ORIGINAL ARTICLE

Efficacy and Safety of Fenofibrate in Patients with Hyperuricemia

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ABSTRACT

Background: Allopurinol is the most frequently used antihyperuricemic drug. Fenofibrate, a derivative of fibric acid, is commonly used in the treatment of hyperlipidemia. Fenofibrate treatment has been shown to decrease serum uric acid levels. This study was conducted to assess the efficacy and safety of fenofibrate in patients with hyperuricemia.
Material and Method: Sixty hyperuricemic patients with serum uric acid level 7.0mg per deciliter or above were enrolled and assigned to take either allopurinol 300mg or fenofibrate 200mg daily for 12 weeks. Drug efficacy was assessed by measuring percentage of subjects achieving serum uric acid level less than 6mg per deciliter at day 90. Drug efficacy was also assessed by measuring percent change in serum uric acid level from day 0 to day 90. Safety of the drug was assessed by reviewing adverse effects (AEs) and laboratory values.
Results: Comparison of percentage of subjects reaching serum uric acid level less than 6.0mg per deciliter at day 90 between the two groups was significant (P=0.14). However, percent change in serum uric acid level from day 0 to day 90 was highly significant between the two groups (P=0.001). Proportions of subjects experiencing any adverse event were higher in fenofibrate group, though the adverse effects leading to treatment withdrawal were higher in allopurinol group.
Conclusion: Fenofibrate 200mg once daily is an effective antihyperuricemic agent.

Key words: Fenofibrate, uric acid, hyperuricemia.

INTRODUCTION

Uric acid is the end product of purine nucleotide degradation. The normal serum uric acid level in men is 5.0 ± 2.0 while in women is 4.0 ± 2.0 mg/dl.[1] In plasma it is found in ionized form as urate.[2] Concentration of plasma uric acid at which it saturates is about 6.8 mg per deciliter.[3]

Hyperuricemia is a biochemical abnormality characterized by serum uric acid level greater than 6.8mg per deciliter.[4] The incidence of hyperuricemia ranges from two to seven percent.[5] In majority of the cases (90 %), hyperuricemia occurs due to decreased excretion of uric acid by kidneys, whereas in remaining cases (10%), there is increased production of uric acid.[6] As the concentration of uric acid increases, its solubility in plasma decreases and urate crystals form.[2] Urate crystals once formed may result in the development of gout or nephrolithiasis. Hypertension, hyperlipidemia, diabetes mellitus, cardiovascular diseases and nephropathy may also be associated with elevated plasma uric acid level.[7-9]

Since the solubility of uric acid in plasma is low (6.8 mg/dl), treatment of hyperuricemia includes lowering of plasma uric acid level to less than 6 mg/dl.[10] The drugs used in the treatment of hyperuricemia include uricostatic agents allopurinol and a newly introduced drug febuxostat, which inhibit production of the uric acid and uricosuric agent probenecid which increase the excretion of uric acid.[11] The most commonly used drug in the treatment of hyperuricemia is allopurinol. However, inefficient lowering of serum uric acid in about half of the patients taking allopurinol and development of adverse effects limit its use.[8,12] Adverse effects e.g. pruritus and dermatitis are as common as 2%.[1] Allopurinol hypersensitivity syndrome is not as common but mortality rate in this condition is up to 20%.[13]

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Fenofibrate, a derivative of fibric acid, is commonly used in the treatment of hyperlipidemia.[14] It has been shown that use of fenofibrate decreases serum uric acid levels by increasing its renal excretion.[15-16] This study was conducted to assess efficacy and safety of fenofibrate in patients with hyperuricemia.

MATERIAL AND METHOD

This is an open label interventional study approved by institutional ethical committee. A written informed consent was taken from all patients. Patients were recruited from the outpatient department of nephrology and outpatient department of rheumatology, Jinnah Postgraduate Medical Center Karachi. Inclusion criteria were male and female patients of ages 40 to 70 years and serum uric acid level 7.0mg per deciliter or above. Exclusion criteria were pregnant and lactating women, chronic kidney disease, active liver disease, myopathy, cholilithiasis, urolithiasis and hypersensitivity to any drug of study and use of other drugs that may alter serum uric acid level. Sixty patients were selected to enter the study and were divided into two equal groups. Allopurinol group assigned to receive Tab. Zyloric (allopurinol) 300mg once daily for twelve weeks and Fenofibrate group assigned to receive Cap. Fenoget (fenofibrate) 200mg once daily for twelve weeks. All patients were followed up as outpatients. Clinical and biochemical assessments (serum uric acid, serum alanine aminotransferase and serum creatine kinase) were measured at day 0, day 30, day 60 and day 90. Samples were tested on automated analyzer at the Main Laboratory, JPMC, Karachi. Drug efficacy was assessed by measuring percentage of subjects achieving serum uric acid level less than 6mg per deciliter at day 90. Drug efficacy was also assessed by measuring percent change in serum uric acid level from day 0 to day 90. Safety of the drug was assessed by reviewing adverse effects (AEs) and laboratory values. These include headache, dizziness, nausea, vomiting, diarrhea, muscle cramps, rashes, acute gout, increase in alanine aminotransferase (ALT) more than 3 times upper normal limit (UNL), increase in creatine kinase more than 5 times upper normal limit (UNL).

RESULTS

A total of 60 subjects with hyperuricemia were randomized to enter the study. Two patients in allopurinol group and one patient in Fenofibrate group discontinued treatment due to adverse effects. The baseline values of all patients are shown in Table 1. The two groups were similar at baseline for age, sex, serum uric acid concentration, body mass index. Similar proportion of patients in each treatment groups presented hyperlipidemia, hypertension and tobacco use. 46.4% of patients in allopurinol group while 41.3% of patients in combination group achieved serum uric acid level less than 6mg per deciliter at day 90. Comparison of percentage of subjects achieving serum uric acid level less than 6.0 mg/dl at day 90 between the two groups was insignificant (P=0.14) (Table 2, Figure 1). In allopurinol group the mean percent decrease in serum uric acid level from day 0 to day 90 was 32.2% while in fenofibrate group the mean percent decrease was 28.4%. Mean percent decrease of serum uric acid level from day 0 to day 90 between the two groups was highly significant between two groups (P=0.001) (Table 2, Figure 2). Proportion of subjects experiencing any adverse event was higher in fenofibrate group (43.3%) than in allopurinol group (26.6%) (Table 3). However proportion of patients who stopped taking medicine because of adverse effects was higher in allopurinol group (6%) than in fenofibrate group (3%). The main reason for withdrawal in allopurinol group was development of rashes and in fenofibrate group was increase in serum alanine-aminotransferase (ALT) more than three times upper normal limit.

Table 1: Baseline Characteristics of Subjects

Variable	Allopurinol 300mg/day n = 30	Fenofibrate 200mg/day n = 30	All subjects n = 60	"P" value
Age in year mean (SD)	53.9 (6.73)	54.0 (5.39)	53.95 (6.04)	0.95
Male sex - No (%)	26 (86.7)	25 (83.3)	51 (85.0)	0.50
Baseline serum urate concentration in mg/dl mean (SD)	8.68 (1.13)	8.54 (0.99)	8.61 (1.05)	0.59
Body mass index mean (SD)	27.62 (2.36)	27.59 (2.17)	27.6 (2.25)	0.96
Hyperlipidemia No (%)	9 (30)	9 (30)	18 (30.0)	0.61
Hypertension No (%)	10 (33.3)	12 (40)	22 (36.6)	0.395
Tobacco use No (%)	9 (30)	8 (26.7)	17 (28.3)	0.50

Table 2: Efficacy Parameters

Group	Subjects with serum uric acid <6mg/dl at day 90 (%)	P value	Percent change in serum uric acid from day 0 to day 90 (Mean ±SD)	P value
Allopurinol 300mg	46.4	0.14	-32.2 ± 2.35	0.001
Fenofibrate 200mg	41.3		-28.4 ± 2.52	

Table 3: Adverse Effects No. (%)

	Allopurinol 300mg/d n=28	Fenofibrate 200mg/d n=29
Headache	2 (6.66)	3 (10)
Dizziness	0 (0)	1 (3.3)
Nausea/vomiting	1 (3.3)	3 (10)
Diarrhea	1 (3.3)	1 (3.3)
Rashes	2 (6.66)	1 (3.3)
AHS	0 (0)	-
Muscle pain/weakness/cramps	0 (0)	2 (6.66)
Acute gout	2 (6.66)	1 (3.3)
AST > 3x UNL	0 (0)	1 (3.3)
CPK > 5x UNL	0 (0)	0 (0)
Any treatment related AE	8 (26.6)	13(43.3)

Key: AST=alanineaminotransferase, CPK=creatinephosphokinase UNL=upper normal limit

DISCUSSION

Allopurinol is the most commonly used uric acid lowering agent. Limitations of allopurinol therapy include ineffective lowering of plasma urate level in up to fifty percent of patients and development of severe adverse effects in up to five percent of patients.[17] Rashes occur in upto 10% of patients taking allopurinol.[18] Allopurinol hypersensitivity syndrome is uncommon but it occurs more frequently in patients with chronic kidney disease.[6] The mortality rate in allopurinol hypersensitivity syndrome is about 20%.[11]

Fenofibrate decreases serum uric acid levels.[19] This three month study was conducted to evaluate the serum uric acid lowering efficacy and safety of fenofibrate 200mg daily by comparing it with allopurinol 300mg daily which is the standard drug in the treatment of hyperuricemia. In our study 46.4% of patients in allopurinol group while 41.3% of patients in fenofibrate group achieved serum uric acid level less than 6mg/dl at day 90. These values are in agreement with several studies[20-21] which also showed the same values in reduction of serum uric acid level using allopurinol and fenofibrate respectively. The mean percentage reduction in patients taking allopurinol 300mg daily was 32.2% and in those taking fenofibrate was 28.4%. The percentage of serum uric acid decrease was in the same range as those previously reported.[3,16] The study treatment was well tolerated in fenofibrate group with 3% of patients discontinuing due to adverse effects as compared to allopurinol group in which 6% of patients discontinuing due to adverse effects. The main adverse effect leading to withdrawal in fenofibrate group involved elevation of serum transaminases more than 3 times upper normal limit. The main adverse effects leading to withdrawal in allopurinol group involved development of rashes. These adverse effects are well documented effects of fenofibrate and allopurinol.[8,13,18]

Although fenofibrate lowered serum uric acid level which is comparable in magnitude with allopurinol, there was no acute attack of gout when fenofibrate treatment was started. This could be due to the antiinflammatory action of fenofibrate and is noted in other studies.[22]

CONCLUSION

Fenofibrate has significant uric acid lowering properties. It can be used as an alternative drug to allopurinol in patients who cannot take allopurinol due to adverse effects. Fenofibrate may be used as a single agent in patients with hyperuricemia along with hyperlipidemia so reducing the need for multiple drug treatments. Further studies are needed to test the role of fenofibrate in the treatment of hyperuricaemia.

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