

Circulating Levels of Histamine and Histaminase under the Influence of An Indigenous Drug 'Abana' in Chemically induced Ischaemic Heart Disease

Lokesh Upadhyaya, Research Fellow, Centre of Experimental Medicine and Surgery,
Urmila Agrawal, Research Associate, Department of Basic Principles,
Rai, D.K., Asst. Medical Superintendent, Radiology, S.S. Hospital,
Shukla, S.S., Ph.D., Scholar, Department of Basic Principles and
Dubey, G.P., Professor and Head, Department of Basic Principles,
Institute of medical Sciences, Banaras Hindus University, Varanasi, India.

ABSTRACT

Eighteen male rabbits were used in this trial, divided into three groups of 6 each. Group A served as controls. Group B were on a placebo and received isoprenaline injections. Group C were treated with Abana and also received isoprenaline. Histamine was measured in all the three groups. A significant increase in histamine levels was observed in the isoprenaline group. Two weeks of Abana therapy brought about a marked reduction in these levels.

Histaminase exhibited a marked reduction after isoprenaline injections. After two weeks of Abana therapy a significant elevation in its levels was observed. In the normal control series the difference in histaminase levels was found insignificant after 2 weeks of therapy. Thus Abana could not influence the circulating histamine and histaminase levels in normal cases.

In the isoprenaline-induced group marked improvement in microcirculation was noticed in comparison to the placebo group. In the normal control series Abana brought about improvement in microcirculation. It can be concluded that Abana has the capacity to regulate abnormal cardiac functions and improve the microcirculation of the heart. Thus Abana can be utilized for supportive therapy in the management of coronary heart disease (CHD).

INTRODUCTION

Regulation of cardiac function is a complex phenomenon. Several hormones and biogenic amines are known to influence the mechanism of cardiac function. Excessive secretion of histamine is reported to produce severe vasoconstriction and myocardial ischaemia (Gilbert, R.P. *et al.*, 1958). Histamine triggers the secretion of norepinephrine which produces vasoconstriction and myocardial infarction (Sarantos, 1983). The biological significance of cardiac histamine was studied by Mannaioni, P.F. (1972). He had studied the action of histamine at cardiac receptor sites with the aim of better understanding the physiological implication of histamine in cardiac function. The importance of histamine in the regulation of heart function has been emphasised by Levi (1972). According to him most of the cardiac functions are mediated by histamine. Godfraind, T. and Miller, R.C. (1983) reported that a high concentration of histamine produces severe vasoconstriction of the coronary arteries. Histamine acts through the H₁ and H₂ receptors, and it produces vasoconstriction through H₁ receptors, while H₂ receptors cause coronary vasodilation. The elevated levels of histamine may increase the blood pressure and heart rate. Sarantos *et al.*, (1983) reported that isoprenaline and histamine stimulate the intramural cardiac sympathetic nerve and are

responsible for the release of noradrenaline. Blink (1966) also pointed out that the nerve within the heart might be excited emphatically by myocardial action potential.

Recently several drugs have been introduced to regulate the cardiac function by influencing the level of various biogenic amines. The pharmacodynamic effects of indigenous cardioactive compounds could not be studied so far. Abana is a known herbomineral compound commonly advocated for the prevention and management of coronary heart disease. This drug has shown a significant vasodilation property in isoprenaline-induced ischaemic heart disease (Shukla et al, 1986). Abana also decreases the heart rate and blood pressure by reducing the catecholamine levels (Dubey et al, 1986) Keeping the above in view the role of Abana on cardiac functions has been studied in relation to histamine and histaminase levels in isoprenaline-induced ischaemic heart disease.

MATERIALS AND METHODS

Eighteen male rabbits of the same strain weighing one kg each were selected. The present experimental study was divided into three groups (6 rabbits in each group). The animals of Group A served as controls and were kept under normal laboratory conditions, whereas animals of Groups B (Placebo) and C (Abana) were injected isoprenaline in the dose of 2 mg/kg body weight once a day for three days. The initial histamine and histaminase levels were measured in all the three groups. In the isoprenaline groups both histamine and histaminase were again measured.

Abana was introduced orally in the dose of 500 mg/kg body weight continuously for two weeks. Placebo was given in the same dose to the placebo series. Successive measurements of histamine and histaminase were carried out at intervals of one and two weeks of therapy. Histamine was measured by the method developed by Shore *et al.* (1972), while histaminase was measured by that of Arsen and Kemp (1964).

Microangiography of two rabbits from each group was carried out at the initial stage, after isoprenaline injection and after two weeks of therapy. In the normal control series (Group A) microangiography was carried out at the initial stage and after 2 weeks of therapy. Two rabbits of each group were taken for microangiography each time. The initial values were compared with those after isoprenaline injection and also after two weeks of drug therapy.

RESULTS

Histamine levels:

A considerable rise in histamine levels was recorded after isoprenaline injection in the placebo as well as the treated groups of rabbits. When the initial histamine level was compared after isoprenaline injection, the difference was found significant in both the groups (Table 1, Groups B and C).

When Abana was introduced a significant decrease in histamine levels was noticed after 2 weeks of therapy. In the placebo group no appreciable change in the histamine level was noticed (Table 1, Group B).

In the normal control series when the initial level of histamine was compared after 2 weeks of Abana therapy the difference was found insignificant (Table 1, Group A, Fig. 1).

Table 1: Changes in histamine levels following Abana therapy					
Groups		Average histamine levels in µg/ml (Mean ± SD)			
		Initial values	After injection of isoprenaline	1st week	2nd week
Isoprenaline	A Normal controls (n=6)	0.85 ± 0.275	–	0.62 ± 0.387	0.59 ± 0.482
	B Placebo (n=6)	0.96 ± 0.275	2.98 ± 0.778	2.70 ± 1.205	2.05 ± 0.995
	C Treated (n=6)	0.78 ± 0.125	2.75 ± 0.895	1.32 ± 0.978	0.98 ± 0.817

Comparison:

Normal control series

Initial vs 2 weeks of therapy $p > 0.05$

Isoprenaline series

Placebo group

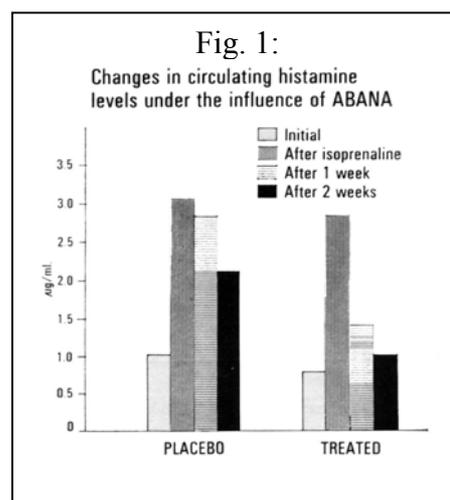
(i) Initial vs Isoprenaline $p < 0.01$

(ii) Isoprenaline vs 2 weeks of placebo therapy $p > 0.05$

Treated group

(i) Initial vs Isoprenaline $p < 0.001$

(ii) Isoprenaline vs 2 weeks of Abana therapy $p < 0.001$



Histaminase levels

Histaminase showed a significant decreasing trend after isoprenaline injection both in the placebo as well as in the treated groups (Table 2, Groups B and C). After Abana therapy a significant rise in histaminase levels was observed in the treated group.

Table 2: Changes in histaminase levels following Abana therapy					
Groups		Average histaminase levels in PU/ml (Mean ± SD)			
		Initial values	After injection of isoprenaline	1st week	2nd week
Isoprenaline	A Normal controls (n=6)	110.6 ± 30.80	–	125.7 ± 35.70	130.5 ± 36.50
	B Placebo (n=6)	125.8 ± 55.50	60.3 ± 60.325	65.6 ± 40.30	80.8 ± 60.36
	C Treated (n=6)	110.5 ± 56.40	55.6 ± 50.70	90.7 ± 56.77	105.4 ± 54.35

Comparison:

Normal control series

Initial vs 2 weeks of therapy $p > 0.05$

Isoprenaline series

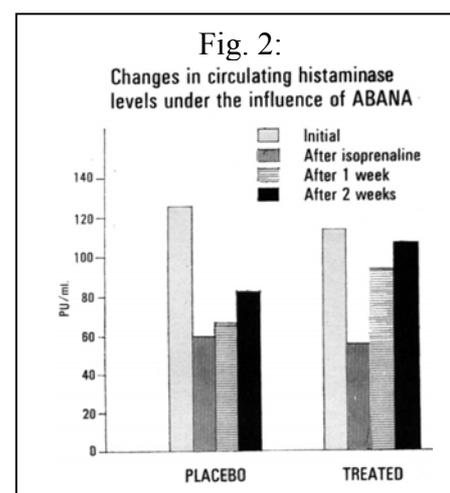
Placebo group

(i) Initial vs Isoprenaline $p < 0.001$

(ii) Isoprenaline vs 2 weeks of placebo therapy $p > 0.5$

Treated group

(i) Initial vs Isoprenaline $p < 0.001$



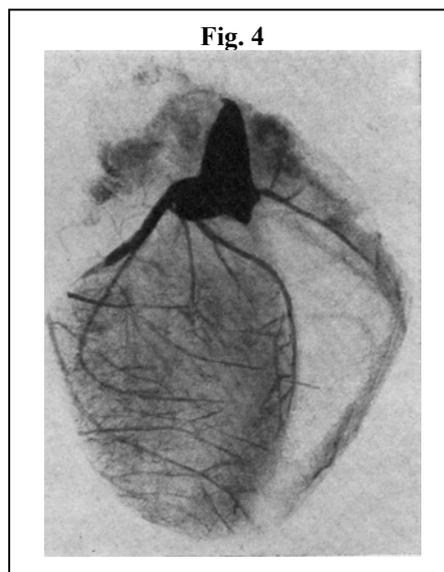
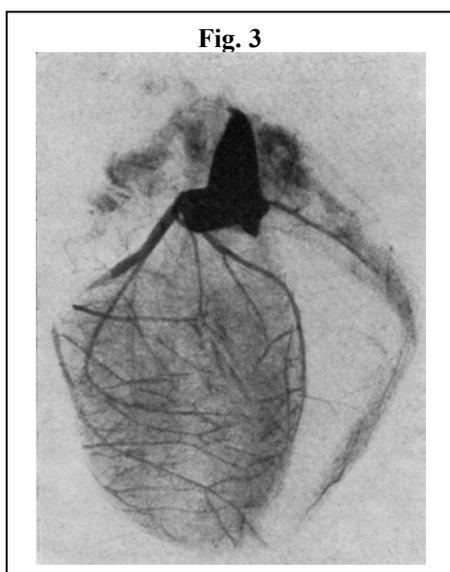
- (ii) Isoprenaline vs 2 weeks
of Abana therapy $p < 0.01$

In the normal control series (Group A) no difference in the histaminase levels could be seen after 2 weeks of Abana therapy (Table 2, Group A, Fig. 2).

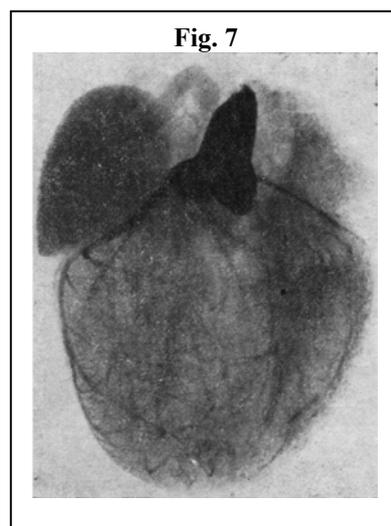
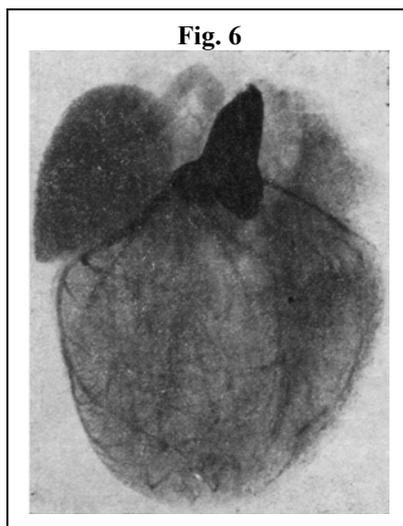
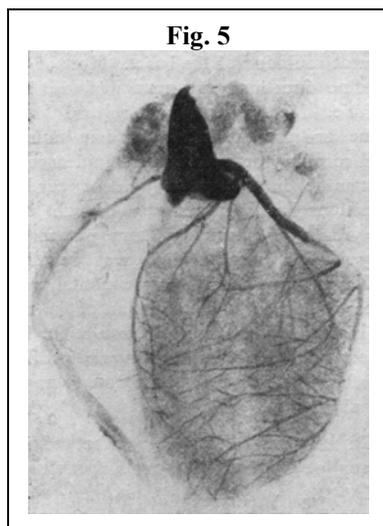
Microangiography studies:

Microangiography in the normal control series (Group A) showed minor improvement in the microcirculation of the heart following 2 weeks of Abana treatment (Group A, Figs. 3 and 4). In the isoprenaline cum placebo treated group a significant contraction of the coronary arteries and ischaemia were observed (Group B, Figs. 5, 6 and 7).

Group A: Microangiographic studies in Group A (Normal Controls)



Group B: Microangiographic studies in Group B (Isoprenaline, Placebo treated)



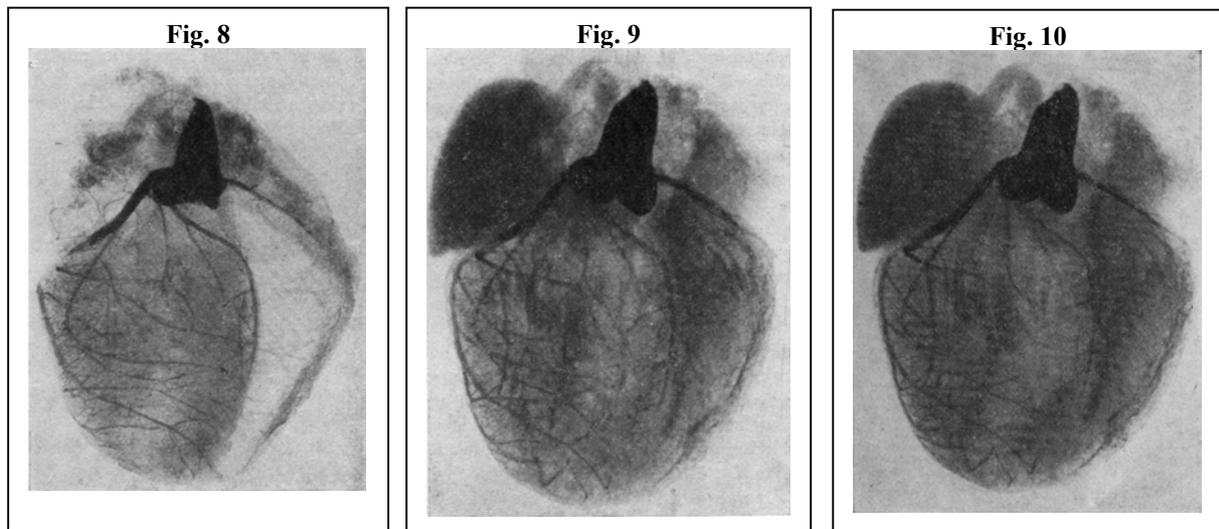
In the isoprenaline cum Abana treated group, a marked contraction of the coronary arteries was noticed, but after two weeks of oral administration of Abana, a significant improvement

in microcirculation was observed in comparison with the placebo group (Group C, Figs. 8, 9 and 10).

DISCUSSION

Histamine has a significant influence on microcirculation of the heart. Most of the cardiac functions are mediated by histamine. Most cells, which release histamine are present in the cardiac muscle and coronary arteries. The significance of histamine in the regulation of cardiac functions has been recently brought into the realm of physiology and pharmacology. This breakthrough was achieved following considerable experimental work directed toward the elucidation of the role of histamine in peripheral circulation. The effect of histamine on coronary blood flow has been demonstrated by coronary angiography.

Group C: Microangiographic studies in Group C (Isoprenaline, Abana-treated)



In the present study the effect of isoprenaline on histamine levels was observed. It is now evident that isoprenaline-induced ischaemic heart disease is associated with excessive secretion of histamine. Abana, which is commonly advocated for the prevention and management of CHD, has shown a significant influence on the histamine and histaminase levels. Abana reduces the histamine levels that are elevated in isoprenaline-induced ischaemic heart disease. This observation indicates that some of the components of Abana reduce the histamine level. Due to this reason, there is a vasodilation of the coronary arteries. It is repeatedly observed that the level of histamine was found elevated in cases of myocardial ischaemia. Kipshidze and Bardghan (1967) reported higher levels of histamine in cases of myocardial infarction. Histamine increases the rate and force of contraction of the heart by activation of the cardiac beta-adrenoreceptors and histamine H₂-receptors respectively. Laska, C.S. *et al*, (1983) have studied the effect of histamine on the release of noradrenaline from rabbit atria following isoprenaline-induced CHD. Klein, M.C. *et al*, (1983) have also reported the cardiovascular action of histamine.

The beneficial effect of Abana has been proved by observing the changes in the coronary microcirculation. In isoprenaline-induced heart disease there is a considerable improvement in the coronary circulation under the influence of Abana. Though the mode of action of

Abana has not yet been completely understood, the improvement in microcirculation of the heart might be due to its neutralizing effect on catecholamine levels.

It has been reported by Dubey *et al.*, (1986) that Abana reduces the catecholamine levels and hence it is useful in the management of sinus tachycardia, sympathetic hyperstimulation and mild cases of essential hypertension. By influencing the norepinephrine levels it might influence the secretion of histamine in cases of myocardial ischaemia. The second possible explanation is that Abana enhances histaminase, which is a degrading enzyme of histamine. Finch, L. and Hicks, P.E. (1977) also observed that histamine increases the blood pressure due to the release of a vasopressor substance or hormone.

It is apparent from the results that in normal cases Abana does not influence the histamine levels. But it reduces the circulating histamine and increases the histaminase levels only in case of myocardial ischaemia.

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