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Effect of Valsartan on Acute And Sub-Acute Models of Inflammation in Male Wistar Rats: An Experimental Study

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Abstract
Recent evidence suggests that arterial stiffness has independent predictive valve for cardiovascular events. A wealth of epidemiological data support a relationship between hypertension and atherosclerosis risk, and excessive clinical trial evidence has established that pharmacologic treatment of hypertension can reduce the risk of stroke, heart failure and CHD events. to evaluate the effect of. valsartan in acute and sub-acute models of inflammation in male Wistar rats. Methods: Animals were divided into five groups (n=6). In acute inflammation, control group received 0.5 ml of 1 % gum acacia suspension, while the other groups received therapeutic equivalent doses of one of the drugs, aspirin, valsartan. Valsartan was administered two hrs prior to the carrageenan injection. The rat paw volume was measured with the help of a plethysmograph at regular intervals and percentage inhibition of edema in various treated groups was calculated. Valsartan showed significant anti-inflammatory effect in acute as well as sub-acute models of inflammation when compared to control. Anti-inflammatory effect of valsartan is comparable to aspirin in acute model of inflammation. In sub-acute model of inflammation, valsartan was found to have anti-inflammatory effect comparable to aspirin Valsartan have shown significant anti-inflammatory activity in acute and sub-acute models of inflammation. In acute model of inflammation, valsartan have shown significant anti-inflammatory effect when compared to control and their effect was comparable to aspirin.

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Key Words
Valsartan, aspirin, inflammation

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INTRODUCTION

Essential to the survival of organisms is their ability to get rid of damaged or necrotic tissues and foreign invaders, such as microbes. The host response that accomplishes these goals is called inflammation. This is fundamentally a protective response and a complex reaction in tissues that consists mainly of responses of blood vessels and leukocytes[1].

The body's principal defenders against foreign invaders are plasma proteins and circulating leukocytes (white blood cells), as well as tissue phagocytes that are derived from circulating cells. The inflammatory response coordinates the reactions of vessels, leukocytes and plasma proteins to achieve this goal. The vascular and cellular reactions of inflammation are triggered by soluble factors that are produced by various cells or derived from plasma proteins and are generated or activated in response to the inflammatory stimulus[1].

Chronic inflammation may follow acute inflammation or be insidious in onset. It is of longer duration and is associated with the presence of lymphocytes and macrophages, the proliferation of blood vessels, fibrosis and tissue destruction[1].

Inflammation may be harmful in some situations. Mechanisms designed to destroy foreign invaders and necrotic tissues have an intrinsic ability to injure normal tissues. When inflammation is inappropriately directed against self tissues or is not adequately controlled, it becomes the cause of injury and disease[1].

Inflammatory reactions underlie common chronic diseases, such as rheumatoid arthritis, atherosclerosis, and lung fibrosis. Inflammation may contribute to a variety of diseases that are not thought to be primarily due to abnormal host responses. For instance, chronic inflammation may play a role in atherosclerosis, type 2 diabetes, degenerative disorders like Alzheimer disease and cancer[1].

Some adrenergic agonists, 2 calcium channel blockers3 and calcium4 have also been reported to possess anti-inflammatory activity in experimental studies. Some other drugs unrelated to NSAIDs, like statins which inhibit HMG-CoA reductase enzyme5 and sulfonamides like sulfamethiazole6 have also been reported to posses anti-inflammatory activity in experimental models. As these drugs are not completely devoid of adverse effects13 there is a need to the search for safer and better anti-inflammatory agents.

In view of role of inflammation in atherosclerosis and hypertension and paucity of published literature regarding effect of angiotensin receptor blockers on inflammation in animal models. The present study was planned to evaluate the effect of valsartan on acute and sub-acute models of inflammation in male Wistar rats

MATERIALS AND METHODS

Adult male healthy Wistar rats weighing 175±25 g were obtained from the central animal house, J. N. Medical College, Belgaum and were acclimatized to 12:12 hour light-dark cycle for 10 days prior to the day of experimentation. They were maintained on standard rat chow pellet and water ad libitum. The study was approved by the IAEC (Institutional Animal Ethics Committee) constituted as per the guidelines of CPCSEA (Committee for the Purpose of Control and Supervision on Experiments on Animals).

Acute inflammation was produced by injecting carrageenan in the hind paw and sub-acute inflammation by implanting foreign body subcutaneously as described below.

Carrageenan Induced Rat Paw Edema: Rats were divided into five groups of six each (n=6). They were starved overnight with water ad libitum prior to the day of experiment. Control group received 0.5 ml of 1% gum acacia suspension, while the other groups received calculated clinical equivalent dose of one of the drug, aspirin, telmisartan, valsartan and irbesartan in 1 % gum acacia suspension. Aspirin was taken as the standard anti-inflammatory drug.

valsartan was administered two hours prior to the induction of edema.

0.05 ml of 1 % carrageenan in normal saline was injected into the sub plantar region of one of the hind paw. 95 A mark was put on the hind limb at the malleolus to facilitate uniform dipping at subsequent readings. The paw edema volume in milliliter was measured with the help of plethysmograph by mercury displacement method at zero hour i.e. immediately after injecting carrageenan (Fig 3). The same procedure was repeated at 0.5, 1, 3, 4 and 5 hours.

Foreign Body Induced Granuloma Method[7]: Rats were divided into five groups of six each (n=6). After clipping the hair in axillae and groin, under thiopentone anesthesia, two sterile cotton pellets weighing l0 mg and two sterile grass piths measuring 25x2 mm were implanted randomly, subcutaneously, through a small incision. Wounds were then sutured and animals were caged individually after recovery from anesthesia. Aseptic precautions were taken throughout the experiment. The treatment was started on the day of implantation and was repeated every twenty-four hours, regularly, for ten days.

On the eleventh day, the rats were sacrificed with an overdose of anesthesia to remove the cotton pellets and grass piths. The grass piths were preserved in 10 % formalin for histopathological studies. The pellets, free from extraneous tissue were dried overnight at 60 °C to note their dry weight. Net granuloma formation was calculated by subtracting initial weight of cotton pellet (10 mg) from the weights noted. Mean granuloma dry

weight for various groups was calculated and expressed as mg/100 g body weight.

The clinical doses[8] for various drugs were converted to rat equivalent doses with the help of table devised by Paget and Barnes[9].

Valsartan: (Cipla, Mumbai) It was administered in the dose of 28.80 mg/kg body weight equivalent to 320 mg of clinical dose orally.

Aspirin I.P: (Cipla, Mumbai) It was administered in the dose of 200 mg/kg body weight equivalent to 2222 mg of clinical dose orally.

Carrageenan: (Sigma Co. St. Louis.) Carrageenan is mixture of polysaccharide composed of sulphated galactose units and is derived from Irish Seamoss. It was administered as a suspension in 1% warm normal saline given in the volume of 0.05 ml per rat paw.

The granulation tissue preserved in 10 % formalin was processed in the Department of Pathology, J. N. Medical College, Belgaum and sections were stained with haematoxylin and eosin and the granulation tissue in each group was studied microscopically.

*Similar groups (n=6 in each group) were included for sub-acute studies and drugs were given once daily for 10 days.

Valsartan was administered two hours prior to carrageenan injection.

Statistical Analysis: The results were analyzed by one way ANOVA (Analysis of variance) followed by Dunnet's test. ANOVA followed by Bonferroni's test was used to compare study groups viz. telmisartan, valsartan and irbesartan with standard i.e. aspirin. Statistical analysis was done using GraphPad Prism 4 software and $p<0.05$ was considered significant.

RESULTS AND DISCUSSIONS

In the present study, valsartan, were investigated for their possible anti-inflammatory effect, in acute and sub-acute models of inflammation in male Wistar rats.

Acute Inflammation (Carrageenan Induced Paw Edema Method): The mean paw edema volumes in milliliter's (ml), as measured by mercury displacement using a plethysmograph, for control group at ½ h, 1 h, 3 h, 4 h and 5 h intervals were 0.991±0.041, 1.258±0.023, 1.458±0.022 respectively. The corresponding mean paw edema volumes in aspirin treated group were 1.108±0.02, 1.117±0.016, 1.092±0.008, 0.983±0.021 and 0.975±0.021 respectively, with the calculated percentage inhibitions of 30.24%, 71.06%, 84.15%, 98.32% and 95.54% respectively. Aspirin treated group showed statistically significant inhibition of paw edema volume ($p<0.01$) when compared to control.

Valsartan showed statistically significant inhibition ($p<0.01$) of paw edema at 1 h, 3 h, 4 h and 5 h, with mean paw edema volumes of 1.1±0.034, 1.1±0.046, 1.017±0.045 and 0.905±0.022 respectively (Table 6, Graph 1), with the calculated percentage inhibition of 63.44%, 74.99%, 84.94% and 97.78% respectively (Table 6, Graph 2) when compared to control.

The above results clearly show the anti-inflammatory effect of valsartan in acute model of inflammation when compared to control. Further anti-inflammatory effect of valsartan, was compared with anti-inflammatory effect of aspirin. It was found that anti-inflammatory effect of valsartan was comparable to aspirin ($p>0.05$) in acute model of inflammation.

Sub-Acute Inflammation (Foreign Body Induced Granuloma Method): The mean dry weight of ten day old granuloma, expressed as mg percent (mg/100 g) body weight of rat, in control group was 14.88±0.3992. In aspirin treated group, it was significantly decreased ($p<0.01$) with the mean value of 10.17±0.627 and percentage inhibition of 31.65%. Similarly Valsartan treated groups exhibited statistically significant decrease in granuloma dry weight ($p<0.01$) with mean value of 12.57±0.4351 with percentage inhibition of 15.52% and 30.77% and 33.55% respectively when compared to control.

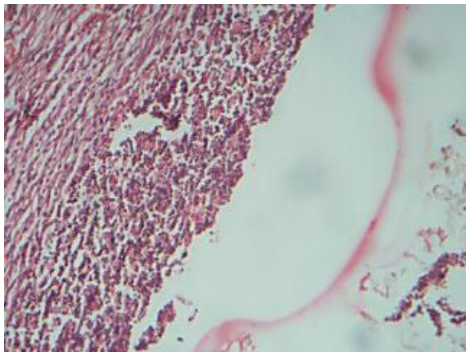

Fig. 1: Photomicrograph showing dense acute inflammatory infiltrate with granulation tissue in the wall of the lesion (H and E STAIN)

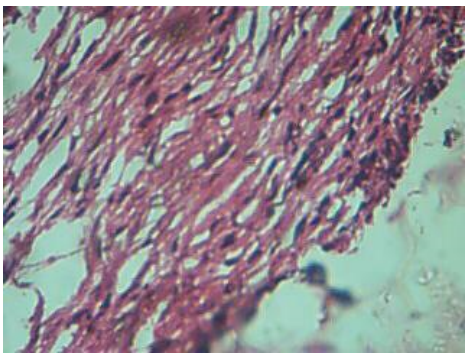

Fig. 2: Valsartan Group (X40)

Table 1: Effect of aspirin and valsartan treatments on carrageenan induced paw edema when compared with control

		Aspirin		Valsartan		ANOVA Result	
Time after carragee-nan injection	Control (Paw edema in ml ± SEM)	Paw edema in ml (±SEM)	Percentage inhibition (%)	Paw edema in ml (±SEM)	Percentage inhibition (%)	$F_{4, 25}$	p Value
½ h	0.991 ± 0.041	1.108 ± 0.020	30.24	1.075 ±0.049	20.03	14.19	<0.0001
1 h	1.258 ± 0.023	1.117 ± 0.016**	71.06	1.100 ± 0.034**	63.44	5.508	0.025
3 h	1.458 ± 0.020	1.092 ± 0.008**	84.15	1.100 ± 0.046**	74.99	25.85	<0.0001
4 h	1.325 ± 0.051	0.983 ± 0.021**	98.32	1.017 ± 0.045**	84.94	14.17	<0.0001
5 h	1.200 ± 0.022	0.975 ±0.021**	95.54	0.950 ± 0.022**	97.78	14.41	<0.0001

Table 2: Effect of irbesartan treatments on carrageenan induced paw edema when compared with aspirin group

	Aspirin		Irbesartan		ANOVA Result	
Time after carrageenan injection	Paw edema in ml (SEM)	Percentage inhibition (%)	Paw edema in ml (SEM)	Percentage inhibition (%)	$F_{3, 20}$	p-value
½ h	1.108 ± 0.020	30.24	1.075 ± 0.049**	20.03	14.19	<0.0001
1 h	1.117 ± 0.016	71.06	1.100 ± 0.034	63.44	5.508	0.025
3 h	1.092 ± 0.008	84.15	1.100 ± 0.046	74.99	25.85	<0.0001
4 h	0.983 ± 0.021	98.32	1.017 ± 0.045	84.94	14.17	<0.0001
5 h	0.975 ± 0.021	95.54	0.950 ± 0.022	97.78	14.41	<0.0001

Table 3: Effect of aspirin and irbesartan treatments on granuloma dry weight when compared with control group

S. No	Drug Treatment	Mean granuloma dry weight mg/100 g body weight (Mean ± SEM)	Percentage inhibition (%)
1.	Control	14.88 ± 0.3992	-
2.	Aspirin	10.17 ± 0.6270**	31.65
5.	Irbesartan	10.30 ± 0.3052**	30.77

Table 4: Effect of telmisartan, valsartan, and irbesartan treatments on granuloma dry weight when compared with aspirin group

S. No	Drug Treatment	Mean granuloma dry weight mg/100 g body weight (Mean ±SEM)
1.	Aspirin	10.17 ± 0.6270
4.	Irbesartan	10.30 ± 0.3052

ANOVA: $F_{3, 20} = 20.39$, $p < 0.0001$, Post hoc analysis by Bonferroni's Test: *$p < 0.05$

Further mean granuloma dry weight of valsartan, group was compared with mean granuloma dry weight of aspirin group. There was no statistically significant difference in mean granuloma dry weight of valsartan group when compared to mean granuloma dry weight of aspirin ($p>0.05$) group. It shows that the anti-inflammatory effect of valsartan was comparable to aspirin in sub-acute model of inflammation (Table 9).

The anti-inflammatory effect of valsartan observed in both, acute and sub-acute studies was further confirmed by histopathological studies. The sections of granulation tissues when stained with haematoxylin and eosin showed dense acute inflammatory infiltrates, increased fibroblasts, thick fibrous tissue and abundant granulation tissue in the control group. Aspirin, valsartan treated groups revealed scanty acute inflammatory infiltrates, less number of fibroblasts, scanty collagen tissue and decreased thickness of fibrous tissue (Fig)[10-19].

Results of the present study clearly indicate that valsartan show significant anti-inflammatory activity in acute and sub-acute models of inflammation when compared to control group. In acute model of inflammation, it was found that the anti-inflammatory effect of valsartan was comparable to that of aspirin. In sub-acute model of inflammation it was found that the anti-inflammatory effect of valsartan was comparable with aspirin.

Observations of the present study are in agreement with the earlier reports stating that selected angiotensin receptor blockers valsartan may have anti-inflammatory activity.

Valsartan inhibits ROS generation by both PMN and MNC with concomitant suppression of NF-κB[10]. It also reduces proinflammatory cytokines TNF-a, serum IL-6[11], IL-1ß by peripheral blood mononuclear cells[12], and plasma IL-18[13]. Observation of the ValMARC trial showed that valsartan lowers the hsCRP levels independent of blood pressure lowering effect[14].

Since ARBs have anti-inflammatory activity, they can provide clinical benefit across cardiovascular disease spectrum-from control of cardiovascular risk factors mostly hypertension, to the early stages of cardiovascular disease and/or renal damage, through to patients in whom cardiovascular disease is already present. Also ARBs should be considered as appropriate therapy for patients with arterial hypertension regardless of the stage of disease. The capacity of ARBs to reduce blood pressure is like that of any other class of antihypertensive agent and there is a considerable evidence base for their ability to provide protective effects beyond blood pressure control for the heart, brain and kidney.

CONCLUSION

In the current study valsartan have shown significant anti-inflammatory activity in acute and sub-acute models of inflammation. In acute model of inflammation, valsartan have shown significant anti-inflammatory effect when compared to control and their effect was comparable to aspirin. In

sub-acute model of inflammation, anti-inflammatory effect of valsartan was comparable with aspirin.

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