Original article:

Effect of Febuxostat in Rat Liver

Dr. C. Adline Misba, Dr. S. S. Rajasekar

Sri Manakula Vinayagar Medical College And Hospital, Madagaipe, Puducherry-605107.

Corresponding author: Dr. C. Adline Misba; Email Id: adlinemisba@yahoo.com

ABSTRACT:

Introduction: The study aimed to evaluate the microscopic changes in liver of adult Albino-Wistar rats administered with oral Febuxostat.

Methodology: 12 adult male Albino-Wistar rats weighing 180-220 g, Dimethyl Sulphoxide as solvent of the drug, Drug Febuxostat, Orogastric tube and Distilled water. Group A Control group comprising of 6 rats were given 10% Dimethyl Sulphoxide for 60 days. Group B Experimental group comprising of 6 rats were given 15 mg/kg Febuxostat orally for 60 days dissolved in 10% Dimethyl Sulphoxide. Group A and Group B animals were sacrificed after 60 days by cervical dislocation. The liver tissues were preserved in formalin, processed and stained with hematoxylin and eosin stain. The slides were examined under Olympus light microscope and the histological changes were seen. The slides were photographed using 6.1 Megapixel Nikon digital Camera.

Results: The histological changes in the liver of rats administered with drug Febuxostat were sinusoidal dilatation, central vein dilatation, parenchymal lymphocytic infiltration and haemorrhage and hepatocyte degeneration.

Conclusion: Hence the drug Febuxostat should be used carefully in those patients who have liver impairment before giving treatment for gout.

Keywords: Febuxostat, gout, liver, Albino-Wistar rats.

INTRODUCTION:

The prevalence of gout has been increasing in epidemic proportions over the last several decades. Hyperuricemia has been shown to be associated with metabolic syndrome and to be an independent risk factor for cardiovascular disease. Associations between hyperuricemia, obesity and aging have provided an impetus in recent years to develop alternative methods of treating hyperuricemia and gout. Febuxostat is a new non-purine xanthine oxidase inhibitor indicated for chronic gout. Febuxostat has been shown to quickly and effectively lower serum urate levels in patients with chronic gout. The most common side effect is liver function abnormalities.

Febuxostat is used to treat gout. Gout is a type of arthritis in which uric acid, a naturally occurring substance in the body, builds up in the joints and causes sudden attacks of redness, swelling, pain, and heat in one or more joints. Febuxostat is in a class of medications called xanthine oxidase inhibitors. It works by decreasing the amount of uric acid that is made in the body. Febuxostat is used to prevent gout attacks, but not to treat them once they occur.

Gout is a rheumatic condition resulting from the deposition of monosodium urate crystals (tophi) in the joints or soft tissues. It is usually associated with
elevated serum uric acid levels (greater than 7 mg/dL). The diagnosis is based on uric acid crystals found in the joints, tissues, or body fluids, as well as on gouty attacks or flares characterized by intense pain, swelling, redness, and heat[4]. The study aim to evaluate the microscopic changes in liver of rats administered with oral Febuxostat.

**METHODOLOGY:**

12 adult male Albino Wistar rats weighing 180 to 220 gms were obtained and housed in the animal house of Sri Manakula Vinayagar Medical College and Hospital, Puducherry in January 2013. All experiments were carried out as per CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals [India]) guidelines. The rats were kept at (23ºC ± 2ºC) controlled room with a 12-h light: 12-h dark cycle and 60% - 70% of humidity. All rats were fed ad libitum, and received humane care in compliance with the institution’s guidelines for the care and use of laboratory animals in research.

Group A - comprising of 6 rats served as control group and treated with 10% Dimethyl sulfoxide via an Oro-gastric tube for 60 days. Group B - comprising of 6 rats served as the experimental group and treated with oral Febuxostat dissolved in 10% Dimethyl sulfoxide via an Oro-gastric tube for 60 days. 4 rat cages were taken and each cage had 3 rats in it.

**Drug used:** Febuxostat

**Dosage and route of administration:** 15 mg/kg doses orally via an Oro-gastric tube[5].

Group A rats were sacrificed at the end of 60 days and Group B at the end of 60 days by cervical dislocation and their livers were collected. It was preserved in neutral buffered formalin, processed and stained with eosin and hematoxylin stain. The slides were examined under Olympus light microscope and the histological changes were seen.

The slides were photographed using 6.1 Megapixel Nikon digital Camera.

**Statistical analysis:** Liver was the organ of study and to rule out hepatomegaly statistical analysis was done to calculate p value of the liver and body weight ratio. The statistical analysis was calculated using a non – parametric test i.e., Mann-Whitney test. The p value was found to be non significant as it was not less than 0.05 as it can be seen in Table 1 and Table 2 and hence there was no hepatomegaly.

**Table of Organ and Body Weight Ratio:**

Table 1: “p” value of Body weight:

<table>
<thead>
<tr>
<th>Animals</th>
<th>Arithmetic Mean</th>
<th>Standard Deviation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>137.67</td>
<td>22.52</td>
<td>0.806</td>
</tr>
<tr>
<td>Test</td>
<td>135.8</td>
<td>37.91</td>
<td></td>
</tr>
</tbody>
</table>

www.ijbamr.com  P ISSN: 2250-284X  E ISSN :2250-2858
Table 2: "p" value of Liver weight:

<table>
<thead>
<tr>
<th>Animals</th>
<th>Arithmetic Mean</th>
<th>Standard Deviation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>4.5</td>
<td>1.12</td>
<td>0.413</td>
</tr>
<tr>
<td>Test</td>
<td>5</td>
<td>1.53</td>
<td></td>
</tr>
</tbody>
</table>

The p value of both liver and body weight is not significant as p value is not less than 0.01

RESULTS:

Control group: Fig. 1:

All the control group showed normal hepatocytes.

Test group: Fig. 2:

Sinusoidal dilatation with surrounding hepatocytes showing cloudy swelling seen in 10x magnification with Haematoxylin and Eosin stain.

Fig.3:

Central vein congestion with dilatation seen in 10x magnification with Haematoxylin and Eosin stain.

Fig.4:

Hydropic degeneration (cloudy swelling of hepatocytes) seen in 20x magnification with Haematoxylin and Eosin stain.
Fig. 5: Parenchymal feathery degeneration (flocculent cytoplasm) seen in 40x magnification stained with Haematoxylin and Eosin.

Fig. 6: Parenchymal haemorrhage with sinusoidal dilatation seen in 40x magnification stained with Haematoxylin and Eosin.

Fig. 7: Pronounced Periportal inflammation seen in 100x magnification stained with Haematoxylin and Eosin.

Fig. 8: Periportal inflammation with surrounding hepatocytes showing ballooning degeneration seen in 20x magnification stained with Haematoxylin and Eosin.

Fig. 9: Parenchymal haemorrhage with loss of hepatocytes seen in 100x magnification stained with Haematoxylin and Eosin stain.

Fig. 10: Pronounced Periportal inflammation seen in 100x magnification stained with Haematoxylin and Eosin.
Parenchymal lymphocytic infiltration seen in 100x magnification stained with Haematoxylin and Eosin.

**DISCUSSION:**
Allopurinol and febuxostat are the sole approved and available ULT agents in Europe, and treatment with allopurinol, the most widely prescribed, often fails to achieve the target of 6 mg/dL (360 µmol/L) because of renal failure that limits the dosage[6]. Uloric (febuxostat) is a xanthine oxidase inhibitor. Febuxostat is chemically 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-1,3-thiazole-5-carboxylic acid[7]. The empirical formula is C\textsubscript{16}H\textsubscript{16}N\textsubscript{2}O\textsubscript{3}S. Uloric is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout. Uloric is not recommended for the treatment of asymptomatic hyperuricemia. The absorption of radiolabeled Febuxostat following oral dose administration was estimated to be at least 49% (based on total radioactivity recovered in urine)[8]. Febuxostat is extensively metabolized in the liver by conjugation via uridine diphosphate glucuronosyltransferase (UGT) enzymes, including UGT1A1, UGT1A3, UGT1A9, and UGT2B7, and, to a much lesser extent, oxidation via CYP1A2, 2C8, 2C9, and non-P450 enzymes[8]. Hepatic dysfunction has been associated with the clinical use of xanthine oxidase inhibitors. The present study with the use of the drug febuxostat to Albino Wistar rats showed the histological changes Sinusoidal dilatation, Central vein congestion with dilatation, Hydropic degeneration (cloudy swelling of hepatocytes), Parenchymal feathery degeneration (flocculent cytoplasm), Parenchymal haemorrhage with sinusoidal dilatation, Pronounced Periportal inflammation and Parenchymal haemorrhage with loss of hepatocytes. These histological changes have also been observed in previous studies. Hande et al. 1984, Allopurinol causes risk, more common in elderly and renally impaired individuals, of reactions that may include rashes (some severe), hematologic cytopenias, hepatitis, vasculitis, and the potentially life-threatening allopurinol hypersensitivity syndrome[9]. Histologically fibrin-ring granulomas, cholestatic jaundice, hepatocyte necrosis are formed with oral intake of xanthine oxidase inhibitors[10]. Central vein area shows cholestasis, swelling of hepatocytes and mild inflammatory infiltrate. Portal area showing inflammatory reaction in Allopurinol given patients[9]. Showing parenchymal non-caseating granulomatous lesion[11]. Hepatic side effects have included liver function abnormalities (4.6% to 6.6%). Hepatic side effects occurring in less than 1% of patients have include cholelithiasis/cholecystitis, hepatic steatosis, hepatitis and hepatomegaly[12]. Liver function abnormality in 1.2% to 1.8% of patients was the most common adverse reaction leading to discontinuation of febuxostat therapy[13,14]. Liver function tests (e.g., AST, ALT) should be performed at 2 and 4 months following initiation of therapy and periodically thereafter[13,14].

**CONCLUSION:**
In conclusion, febuxostat caused histological changes similar to other xanthine oxidase inhibitors in liver of Albino Wistar rats. Hence Febuxostat should be used cautiously in patients with hepatic impairment.

**REFERENCES:**


[5]. European Medicines Agency Evaluation of Medicines for Human Use 7 Westferry Circus, Canary Wharf, London, E14 4HB, UK E-mail: mail@emea.europa.eu


