ORIGINAL ARTICLE

Changes in histopathology of liver of mice given altered doses of diclofenac sodium

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ABSTRACT

Diclofenac sodium belongs to the family of nonsteroidal anti-inflammatory drugs which is used to treat pain , inflammation & arthritis .The drug causes damage to various tissues due to oxygen reactive species formation . Following study is designed to evaluate the effects of altered doses of diclofenac sodium (6mg /kg body weight & 16mg/kg body weight) on histopathology of liver from 10 -30 days . Administration of diclofenac sodium leads to degeneration of liver & formation of wide gaps called as si nusoidal fenestrations . Various stages of investigations revealed fibrosis of liver due to oxygen reactive oxygen species & inflammation . Maximum damage to the liver was observed due to degenerative changes . During later stages widening of sinusoids & necrosis was evident .

Keywords: Diclofenac sodium, liver, histopathology

INTRODUCTION

Drugs are considered as foreign particles by human body & undergo different types of reactions which are responsible for their elimination . Endoplasmic reticulum in the liver is the main organelle for metabolizing both exogenous & endogenous particles .

Diclofenac sodium is used for treatment of inflammatory conditions & rheumatoid arthritis in the body . Liver converts the drug into forms that can be effectively removed from the body . The hepatic toxicity is due to release of harmful chemicals & binding of drug to various proteins in the liver .

The present study is designed to highlight the effects of these metabolites on the liver which causes gross changes in liver architecture specifically degeneration of liver . Although different studies have done on the effects of diclofenac on liver the present study is focused on the effect of moderate & high doses of drug on liver tissue .

MATERIALS & METHODS

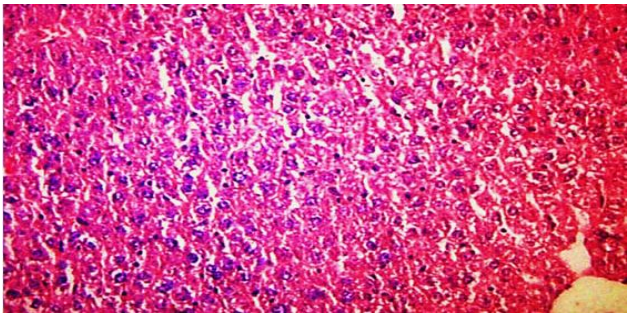
For this investigation albino mice weighing 25-30 g were obtained from animal house of post graduate medical institute . They were put in iron cages & provided with specific feed & provided with water ad libitium. Drug was administered orally through canulas. Control group was given normal saline. The low dose group was given 6mg /kg body weight & high dose group was given 16mg / kg body weight . so three groups were Control group, Low dose group (6mg /kg body weight) AND High dose group (16mg /kg body weight). The days selected for sacrificing the animals were 15 , 22 & 30 days respectively . Liver was taken out for weighing & put in normal saline. For studying histopathological changes tissue was first fixed & eosin haematoxylin staining was done to see histopathology of liver tissue .

RESULTS

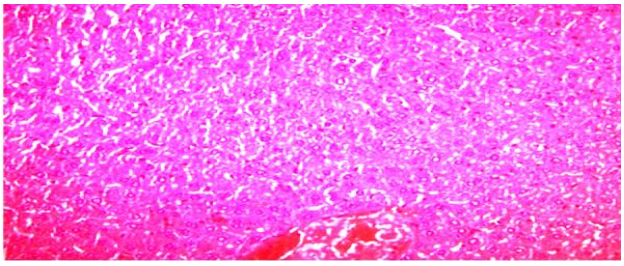
Control liver : Examination of control liver by microscope revealed normal structure of hepatic lobules & hepatocytes extend from central vein to the lobules at the periphery . The cells are polyhedral with thick cytoplasm & central nucleus . The sinusoids lined by kupffer cells which are irregular with cytoplasmic processes . Hepatic artery is also seen in sections

Normal liver (control)

Liver treated with diclofenac sodium: Low dose treatment with diclofenac 6mg/kg body weight for 8 days revealed mild changes in the histology of liver . Wide sinusoidal gaps were evident due to degeneration of hepatic tissue . No change was observed in the structure of hepatic vessels & kupffer cells . Continuation of treatment for 22 days showed necrosis of parenchyma presenting tissue damage & marked deterioration of central region of lobule



Low dose group (6mg/kg)



Diclofenac treatment for 15 days revealed marked changes in the liver , there is increase in size of nuclei, marked increase in macrophages & deterioration of shape of hepatocyte is seen .

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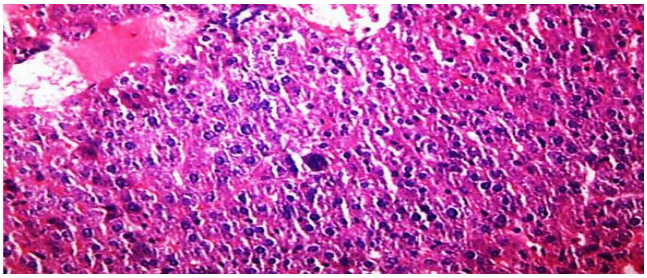
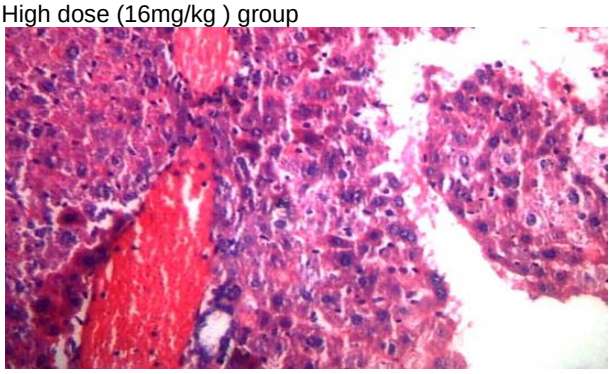


Thirty days of treatment of low dose group showed more degeneration & accumulation of kupffer cells at sinusoidal spaces . Marked necrosis with distorted nuclei was visible which lead to extensive fibrosis due to degeneration. Treatment with high doses (16mg/kg) leads to marked infilteration of lymphocytes in hepatic sinuses . Necrosis of parenchyma & increased number of enucleated areas are also visible . Damage markedly increases during 22-30 days of treatment . Thrombosis of portal vessels was evident .

High dose (16mg/kg) group



DISCUSSION

Marked histopathological changes were observed between high & low dose groups which showed that changes are dependent on dose . Irreversible cellular changes & acute hepatitis were seen after treatment with high dose[4] . It is suggested by some studies that adverse effects of diclofenac are due to impairment of mitochondria with ADP[3]

Observation of histology of liver treated both with high & low doses showed marked damage of liver tissue Histology of control mice liver showed normal structure with normal polygonal hepatocyte with rounded nuclei lying close to each other & blood vessels also showed regular appearance .

Drug administration in mice revealed disrupted structure due to degeneration of hepatocytes & formation of sinusoidal gaps . Administration of diclofenac in some individuals can lead to liver damage due to reactive metabolites which are formed[5] The present study revealed interstitial & periportal inflammation , tissue fibrosis & necrosis indicating acute hepatitis . These changes are aggravated on prolongating the treatment.

Same changes are also observed in other studies as congested central& portal veins with infiltration in portal areas & widened blood sinusoids [7,8] . The fibrosis of liver observed in this study is due to inflammation & oxygen reactive substances which stimulate hepatocytes . The destruction of hepatic organization is due to increased deposition of extracellular matrix proteins which leads to damage of liver [9] . It occurs mainly in periportal hepatocytes due to increased oxygen species in the region. Other alterations in histopathology are degeneration , vacuolation & necrosis in rats treated with 16 mg /kg [11] . Different other studies also revealed the toxicity of liver induced by diclofenac sodium. The increased level of degeneration seen during later stages revealed maximum damage of liver [11] . Infiltration of blood into sinusoids was seen due to extensive haemolysis in liver [9] . Other studies showing effects of diclofenac on liver revealed hepatic degeneration with specific areas of necrosis of liver[10] .

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