FAILURE OF ACETYL SALICYLIC ACID (ASPIRIN) TO REDUCE EXPERIMENTAL MYOCARDIAL ISCHAEMIC DAMAGE

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Summary : Rats fed on acetylsalicylic acid (aspirin) 1.5 *mg*/100 *g* body weight for a period of three weeks were subjected to myocardial infarction by s.c. administration isoprenaline hydrochloride 8.5 *mg*/100 *g* of body weight on two consecutive days.

Heart specimens were taken for histological examination at 24 hr, on 5th day and 12th day. An equal number of rats were given saline to serve as control. As compared to controls aspirin-treated rats were found to have macroscopically bigger infarcts and microscopically showed persistent oedema on the 12th day. Further, no histological evidence of favourable action of aspirin was seen on the fifth day and after twentyfour hr.

Key words : myocardial infarction isoprenaline acetylsalicylic acid

INTRODUCTION

Ischaemic heart disease represents the most common serious health hazard of contemporary society. Treatment is mainly directed towards arrhythmias and myocardial pump failure. A different approach is, an attempt to influence the natural evolution of the development of myocardial necrosis by interrupting it while it is still in the reversible phase and thus reducing the size of eventual infarction. The rationale for this approach is, that this reduction of the extent of necrosis will result in larger mass of variable contracting cells with less complications. Reduction of infarct size by gluco-corticoids (14) and propranolol (16) has been tried ; the effect of acetylsalicylic acid (aspirin) in myocardial infarction, especially as a result of catecholamine stress has never been investigated. The spectrum of actions ascribed to this class of drugs are, inhibition of prostaglandin synthesis (1,9,25) inhibition of platelet aggregation (2,26) curtailment of granulocyte adherence (17) and inhibition of neutrophil chemotaxis (4,20,27). In addition to the above properties, aspirin also reduces lipogenesis by partially blocking incorporation of acetate into fatty acids (11) and causes increased oxidation of fatty acids and thus lowers the concentration of free fatty acids in plasma. It has been suggested that these drugs may thus be useful in preventing coronary insufficiency in conditions of cardiac stress (24). Besides acting as coronary dilator (7), aspirin has been observed to reduce catecholamine induced vaso

constriction (22). An inhibitory action of aspirin on catecholamine in the myocardium may be the basis for an antiarrhythmic response during acute ischaemia (23).

In this study, the prophylactic use of this drug and its effect on 24 hr, 5th day and 12th day myocardial infarct produced by catecholamine stress has been investigated.

MATERIALS AND METHODS

Myocardial infarction was produced by the method of Rona *et al.* (19). Albino rats of either sex, weighing 200 ± 25 *g*, were given sc injection of isoprenaline hydrochloride 8.5 *mg*/100 *g* body weight daily on two consecutive days. Prior to the administration of isoprenaline the animals were divided into two groups of 12 rats each. In one group aspirin 1.5 *mg*/100 *g* body weight in 1 *ml* of saline was administered through a stomach tube daily for three weeks. The control group was fed with an equal volume of saline. During this period both groups were given standard rat feed (Hindustan Lever) and water *ad libitum*. At the end of three weeks both the drug-treated and the control groups were divided into three sub-groups of four animals each. The animals were sacrificed and hearts removed (a) at 24 hr, (b) on 5th day and (c) on 12th day subsequent to production of myocardial infarction.

RESULTS

Macroscopic : The site of the infarcted area was the same in both the drug-treated and the control animals (Table I). The difference was only in size as compared to controls. The drug-treated animals showed a larger area of infarct at the three intervals studied (Table II). Further, all control animals survived whereas 3 of the total drug-treated animals died.

TABLE I : Site of myocardial infarct.

Drug	*Appex*	*Right heart*	*Interventricular septum*	*Anterior region of left ventricle*
Aspirin	+++	- - - - -	+++	+++
Control	++	- - -	++	++

TABLE II : Macroscopic size* of the infarcts.

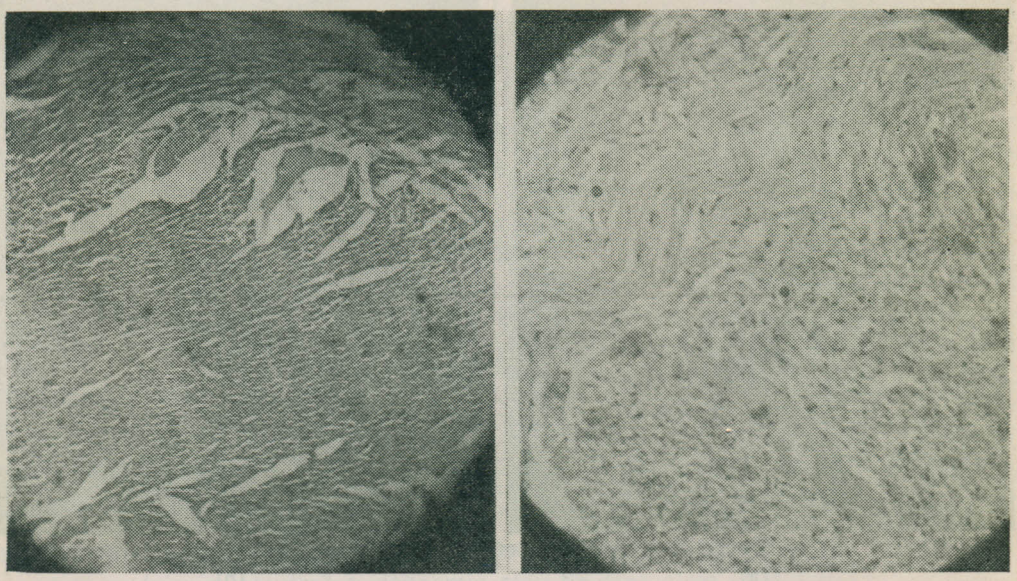
Drug	*24 hr*	*5th day*	*12th day*
Aspirin	2/3rd	2/3rd	1/3rd
Control	1/3rd	1/3rd	1/6th (almost healed)

*External fractions of the total heart area.

Histological appearance : At 24 hr, there was no histological difference in the groups. Only slight leucocytic infiltration was seen in the areas showing necrosis.

On 5th day : In the drug-treated group, lesser inflammatory changes were seen at the periphery of oedematous area and areas of hyaline changes.

On 12th day : In the drug-treated group, oedematous changes persisted and the process of healing of the infarcted area was slower than in controls.



(a) (b)

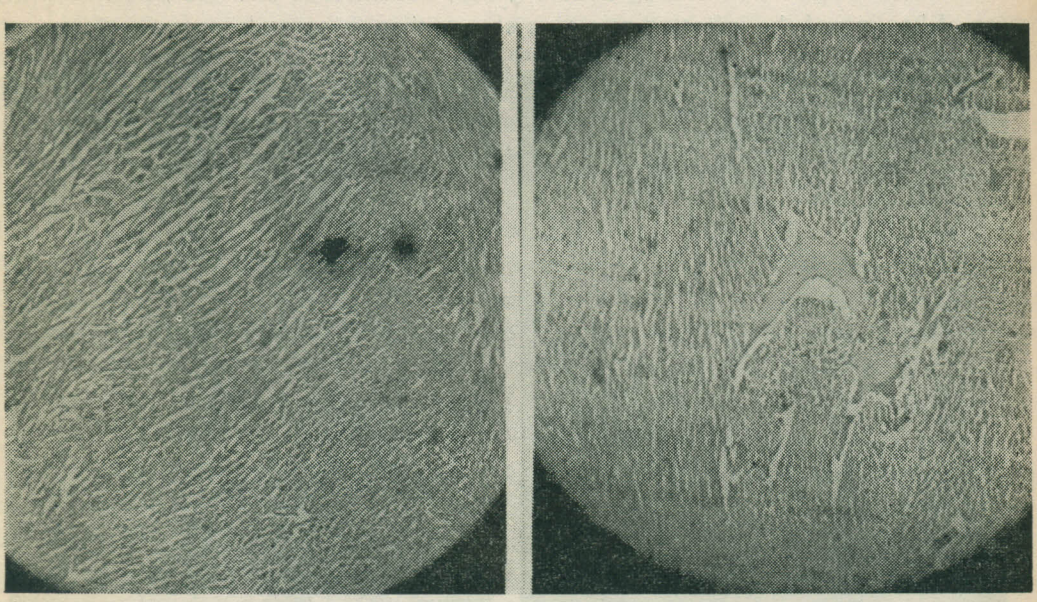
Fig. 1 : (a): Control.

(b): Aspirin–treated : Histological section of rat ventricle on 5th day of drug treatment. Hyaline changes in the fibres with loss of striations are seen. They are deeply eosinophilic stained. At some areas small blood vessels are also seen undergoing necrosis. At the periphery of the infarcted area, many inflammatory cells are seen in the control slides and less inflammatory cells with few fibroblasts are seen in the drug treated–group. Oedema and local haemorrhages are seen in both the groups.

DISCUSSION

Intentional use of aspirin and like-drugs inhibiting platelet aggregation alongwith oral anticoagulants is being actively explored for the prophylaxis of coronary and cerebral arterial thrombosis (2,26). Aspirin is known to inhibit prostaglandin synthesis (9) and enhance metabolic coronary dilatation (MCD) by suppression of prostaglandin feed back control (24). MCD is inhibited by prostaglandin E_1 (21). Aspirin by inhibiting prostaglandin synthetase activity (25) increases the level of cyclic AMP which helps in the dilatation of coronaries in conditions of stress. Aspirin also reduces lipogenesis (11) and

lowers the concentration of free fatty acids in the plasma. It has been suggested that these drugs may be useful in preventing coronary insufficiency in conditions of cardiac stress (24). However, prophylactic use of aspirin in myocardial infarction as a result of catecholamine stress has never been investigated. Hence this attempt was made to find out the role of aspirin in the prevention and extension of infarct in rats. The effects of this



(a) (b)

Fig. 2 :(a): Control.

(b): Aspirin–treated : Histological section on the 12th day of drug treatment. Fine collagen fibres at the periphery of the infarction are seen. There are areas in the control slides where necrotic muscle fibres are completely removed. This process seems delayed in the drug–treated group. Numerous pigmented macrophages, few lymphocytes, plasma cells and eosinophils are also present in both the groups. At some areas in the drug–treated groups, slight oedema of the heart muscle still persists.

drug on 24 hr. 5th day and 12th day, myocardial infarcts were examined. Boston collaborative drug surveillance group reported two case control studies indicating that daily aspirin intake was associated with less incidence of myocardial infarction (3). Our results are not in accordance with this study. Firstly, all the rats which died in the drug-treated group had full thickness transmural infarcts with involvement of the entire thickness of the ventricular walls. No control animals died.

Macroscopically the area of infarction was less in rats which were not given the drug. This shows that the drug had no protective effect, even though the site of occurrence of infarcts bore the same pattern i.e. in both cases all infarcts occurred near the anterior

region of the left ventricle including the apex and 2/3rd of the interventricular septum. Right ventricle was spared from infarction in both the cases. On histological examination of 24 hr specimen, no differences were seen, though 5th day and 12th day sections were more conclusive. Oedema persisted in the drug-treated group even on 12th day suggesting that aspirin on the other hand had a deleterious effect and prevented early healing of the infarcted area.

Our findings are in accordance with Coronary Drug Project Group (6) which studied 1529 men in 53 clinics. Comparing 324 *mg* tds aspirin a day versus placebo after 28 months treatment, the mortality of aspirin group was 8.3% comprared to 5.9% in the placebo group. Our results also tally with the report of Medical Research Council where 1239 men were daily given either 300 *mg* aspirin or identical placebo (8). Although there was 34% difference in favour of aspirin after 24 months, these differences did not reach a statistical significance.

Our findings do not agree with Moschos *et al.* (18) where, aspirin-treated group exhibited less loss of potassium and gain of sodium and water compared to untreated animals. This potassium conserving action has been shown to be the plausible antiarrhythmic mechanism of action of aspirin. It is just possible that anti-adrenergic and inhibitory action of aspirin on catecholamines (23) during acute myocardial ischaemia may be the basis of anti-arrhythmic action.

Our findings are more close to Hamberg *et al.* (12) where they have given indomethacin, another anti-inflammatory agent to inhibit prostaglandin synthesis during myocardial ischaemia and found evidence of enhanced injury suggesting that prostaglandins instead of promoting injury during ischaemia may be protective (13).

The failure of aspirin in preventing myocardial damage, observed in the present study may be due to : (a) Inhibition of prostaglandin synthesis or interactions of aspirin with adenylate cyclase system observed *in vitro* (15). (b) Aspirin once absorbed is rapidly hydrolysed by serum and hepatic esterases (10). It is not known how much unhydrolysed aspirin penetrates sites of inflammation and could thus acetylate enzymes or other proteins involved in the inflammatory process (5). (c) The volume of distribution of drug and its therapeutic availability in the body appears to be less in patients with disease than in normal subjects This may be due to long term drug ingestion and variation in total binding of drug in the body tissues (10)

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