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 sinusoidal 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 libitum. 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.

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.

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 infiltration 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. It is suggested by some studies that adverse effects of diclofenac are due to impairment of mitochondria with ADP. 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. The present study revealed interstitial & perportal inflammation, tissue fibrosis & necrosis indicating acute hepatitis. These changes are aggravated on prolonging the treatment.

Same changes are also observed in other studies as congested central & portal veins with infiltration in portal areas & widened blood sinusoids. 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. It occurs mainly in perportal hepatocytes due to increased oxygen species in the region. Other alterations in histopathology are degeneration, vacuolation & necrosis in rats treated with 16 mg/kg. 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. Infiltration of blood into sinusoids was seen due to extensive haemolysis in liver. Other studies showing effects of diclofenac on liver revealed hepatic degeneration with specific areas of necrosis of liver.

REFERENCES