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TOXIC CHANGES INDUCED BY ADMINISTRATION OF ASPIRIN IN DEVELOPING MICE

Anatomy

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ABSTRACT

Aims and Objective: Aspirin a non-steroidal anti-inflammatory drug having antipyretic, analgesic and anti-inflammatory actions. It is also used in prevention of myocardial infarction. However its effect on the liver of developing embryo has not been explored yet.

Material and methods: Aspirin was given to pregnant mice in the dose of 100mg/kg body weight and the liver of 19th day fetus was studied for any microscopic changes.

Results: On histological observation the treated liver shows many pathological changes. Various empty lacunar spaces can be seen due to degeneration of hepatocytes which are present as cell debris. At some places these lacunar spaces have aggregated to form large vacuolar space giving a spongiform or honeycomb appearance. The cyto - architecture of the liver is lost showing marked necrosis of hepatocytes at various places.

Conclusion : Aspirin has toxic effects on liver of developing embryo so should be used with caution in pregnancy.

KEYWORDS

Teratogenecity, Hepatocytes, Necrosis

INTRODUCTION

Aspirin is one of the Non-steroidal anti-inflammatory drugs. It has antipyretic, analgesic and anti-inflammatory actions.

Several previous studies showed that NSAIDs use on late pregnancy can be associated with severe adverse neonatal outcomes including increased risks of persistent fetal pulmonary hypertension, increased risk of congenital heart defects, intracranial hemorrhages, renal toxicity in fetus, and orofacial clefts.

Despite more than 100 years of use, acetyl salicylic acid (aspirin) has only been recognized for the prevention of myocardial infarction (MI) and ischemic stroke for the past 25 years. Over this period, based antithrombotic effectiveness of aspirin is related to its inhibition of the cyclooxygenase (COX) enzyme that metabolizes arachidonic acid to a variety of prostanoids, including thromboxane A2 (J. R. Vane et al, 1971).[1] Platelet-derived cyclooxygenase-1 (COX-1) generates thromboxane A2, a potent vasoconstrictor and platelet agonist. With the inhibition of platelet COX-1 activity, there is a decrease in platelet aggregation, leading to a reduced thromboembolic potential and prolonged bleeding time. Thus, it is not surprising that the major risks associated with aspirin relate to bleeding complications.

Looking at very few and inconclusive reports about the teratogenicity of aspirin and histopathological changes induced by it on the liver of the developing fetus, the present study has been undertaken. In the present study, the drug has been experimented upon the swiss albino mice to elucidate its effects on the offspring.

MATERIAL AND METHODS

Adult female swiss albino mice weighing 20- 25 gm (average age of 80-100 days) were used after approval of institution The female mice in their pre-oestrous phase were transferred in the evening to the cages having a male mice in the ratio of 2:1. The presence of vaginal plug on the following morning indicated pregnancy and was designated as day zero(0) of gestation. The pregnant mice were divided into following groups

Group 1 : Control (given equivalent amount of tap water)

Group 2 : Treated with Aspirin 100mg/kg of body weight from day 3 to day 5 of gestation.

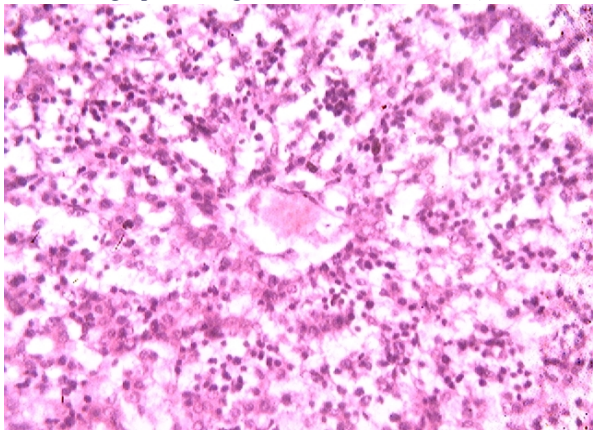
The mouse of each group was sacrificed on day 19th of gestation by deep ether anaesthesia and fetuses were collected after uterotomy . After gross examination and photography the fetuses were preserved in 10% neutral formalin solution for seven days. After fixation the liver of the embryos were dissected out . For histological study the liver were processed, sections were cut and stained with haemotoxylin and eosin.

OBSERVATION AND RESULTS

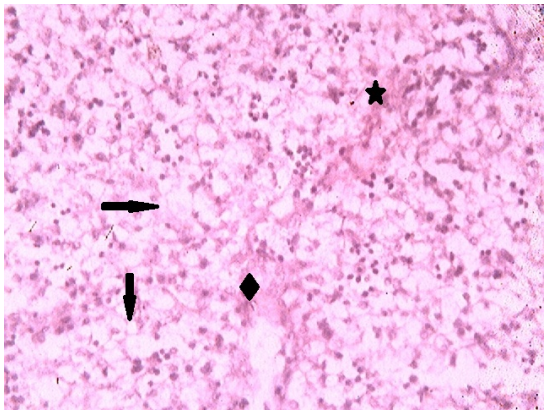
On histological observation the treated liver shows many pathological changes. At various places on the slide the liver shows reduction of hepatocyte population. The granulocyte cell concentration in subcapsular and perivascular areas is also diminished. The sinusoid pattern between the hepatocyte cords is less demarcated.

Various empty lacunar spaces can be seen due to degeneration of hepatocytes which are present as cell debris. At some places these lacunar spaces have aggregated to form large vacuolar space giving a spongiform or honeycomb appearance. The cyto-architecture of the liver is lost showing marked necrosis of hepatocytes at various places.

Photomicrograph showing control liver (H & E, 400 X).



Photomicrograph showing treated liver (H & E, 400 X). Reduced cellular density (→) and loss of normal architecture around central vein (♦).



DISCUSSION

Alex Schoenfeld et.al. (1992) reported constrictive effect of Aspirin on fetal ductus arteriosus. They stated that Aspirin use during pregnancy is related to teratogenesis, maternal bleeding, fetal and neonatal bleeding, effects on the pulmonary circulation.[2]

Bort. R *et al.,* (1999) studied on the rat liver and proposed that NSAIDs uncouples oxidative phosphorylation, decreases hepatic ATP content and induces hepatocyte injury. The in vitro cytotoxicity correlated well with the formation of various intermediate metabolite that particularly inhibited ATP synthesis leading to death of hepatocytes damage.[3]

N. O' Connor *et al.,* (2003) reviewed the hepatotoxic effects of various Non steroidal anti inflammatory drugs in the human liver cells as well as animal models. In the clinical trials they found the NSAIDs to cause hepatitis with jaundice and greatly elevated trans aminases. On histological studies peri-portal inflammation with plasma and lymphocyte infiltration and fibrosis extending into the lobule were common findings. They stated that mainly two mechanisms were responsible for hepato-toxicity of NSAIDs namely, hypersensitivity and metabolic aberreations.[4]

Ki-Wan Oh *et al.,* (2003) studied on the rat hepatocytes and found that aspirin lowers the threshold for apoptotic and necrotic cell killing. In the present study, the hepatocyte damage may be due to this reason. They found that aspirin enhances onset of mitochondrial permeability transition (MPT) caused by three different classes of inducers in hepatocytes – calcium inophore, oxidant stress and TNF-α. These changes were responsible for the lowering of threshold of hepatocytes to apoptosis and acute cytotoxicity.[5]

In our present study, microscopic examination of the treated fetal liver revealed loss of hepatocytes and haemopoetic stem cells, empty lacunar spaces, loss of cyto-architecture and marked necrosis of hepatocytes. The present findings are well supported and explained by various mechanisms proposed by the above mentioned authors and their hypothesis.

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