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Original Research Paper

Anatomy

EFFECT OF CHRONIC EXPOSURE OF IBUPROFEN ON CARDIAC MUSCLE OF SWISS ALBINO MICE

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ABSTRACT

Context: Adverse effects of Ibuprofen on liver, gastrointestinal tract, kidneys, are well documented in the literature. The present study was carried out with the aim to investigate the effect of Ibuprofen on Cardiac Muscle of Swiss Albino Mice.

Methods: Fifty adult Swiss albino mice grouped as 25 controls and 25 experimental were used for the experimental purpose. Control group was treated with distilled water & experimental group with Ibuprofen suspension given orally in the dose of 40mg/kg/day for 6 weeks. After sacrificing and careful dissection of mice, hearts were removed and processed for routine histological tissue procedures.

Results: There occurred significant loss of body weight in experimental mice as compared to controls. Increased weight of heart was observed in experimental mice. Mean diameter of cardiac myocyte was statistically increased in experimental group (p=0.0001, t=8.28). We found significantly reduced volume proportion of cardiac myocytes versus stroma in experimental mice.

Conclusions: Ibuprofen, most widely prescribed NSAID, should be used minimally and in lowest possible dose in patients with pre-existing cardiovascular disorders because of its association with cardiovascular events.

KEYWORDS : Cardiac myocyte, cardiovascular disorders, nonsteroidal anti-inflammatory drug

INTRODUCTION:

Non-steroidal anti-inflammatory drugs (NSAIDs) include a group of drugs used to provide analgesic, antipyretic and in high doses give anti-inflammatory effects. NSAIDs impart its therapeutic effects by inhibiting the synthesis of prostaglandins. There are no preexisting depots of prostaglandins but are synthesized locally in response to various chemical or mechanical stimuli1. In our study, we have used the drug Ibuprofen which is a non-selective cyclooxygenase (COX) inhibitor NSAID1. American Heart Association (2007) published a warning relating to the use of NSAIDs in patients with established cardiac diseases 2. European Medicines Agency's Pharmacovigilance Risk Assessment Committee picked up diclofenac as a high risk NSAID with regard to its effect on the heart on systemic administration as capsules, tablets or injections [3].

Since there is paucity of available data in literature showing direct toxic role of Ibuprofen on heart and most of the documentations includes the clinical parameters like blood pressure, electrocardiographic changes or biochemical parameters 3 hence we decided to perform a case-control study in Swiss albino mice to study the histological changes in cardiac tissue as an effect of chronic use of NSAID, Ibuprofen in human equivalent doses.

Material and methods:

Present study was a case control study performed on Swiss albino mice to study the effect of Ibuprofen on the structure of heart. Institutional Ethics Committee for animals has given the approval for the present study. We used fifty adult Swiss albino mice and divided them as 25 controls and 25 experimental groups. Control group was treated with distilled water whereas experimental group with Ibuprofen suspension in the dose of 40mg/kg/day for six days per week for a period of six weeks. Drug was administered orally using specially derived non-injurious metal canula attached to disposable insulin syringe by gastric gavage method. After sacrificing mice hearts were dissected out and processed for routine histological tissue processing and light microscopy after staining with haematoxyline and eosin and masson's trichrome stain.

Results:

We observed statistically significant loss of body weight in experimental mice (p=0.0001, t=9.11). There was significantly increased weight of heart in experimental mice (p=0.0001, t=8.28) (Table 1). We didn't find any morphological defects such as curling of muscle fibers, breaks, vacuolation of cardiac myocytes, and necrosis in any groups.

Mean diameter of cardiac myocyte was statistically raised in experimental group (p=0.0001, t=8.28) (Table 1). There was an apparent enlargement of diameter of cardiac myocyte nucleus in experimental group. The intervals between cardiac myocytes were increased with unstained intervals when stained with Haemotoxylin and eosin as well as Masson's trichrome stain showing the accumulation of edema fluid in the myocardial stroma without any evidence of fibrosis or deposition of collagen fibers in the unstained intervals (Figure 1 & 2) We observed reduced volume proportion of cardiac myocytes versus stroma in experimental group of mice and difference in two groups was found to be significant (p=0.0001,t=10.43) (Table1).

Table 1: Comparison of different parameters between control and experimental mice

Parameters Mean±SD	Control mice	Experimental mice	t-value	p-value
Mean change in body weight(gm)	-0.54±1.35	-4.81±1.91	9.11	0.0001,S
Mean weight of heart(gm)	0.20±0.01	0.27±0.04	8.28	0.0001,S
Mean diameter of cardiac myocyte (µm)	8.98±0.62	10.99±1.04	8.28	0.0001,S

Mean vertical diameter of nucleus of cardiac myocyte (µm)	9.64±0.75	10.04±0.81	1.78	0.081,NS
Mean horizontal diameter of nucleus of cardiac myocyte (µm)	3.08±0.35	3.26±0.44	1.55	0.127,NS
Mean volume proportion of myocardium versus stroma	0.92±0.03	0.74±0.07	10.43	0.0001,S

Figure 1: Microphotograph of myocardium showing densely arranged muscle fibers (control, H & E, X400)

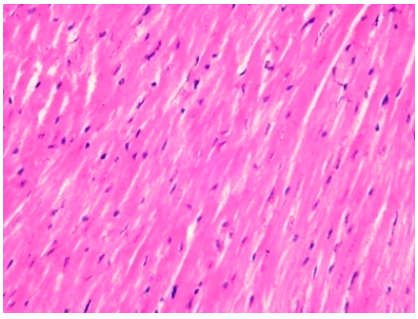
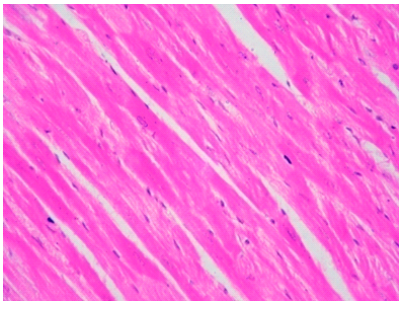


Figure 2: Microphotograph of myocardium showing widely separated muscle fibers (Experimental, H & E, X400)



DISCUSSION:

Cardiovascular problems like heart failure, myocardial infarction, stroke, cardiovascular deaths occurring as a result of use of NSAIDs are also well documented. NSAIDs evoked cardiovascular consequences are due to its interference with cardiovascular homeostasis promoting platelet aggregation and vasoconstriction4. Cappon et al (2005) reported the tendency for induction of ventricular septal defect with Ibuprofen to be 3.7% of fetuses per litter in a study conducted on rats [5].

Studies on whole rat embryo culture model reported the diclofenac-induced teratogenecity during the period of organogenesis. Malformations produced due to the exposure of NSAIDs like Aspirin, diclofenac resulted from inhibition of synthesis of vasodilatory prostaglandins leading to sudden vasoconstriction, disturbed blood supply [6].

When we have gone through literature recommended therapeutic dose of Ibuprofen in human was 8-10mg/kg/dose for three times or four times a day which matches with the dose of 40mg/kg/day used in our study 7.In our study Swiss albino mice were exposed to ibuprofen for a dosing period of 6 weeks which partly coincides with the Chopra et al (2007) and Sood et al (2008) who have given different NSAIDs for roughly four weeks [8, 9].

In the present study there occurred statistically significant decrease in body weight in experimental mice treated with ibuprofen. Cappon et al (2005) observed that administration of NSAIDs to pregnant rats on gestational days 9-10 resulted in decreased maternal body weight as well as fetal weight and it also concurred with our findings 5. Dudkiewicz et al (1981) and Suwa et al (1987) commented upon the decrease in body weight in rats following the administration of NSAIDs including Ibuprofen which coincides with our study [10, 11].

In the present study weight gain of heart in experimental group found to be due to accumulation of edematous fluid in the myocardial stroma which was proved by statistically significant decreased volume proportion of myocytes versus myocardial stroma in experimental group. To confirm it masson's trichrome stained sections were examined which clearly showed that there was absence of extra collagen deposition in the wall of heart. Zabka et al (2009) used Masson's trichrome stain for detecting the collagen deposition and found collagen deposition around the vessel walls in the heart as a result of chronic inflammation 12. In the present study there was no evidence of any inflammatory reaction but there was an increased diameter of cardiac myocytes may be to compensate the cardiac myocytes lost at an early dosing period. Thus this hypertrophy of cardiac myocytes along with accumulation of edematous fluid in the myocardial stroma seems to be effect of remote toxic effect of Ibuprofen. Jain et al (2009) observed the necrosis of heart muscle fibres, edema and thickening of epicardium due to the presence of acellular eosinophilic material in experimental bird receiving diclofenac sodium orally [13].

In our study we observed increase in diameter of cardiac myocytes thus hypertrophy in experimental group of mice treated with ibuprofen. Niranjan et al (2010) concluded that there occurred hepatocyte enlargement in albino rats treated with NSAID diclofenac 14. Kumar et al (2004) stated that there occurs the hypertrophy of skeletal as well as cardiac muscles as an adaptive response to compensate the overload due to increased synthesis of structural components of cells and not due to actual swelling of cells 15. However the exact mechanism behind hypertrophy of cardiac myocytes and decrease volume proportion of cardiac myocytes versus myocardial stroma following administration of ibuprofen is not fully understood. Further studies should be carried out to elucidate the reason behind it.

NSAIDs lead to cardiovascular related toxicity especially in hypertensive subjects. Inhibition of COX-2 leads to retention of sodium and water in body which further increases peripheral vascular resistance and hazardous effects on heart such as hypertension, heart failure 3. Administration of NSAIDs in patient with the history of cardiovascular disorders should be at lowest dose with shortest possible time period.

CONCLUSION:

NSAIDs like Ibuprofen are mostly used as an analgesic in painful disorders like rheumatoid arthritis, osteoarthritis, musculoskeletal disorders etc. Usages of these drugs are associated with cardiovascular events such as heart failure, myocardial infarction, and stroke. Hence these drugs should be used cautiously in patients having a high pre-existing cardiovascular risk profile.

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