Original article

Zaltoprofen induced histological changes in kidneys of albino rats

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Abstract

**Introduction:** Non steroidal anti inflammatory drugs (NSAIDs) are the most commonly prescribed medications. The newer NSAIDs continue to be nephrotoxic as conventional NSAIDs. Zaltoprofen is a NSAID used commonly as an analgesic in the treatment of painful disorders. Our aim was to determine the histological changes in the kidneys of Albino rats after varying periods of oral Zaltoprofen administration.

**Materials:** 36 adult male Albino Wistar rats and the drug Zaltoprofen in a dose of 40mg/kg body weight of Albino rats. 10% Dimethyl Sulphoxide was used as the solvent for the drug.

**Methodology:** Groups A1, B1 and C1 - each comprising of 6 rats served as control groups and was treated with 10% Dimethyl sulphoxide, orally for 7, 14 and 21 days respectively. Groups A2, B2 and C2 - each comprising of 6 rats served as the experimental group and was treated with the drug Zaltoprofen dissolved in 10% Dimethyl Sulphoxide orally for 7, 14 and 21 days respectively. The rats were sacrificed 24 hours after the last dose of drug and their kidneys were collected.

**Results:** The histological changes noted at the end of 7 days of Zaltoprofen administration was interstitial inflammation and tubular necrosis. At the end of 14 days, there was lymphocytic infiltration in the glomerulus and interstitium, congestion of blood vessels and tubular necrosis. At the end of 21 days, the histological changes noted were tubular necrosis and hypoplasia of glomerulus.

**Conclusion:** Zaltoprofen should be used cautiously in patients with kidney diseases.

**Key words:** NSAID, Zaltoprofen, kidneys, histology
inhibition\(^7\). It is used in the treatment of Rheumatoid Arthritis \(^8\), Osteoarthritis \(^9\) as well as to relieve pain after surgery, injury and tooth extraction\(^{10,11}\). After oral administration of Zaltoprofen to humans, 62\% of the dose is excreted as conjugates in the urine and only 3\% is excreted unchanged\(^{12}\). Also the involvement of liver microsome CYP2C9 and UGT2B7 in the metabolism of Zaltoprofen is established\(^{12}\). The present study aims to observe the histologic changes in kidneys of albino rats treated with varying periods of Zaltoprofen.

**Materials and methods:**
36 adult male Albino Wistar rats, weighing 180-220gm were obtained from Animal house of Sri Manakula Vinayagar Medical College and Hospital, Puducherry. The experimental protocol was approved by the Institutional Animal ethics Committee following the guidelines of CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals for laboratory animal facility).

The drug Zaltoprofen, obtained from Ipca Pharmaceuticals, was diluted in 10\% Dimethyl Sulphoxide and given as 40mg/kg body weight/day \(^{13}\) orally to the experimental group rat. The rats were acclimatized for a period of 7 days before starting the study. Standard environmental conditions such as temperature (24\+/-2C), humidity (60-70\%) and 12 hours of light / dark cycle were maintained. Food and water were allowed ad libitum under strict hygienic conditions.

**STUDY GROUPS:**
- Groups A1, B1 and C1 - each comprising of 6 rats served as the control groups and were treated with isovolumetric quantities of 10\% Dimethyl Sulphoxide, orally via an oro-gastric tube, for 7,14 and 21 days respectively.
- Groups A2, B2 and C2 - each comprising of 6 rats served as the experimental group and were treated with the drug Zaltoprofen in a dose of 40mg/kg body weight/day \(^{13}\) dissolved in 10\% Dimethyl Sulphoxide, orally via an oro-gastric tube, for 7,14 and 21 days respectively.

Blood samples were collected from the tail vein of the rats before they were sacrificed, for biochemical analysis of Blood urea nitrogen (BUN) and Serum Creatinine. The rats were sacrificed 24 hours after the last dose of the drug by cervical dislocation and their kidneys were collected. The organs were preserved in 10\% formalin, processed and stained with eosin and hematoxylin stains. The program Epi info version 3.4.3 was used in the statistical evaluation of the biochemical results. Mean and standard deviation was calculated for each of the groups. ‘F’ test was used to determine the ‘p’ value for each of the parameters. A ‘p’ value < 0.05 was taken to be statistically significant.

**Results:**
On histological examination, the kidneys of the control group rats were normal (Figure 1). The kidneys of the rats treated with the drug Zaltoprofen for 7 days (A2 group) showed interstitial inflammation and tubular necrosis. There was lymphocytic infiltration in the interstitium (Figure 2). Blood urea nitrogen and serum creatinine were not significantly increased in the experimental A2 group (Table 1).

The histological changes observed in the kidneys of the rats treated with Zaltoprofen for 14 days (B2 group) were lymphocytic infiltration in the glomerulus and interstitium, congestion of blood
vessels and tubular necrosis (Figure 3). Blood urea nitrogen levels were significantly elevated in the B2 group with a ‘p’ value of 0.01 (Table 1).

The histological changes observed in the kidneys of the rats treated with Zaltoprofen for 21 days (C2 group) were, congestion of blood vessels, extensive tubular necrosis and hypoplasia of the glomerulus (Figure 4 & 5). There was less of lymphocytic infiltration compared to A2 and B2 groups. Blood urea nitrogen levels were significantly elevated in the C2 group with a ‘p’ value of 0.01 (Table 1).

Figure 1: Kidney of control group rat

Figure 2. Kidney of A2 group rat. The thin arrow indicates interstitial lymphocytic infiltration and thick arrow indicates tubular necrosis.

Figure 3: Kidney of B2 group rat. The thin arrow indicates lymphocytic infiltration and thick arrow indicates tubular necrosis.

Figure 4: Kidney of C2 group rat. The thin arrow points to hypoplasia of glomerulus and the thick arrow points to tubular necrosis.
TABLE 1: BIOCHEMICAL PARAMETERS

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<tr>
<td>Blood urea nitrogen mg/dl</td>
<td>14.84+/ -3.24</td>
<td>16.02+/ -2.8</td>
<td>0.399</td>
<td>14.81+/ -2.10</td>
<td>17.69+/ -1.14</td>
<td>0.010</td>
<td>14+/ -1.55</td>
<td>17.19+/ -1.14</td>
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<tr>
<td>Serum Creatinine mg/dl</td>
<td>0.71+/ -0.09</td>
<td>0.73+/ -0.08</td>
<td>0.685</td>
<td>0.85+/ -0.05</td>
<td>0.93+/ -0.1</td>
<td>0.101</td>
<td>0.63+/ -0.05</td>
<td>0.68+/ -0.16</td>
<td>0.427</td>
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Discussion:
Nephrotoxicity has been associated with clinical use of NSAIDs. The present study with varying periods of Zaltoprofen administration to Albino rats showed that there was borderline increase in Blood urea nitrogen. The histological changes observed were interstitial lymphocytic infiltration, congested and dilated blood vessels, tubular necrosis and hypoplasia of glomerulus. These histological changes have also been reported with the use of other NSAIDs in Albino rats. Loh A H L, et al.,(14) have reported that NSAID induced Renal Tubulo interstitial nephritis is...
due to immune mediated reactions, vascular congestion is due to capillary or ischemic damage and glomerular injury is due to alterations in Renin-angiotensin system or Prostaglandin synthesis in humans. Ejaz P, et al.,(15) have reported that chronic administration of NSAIDs to patients with painful disorders caused acute tubular necrosis and acute renal failure. Papillary necrosis has been incriminated in the development of chronic renal failure secondary to NSAIDs. Kitahara M, et al.,(16) in their study have reported that selective cyclo oxygenase 2 inhibitors-Rofecoxib and Celecoxib, impaired glomerular capillary healing in experimental Glomerulonephritis in Albino rats. Jain N, et al.,(17) studied the renal histological effect in albino rats after oral Aspirin administration. They observed damage in the tubular epithelial cells, vacuolar degeneration and marked tubular atrophy with interstitial fibrosis. Ucheya R E, et al.,(18) studied the histological changes in kidneys of pregnant Sprague Dawley rats after administration of Paracetamol. They observed shrunken glomerulus, vascular congestion, haemorrhage and tubular necrosis. Burell J H, et al.,(19) observed renal papillary necrosis in female Fischer 344 rats after treatment with Aspirin and Paracetamol. Necrosis of the epithelium of the thin limbs of the loop of Henle, cortical interstitial fibrosis and tubular atrophy were observed.

**Conclusion:**
Zaltoprofen caused renal histologic changes similar to other NSAIDs, hence they should be used cautiously in patients with renal diseases.

**References:**


