatment using anti-hyperuricaemic agents with fenofibrate and/or losartan on uric acid metabolism. Ann Rheum Dis. 2003;62(6):572-5.
5. Letho S,Niskanen L,Ronnemaa T, Laakso M. Serum uric acid is a strong predictor of stroke in patients with non insulin-dependent diabetes mellitus. Ann epidemiol 1996;6:331-340.
6. Mazza A,Pessina AC,Pavei A,Scarpa R, tikhonoff V Casiglia E. Predictors of stroke mortality in elderly people from the general population. The cardiovascular study in the elderly. Eur J Epidemiol.2001;17:1097-1104.
7. Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Schumacher HR, Saag KG. Gout epidemiology: results from the UK general practice Research Database, 1990-1999. Ann Rheum Dis 2005; 64:267-272.
8. Goicoechea M, Vinuesa GS, Verdalles U, Ruiz-Caro C, Ampuero J, Abraham Rinco´n, David Arroyo et al. Effect of Allopurinol in Chronic Kidney Disease Progression and Cardiovascular Risk. Clin J Am Soc Nephrol.2010; 5:1-5.
9. Becker T, jolly M. Hyperuricemia and associated diseases. Rheum Dis Clin North Am 2006; 32: 275-93.
10. Roch-Ramel F, Guisan B, Diezi J. effects of uricosuric and antiuricosuric agents on urate transport in human brush- membrane vesicles. J Pharmacol Exp Ther 1997;280:839-45.
11. Shahinfer S, Simpson RL, Cardies AD. Thiyagarajan B, Nakagawa Y, Umans JG, et al. Safety of losartan in with thiazide induced-hyperuricemia. Kidney Int 1999; 56:1879-85.
12. Burnier M, Roch-Ramel F, Brunner HR, Renal effects of angiotensin II receptor blockade in normotensive subjects. 1996; 49: 1787-90.
13. Z Gesamate Inn Med 1990 Dec 1; 45(23):719-20
14. Warzner G, Gerster JC, Chiolero A, Maillard M, Fallab-Stubi CL, Brunner HR, et al. Comparative effects of Losartan irbesrtan on serum uric acid in hypertensive patients with Hyperuricemia and gout. J Hypertens 2001;19: 1855-60.

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