TO STUDY THE EFFICACY AND SAFETY OF COMBINATION TREATMENT USING ALLOPURINOL AND FENOFIBRATE IN PATIENTS WITH HYPERURICEMIA

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ABSTRACT

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 urate levels. This study was conducted to compare the efficacy and safety of combination treatment using allopurinol 100mg and fenofibrate 67mg daily with allopurinol 300mg daily. Sixty hyperuricemic patients with serum uric acid level 7.0mg per deciliter or above were enrolled and assigned to take either allopurinol 300mg or combination treatment using allopurinol 100mg + fenofibrate 67mg 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. Comparison of percentage of subjects reaching serum uric acid level less than 6.0mg per deciliter at day 90 between the two groups was highly significant (P=0.001). Similarly percent change in serum uric acid level from day 0 to day 90 was also highly significant between the two groups (P=0.001). Our results showed that allopurinol 300mg once daily is more effective than combination treatment using allopurinol 100mg plus fenofibrate 67mg. However proportions of subjects experiencing any adverse event were higher in allopurinol 300mg group. Similarly the adverse effects leading to treatment withdrawal were higher in allopurinol group. Allopurinol 300mg once daily is more effective antihyperuricemic agent than combination treatment using allopurinol 100mg plus fenofibrate 67mg.

Keywords: Allopurinol, fenofibrate, 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 (Dincer, 2002). In plasma it is found in ionized form as urate. Normal plasma urate level ranges from 3.3 to 6.9 mg/dL. Concentration of plasma uric acid at which it saturates is about 6.8 mg per deciliter (Becker, 2005).

Hyperuricemia is a biochemical abnormality characterized by serum uric acid level greater than 6.8mg per deciliter (Sunkureddi, 2006). The incidence of
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hyperuricemia ranges from two to seven percent. (Akkasilpa, 2004). In majority of 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 (Canella, 2005). As the concentration of uric acid increases, its solubility in plasma decreases and urate crystals form (So Alexander, 2008). 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 (Preitner, 2009).

The aim of antihyperuricemic therapy is to prevent complications (Alldred, 2005). The primary goal is reduction and maintenance of serum uric acid to the level well below saturating range i.e., <6.0 mg/dl (Schumacher, 2009). The drugs used in the treatment of hyperuricemia include uricosatic agent, allopurinol which inhibits production of the uric acid and uricosuric agent, probenecid which increases renal elimination of uric acid. The most commonly used drug in the treatment of hyperuricemia is allopurinol. However, ineffective lowering of plasma urate level and development of severe adverse effects are the major limitations of its use (Moreland, 2005).

Fenofibrate is a derivative of fibric acid that is commonly used in the treatment of hyperlipidemias (Feher, 2003). Several studies have shown that use of fenofibrate results in the reduction of serum uric acid levels (Tsimihodimos, 2005, Nuki, 2006). This study was conducted to compare the efficacy and safety of the combination treatment using allopurinol 100mg and fenofibrate 67mg daily with allopurinol 300 mg daily.

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, cholelithiasis, 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 combination group assigned to receive Tab. Zyloric (allopurinol) 100mg + Cap. Fenoget (fenofibrate) 67mg 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 AND DISCUSSION

A total of 60 subjects with hyperuricemia were randomized to enter the study. Two patients in allopurinol group discontinued treatment due to adverse effects. Two patients in combination group discontinued treatment due to loss of follow-up and non compliance to
drug treatment respectively. 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 14.2% 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 highly significant (P=0.001) (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 combination group the mean percent decrease was 20.2%. Mean percent decrease of serum uric acid level from day 0 to day 90 between the two groups was also significant between two groups (P=0.001) (Table 2, Figure 2). Proportion of subjects experiencing any adverse event was higher in allopurinol group (26.6%) than in combination group (23.3%) (Table 3). Proportion of patients who stopped taking medicine because of adverse effects was higher in allopurinol group (3%) than in combination group (0%). The main reason for withdrawal in allopurinol group was development of rashes.

The most commonly used drug in the treatment of hyperuricemia is allopurinol. There is significant dose–response relationship between allopurinol and serum uric acid. (Zhang, 2006). The usual dose of allopurinol ranges from 100 to 600 mg daily (Allred, 2005). 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 (Moreland, 2005). It has been shown that increasing the dose

<table>
<thead>
<tr>
<th>Variable</th>
<th>Allopurinol 300mg/day n = 30</th>
<th>Allopurinol 100mg/day + Fenofibrate 67mg/day n = 30</th>
<th>All subjects n = 60</th>
<th>“P” value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in year (±)</td>
<td>53.9 (6.73)</td>
<td>54.6 (6.17)</td>
<td>54.25 (6.41)</td>
<td>0.676</td>
</tr>
<tr>
<td>Male sex - no (%)</td>
<td>26 (86.7)</td>
<td>26 (86.7)</td>
<td>52 (86.6)</td>
<td>0.64</td>
</tr>
<tr>
<td>Baseline serum urate concentration in mg/dl (±)</td>
<td>8.68 (1.13)</td>
<td>8.48 (0.96)</td>
<td>8.58 (1.04)</td>
<td>0.465</td>
</tr>
<tr>
<td>Body mass index (±)</td>
<td>27.62 (2.36)</td>
<td>27.37 (1.95)</td>
<td>27.49 (2.15)</td>
<td>0.657</td>
</tr>
<tr>
<td>Hyperlipidemia no (%)</td>
<td>9 (30)</td>
<td>8 (26.7)</td>
<td>17 (28.3)</td>
<td>0.500</td>
</tr>
<tr>
<td>Hypertension no (%)</td>
<td>10 (33.3)</td>
<td>9 (30)</td>
<td>19 (31.6)</td>
<td>0.500</td>
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<tr>
<td>Tobacco use no (%)</td>
<td>9 (30)</td>
<td>8 (26.7)</td>
<td>17 (28.3)</td>
<td>0.500</td>
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<tr>
<th>Group</th>
<th>Subjects with serum uric acid &lt;6mg/dl at day 90 (%)</th>
<th>P value</th>
<th>Percent change in serum uric acid from day 0 to day 90 (Mean ±SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol 300mg</td>
<td>46.4</td>
<td>0.001</td>
<td>-32.2 ± 2.35</td>
<td>0.001</td>
</tr>
<tr>
<td>Combination</td>
<td></td>
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<tr>
<td>Allopurinol 100mg +</td>
<td>14.2</td>
<td>0.001</td>
<td>-20.2 ± 1.24</td>
<td></td>
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<tr>
<td>Fenofibrate 67mg</td>
<td></td>
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</tbody>
</table>
To study the efficacy and safety of combination treatment

Increases the efficacy of allopurinol (Wei, 2010) but some of the toxicities too are dose-dependent. Allopurinol hypersensitivity syndrome is a rare condition but it occurs more frequently in patients with chronic kidney disease. The mortality rate in allopurinol hypersensitivity syndrome is about 20% (Canella, 2005). FDA has recommended reduced doses of allopurinol in renal failure to lessen drug toxicity. Allopurinol dose should not exceed 200mg per 24 hours in patients with moderate renal failure and 100mg per 24 hours in patients with severe renal failure (Terkultaub, 2009).

Hyperuricemia and hyperlipidaemia coexist frequently particularly in patients with hypertriglyceridaemia (Hepburn, 2001). Fenofibrate significantly lowers serum uric acid levels. In a study conducted by Feher 2003, daily dose of fenofibrate 200mg lowers serum uric acid by 19%. Another study conducted by Hepburn 2001, daily dose of fenofibrate 200mg resulted in 29% decrease in serum uric acid. It may be particularly useful in patients with gout with concomitant hyperlipidemia (Canella, 2005).

Fig. 1. Subjects with serum uric acid level <6.0 mg/dl a day 90.

Fig. 2. Percent change in serum uric acid level from day 0 to day 90
In this study we combined fenofibrate 67mg daily with allopurinol 100mg daily and the results are compared with standard dose of allopurinol 300mg daily. It was suggested that combining the two drugs would give additive or synergistic results and allow us to decrease the dose of both drugs in achieving target serum uric acid. In our study 46.4% of patients in allopurinol group while 14.2% of patients in combination group achieved serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agreement with the study conducted by Schumacher 2008 and Takahashi 2003 which also showed the same values in reduction of serum uric acid level less than 6mg/dl at day 90. These values are in agree...
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