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EFFECT OF FEBUXOSTAT ON URICACID IN PATIENTS WITH CHRONIC RENAL FAILURE – STAGE III

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ABSTRACT

TITLE : Effect of febuxostat on uricacid in patients with chronic renal failure – Stage III. **OBJECTIVES :** To evaluate the efficacy of Febuxostat in reducing serum uric acid levels in patients with moderate renal impairment and hyperuricemia. **METHODOLOGY:** 30 adult patients of both sexes, with chronic renal failure – III(ie. eGFR 30- 59 ml/min) and hyperuricemia (serum uric acid >6.6mg/dl in men and >6mg/dl in women) were treated with tablet Febuxostat 40 mg once daily for 4 weeks. **RESULTS :** Treatment with tablet Febuxostat resulted in significant reduction in serum uric acid levels (p value < 0.01). Liver function and estimated glomerular filtration rate (eGFR) were not significantly altered. **CONCLUSION :** The prevalence of elevated serum uric acid in patients with chronic kidney disease (CKD) is higher. Allopurinol , which remains the mainstay of treatment in hyperuricemia, requires dose reduction in renal impairment. Febuxostat was found to be a safe & potent hypouricemic drug in patients with moderate renal impairment.

INTRODUCTION

Renal diseases are on the rise with increasing life span and increase in non communicable diseases. The past decade has seen progress in the treatment of chronic kidney disease (CKD). The identification of novel risk factors and new treatments for CKD remains a major goal of medical research. And some "old" risk factors are reemerging, One such risk factor is uric acid[(1)]. The prevalence of elevated serum uric acid in patients with CKD is higher. Once uric acid enters a cell, it can cause oxidative stress and activate the local rennin - angiotensin system[(1)].Hyperuricemia also induces vascular disease via cyclooxygenase-2 dependent pathway[(1)]. More studies are needed to determine if early treatment of hyperuricemia can slow progressive renal disease in humans.

For the past 30 years, allopurinol, has been the mainstay of chronic treatment in patients with hyperuricemia. 20% of patients using allopurinol reports adverse events and 5% discontinue its use [(3)]. The mortality due to allopurinol hypersensitivity syndrome may reach 25%. Particularly, people with kidney failure or having concomitant thiazide diuretic therapy are the vulnerable group[(4)]. Also, allopurinol requires dose reduction in renal impairment, this being its route of excretion[(4)]. Febuxostat is a non-purine, selective xanthine oxidase inhibitor that does not interfere with other enzymes in the purine / pyrimidine pathways. Studies show that Febuxostat 10-120 mg daily behaves linearly. It is metabolized and excreted by the liver, so no dose adjustment is necessary in patients with mild-to-moderate renal impairment or mild to-moderate hepatic impairment[(5)]. This study evaluates the efficacy of Febuxostat in reducing serum uric acid levels in patients with moderate renal impairment and hyperuricemia.

MATERIALS AND METHODS

This single centred, open labeled, prospective, interventional,clinical study was conducted in the outpatient department of Nephrology, Government Rajaji Hospital, Madurai,after obtaining clearance from Institutional ethical committee. Written informed consent was obtained from all the patients. Baseline serum uric acid was defined as the value obtained at the time of enrollment. Adult patients of both sexes, with chronic renal failure – III(ie. eGFR 30- 59 ml/min) and hyperuricemia (defined as serum uric acid >6.6mg/dl in men and >6mg/dl in women) were included for this study.(Fig.1) The patients with following conditions were excluded. Secondary hyperuricemia due to malignancy, tumour lysis syndrome, organ transplant recipients; Acute Gout ; Patirnts with severe renal impairment(creatinine clearance $<$ 30 ml/min), active liver disease; patients on concomitant

medication - Azathioprine, thiazides, aspirin>325mg/day, other salicylates; Nursing and pregnant women; Women of child bearing age group not following any acceptable contraceptive procedures.

METHODOLOGY

About 200 patients were screened of which 30 patients were fit for the study. Detailed history was obtained from all the patients enrolled and recorded in the proforma designed. Basic investigations like hemoglobin, serum electrolytes, fasting blood sugar, urine routine, liver function tests were done. All patients received febuxostat - 40mg daily for 2 weeks. Patients were seen at the end of first, second and four weeks. Dose of febuxostat was titrated to 80mg at the end of 2 weeks in order to maintain serum uric acid at <6mg/dl.

Assessment at the end of first week included a detailed history, physical examination, recording of vital signs and assessment of adverse events. At the end of second week, complete physical examination, assessment of adverse events and the laboratory investigations which includes serum uric acid, serum creatinine, liver function tests were done. Patients whose dose was titrated to 80 mg/day were seen at the end of 4 weeks and were evaluated similarly.

STUDY END POINTS

Efficacy analyses were carried out on all subjects who received 40mg/ day febuxostat for at least 2 weeks. The primary efficacy end point was the proportion of subjects who achieved serum uric acid levels of ≤ 6mg/dl. The secondary end point was the percentage reduction from baseline serum uric acid.

Safety was analyzed by assessing adverse events, by comparing eGFR and liver function tests before study and at the end of 2 weeks. For those who required dose titration, safety was analyzed again at the end of 4 weeks.

RESULTS

BASE LINE CHARECTERISTICS

Serum uric acid levels were obtained before and after taking the drug for 2 weeks (Fig.2). Statistical analysis was done using student's paired t test. Among the 30 subjects, 80% were male (24/30). Mean age of the subjects was 48.4 years. Mean body weight was 53.3kg. Mean serum uric acid level at the time of enrollment was 9.73mg/dl. 26.6% had serum uric acid levels ≥ 10 mg%. Most common comorbid conditions were hypertension 83.3% (25/30) , hyperlipidemias 26.6% (8/30), diabetes 20% (6/30), coronary artery disease 6% (2/30) and retinopathy3%(1/30). During study,

almost all patients were on other drugs, commonly anti hypertensives, anti dyslipedemics, hypoglycemic agents and 36.6% (11/30) were on frusemide.

SUBJECT DISPOSITION

In majority of patients 96.6% (29/30), no change was made in initial drug dosage. Dose was increased to 80mg /day at the end of 2 weeks for one patient, as his serum uric acid level was not declining.

EFFICACY

Treatment with tablet Febuxostat resulted in significant reduction in serum uric acid levels (p value < 0.01).Primary end point was the proportion of patients with serum uric acid ≤6mg% at the end of 2 weeks.43.3% (13/30) of all subjects had serum uric acid levels < 6 mg% at the end of 2 weeks.Achieving the primary end point was maximum when initial uric acid levels were 9- 10 mg%. The secondary efficacy end point was the percentage reduction from the initial serum uric acid levels at the end of the 2 weeks. Mean percentage reduction was 47.3%.

SAFETY AND ADVERSE EFFECTS

eGFR and liver enzymes were not significantly affected. (p value> .05).Adverse effects were seen in 2 patients. They were mild and self limiting; reversed after stopping the drug. The adverse effects were cough (1/30) and epigastric pain (1/30).

DISCUSSION AND CONCLUSION

Hyperuricemia is common in patients with renal disease, but it is never considered as risk factor for progression. Two studies found that hyperuricemia is an independent risk factor for progression of IgA nephropathy[6,7]. Another recent population-based sample of Appalachian adults found that increasing serum uric acid levels were positively associated with CKD. This association appeared to be independent of age, gender, smoking status, alcohol intake, education, diabetes mellitus, hypertension, body mass index and total cholesterol levels[8].

But the best way to evaluate the role of uric acid in the pathogenesis of CKD is to determine whether lowering uric acid slows renal progression. Lowering of uric acid was found to slow the renal disease progression in three separate studies, two with allopurinol and other with febuxostat[2,9,10] .

Even though allopurinol is the widely used urate lowering drug because of its efficacy and once daily dosage, accumulation of oxypurinol (the principal metabolite of allopurinol) in renal insufficiency is considered a crucial factor for the development of allopurinol hypersensitivity syndrome and may lead to tissue damage by toxic or immunological

mechanisms[11,12].The inadequacies of allopurinol, in terms of limited efficacy at the usual dose of 300mg/day, need for dose adjustment in patients with renal impairment and undesirable side effects have highlighted the need for additional treatment for hyperuricemia. Febuxostat is an orally administered nonpurine selective inhibitor of xanthine oxidase (XO) [13] .Febuxostat is a potent ligand for, and inhibitor of, both the oxidized and reduced forms of XO[14,15]. Clinical studies have also shown that febuxostat produces significant dose-dependent decreases in serum uric acid levels[5]. In addition, febuxostat has minimal effects on other enzymes of purine and pyrimidine metabolism[14]. Febuxostat is primarily metabolized by hepatobiliary conjugation, unlike allopurinol and oxypurinol, which are excreted primarily via the kidneys. The serum urate–lowering effect of febuxostat was unaltered in patients with mild-to-moderate renal failure[16]. Also, febuxostat was found to reduce serum uric acid levels in majority of subjects within 7 days of therapy[17].

In the present study with 30 patients, majority were in the age group of 45 to 65 years of age. About 46% had serum uric acid levels of 9 to 10 mg%. Two weeks treatment of Febuxostat resulted in prompt and statistically significant reduction of serum uric acid levels. Patients' compliance was good. There were minimal adverse effects. And there were no statistically significant changes in eGFR and in liver function tests.

If supported by future prospective studies, uric acid-lowering medication may be an effective strategy to prevent and/or arrest chronic kidney disease.

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Figure 1

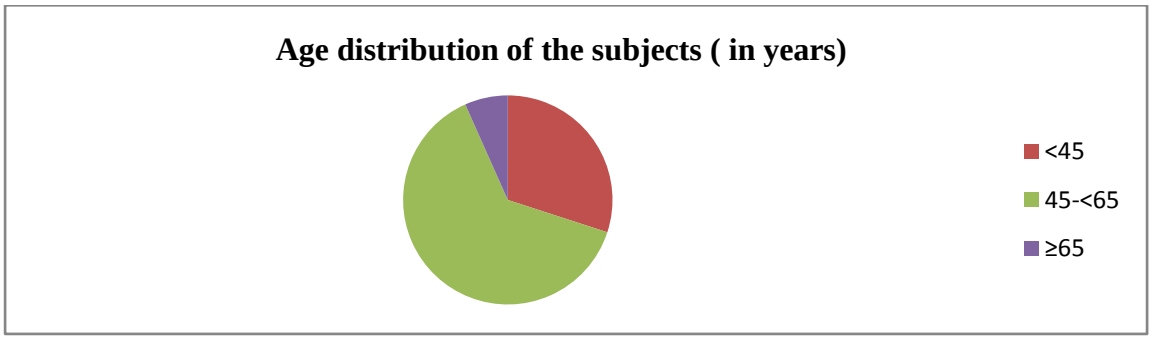

Figure 2 : Serum uric acid levels :