

Research Article

Effect of telmisartan on acute model of inflammation in male Wistar rats: an experimental study

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ABSTRACT

Background: The objective of the study was to investigate the influence of telmisartan on acute model of inflammation in adult male Wistar rats.

Methods: After obtaining ethical clearance from Institutional Animal Ethics Committee, animals were allotted to the three groups i.e. control, aspirin and telmisartan (n=6 animals in each group). The effect of telmisartan, administered orally, on inflammation was studied using acute (Carrageenan induced rat paw edema) model. Experiment was conducted according to the Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines. Analysis was done using one way ANOVA followed by post hoc tests of Dunnet's and Bonferroni's. $P < 0.05$ was considered as statistically significant.

Results: Telmisartan, used orally in the present study, showed significant anti-inflammatory activity in acute model of inflammation.

Conclusions: In view of role of inflammation in the pathogenesis of atherosclerosis and their complications, treatment by telmisartan can reduce complications by virtue of its anti-inflammatory activity, in addition to its antihypertensive effect. Also this study may help to open new avenues for therapeutic indications of telmisartan.

Keywords: Telmisartan, Aspirin, Inflammation

INTRODUCTION

Cardiovascular diseases remain the major cause of death and premature disability in developed societies. Current predictions estimate that by the year 2020 cardiovascular diseases, notably atherosclerosis and hypertension will become leading global causes of total disease burden.¹

In United States, 28.7% of adults have hypertension and prevalence has increased among aged ≥ 60 years to 65.4%. Hypertension doubles the risk of cardiovascular diseases, including coronary heart diseases, congestive

heart failure, ischemic and haemorrhagic stroke, renal failure and peripheral arterial diseases. It has been estimated that hypertension accounts for 6% deaths worldwide.¹ In India prevalence of hypertension is 59.9 and 69.9 per 1000 in males and females respectively in urban and 35.5 and 35.9 per 1000 in male and females respectively in rural population.²

Chronic inflammation is a common link between cardiovascular risk factors and hypertension and acts as independent determinant of arterial blood pressure.³ Patients with essential hypertension have increased

concentration of circulating interleukin 1 β (IL-1 β).⁴ Recent work has shown that the key proinflammatory transcription factor nuclear factor- κ B (NF- κ B) is activated in proinflammatory states including atherosclerosis.⁵

Inflammatory cells and pathways contribute to the initiation, progression and complications of atherosclerotic lesion. Monocytes initiate the endothelial inflammation leading to atherosclerosis. Macrophages avidly engulf lipoproteins including oxidized low density lipoprotein (LDL) which augments macrophage activation and cytokine production [e.g. Tumor Necrosis Factor (TNF)]. This further increases leukocyte adhesion and production of chemokine's (e.g. monocyte chemoattractant protein-1). Also, activated T-cells in growing intimal lesions elaborate inflammatory cytokines [e.g. Interferon- γ (IFN- γ)].⁶

One of the strategies for the management of atherosclerosis in hypertensive patient is to reduce blood pressure. However, it may be difficult to reduce serum inflammatory cytokines and markers only by reducing blood pressure.⁴ Hence it could be hypothesized that drugs with antihypertensive and anti-inflammatory activity would be of dual benefit in the treatment of atherosclerosis in hypertensive patients.

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 h light-dark cycle for 10 days prior to the day of experimentation. They were maintained on standard rat chow pellet and water ad libitum.

Aspirin (Cipla Limited, Mumbai) was administered in the dose of 200 mg/kg body weight of rat, equivalent to 2222 mg of clinical dose orally.^{7,8} Telmisartan (Cipla Limited, Mumbai) was administered in the dose of 7.20 mg/kg body weight of rat, equivalent to 80 mg of clinical dose orally.^{7,8} Carrageenan (Sigma Co. St. Louis) was administered as a suspension in 1% warm normal saline given in the volume of 0.05 ml per rat paw.

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 into one of the hind paws as described below.

*Carrageenan induced rat paw edema*⁹

Rats were divided into three groups of six animals each (n=6). They were starved overnight with water ad libitum prior to the day of experiment. Control group received

0.5ml of 1% gum acacia suspension, orally, while the other two groups received calculated clinical equivalent doses of aspirin and telmisartan in 1% gum acacia suspension, orally. Aspirin was taken as the standard anti-inflammatory drug.

Drugs were administered thirty minutes prior to the induction of edema, by oral route. 0.05ml of 1% carrageenan in normal saline was injected into the sub plantar region of one of the hind paws. A mark was put on the hind limb at the malleolus to facilitate uniform dipping at subsequent readings. The paw edema volume in millilitres was measured with the help of a plethysmograph by mercury displacement method at zero hour i.e. immediately after injecting carrageenan. The same procedure was repeated at 1/2, 1, 3, 4 and 5 hours. The difference between 0 hour and subsequent reading was taken as actual edema volume. The percentage inhibition of edema in the various treated groups was then calculated by using the formula,

Percentage inhibition of edema = $[1 - (\text{mean increase in paw volume in treated group} / \text{mean increase in paw volume in control group})] \times 100$.

Statistical analysis

The results were analysed by one way ANOVA (Analysis of Variance) followed by Dunnet's test. ANOVA followed by Bonferroni's test was used to compare the study groups i.e. telmisartan with standard i.e. aspirin (Graph Pad Prism Software, Inc.).

RESULTS

In the present study, telmisartan in therapeutic equivalent dose was investigated for its possible anti-inflammatory effect, in acute model of inflammation.

Carrageenan induced acute inflammation

The mean paw edema volumes in milliliters (ml), as measured by mercury displacement using a plethysmograph, for control, aspirin and telmisartan group are shown in (Table 1). Aspirin as well as telmisartan treated groups showed statistically significant inhibition of paw edema volume ($p < 0.01$) when compared to control at 1h, 3h, 4h, and 5h intervals.

The above results clearly show the anti-inflammatory effect of telmisartan in acute model of inflammation when compared to control. Further, when anti-inflammatory effect of telmisartan was compared with that of aspirin (Table 2), there was no statistically significant difference between the two groups in the inhibition of paw edema volume at 1hr, 4hr and 5hr intervals. This shows comparable anti-inflammatory activity of telmisartan and aspirin.

DISCUSSION

The ability of angiotensin receptor blockers (ARBs) to reduce mortality and morbidity of cardiovascular diseases has been ascribed not only to antihypertensive activity

but also to a number of additional protective effects like inhibition of smooth muscle cells growth and left ventricular hypertrophy as well as improvement in endothelial dysfunction.¹⁰⁻¹²

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

Time after carrageenan injection	Control	Aspirin	Percentage inhibition	Telmisartan	Percentage inhibition	ANOVA result	
	Paw edema in ml (Mean \pm SEM)	Paw edema in ml (Mean \pm SEM)		Paw edema in ml (Mean \pm SEM)		F _{2,15}	p value
½ hr	0.991 \pm 0.041	1.108 \pm 0.020*	30.24	1.233 \pm 0.024**	24.77	15.93	0.0002
1 hr	1.258 \pm 0.023	1.117 \pm 0.016**	71.06	1.158 \pm 0.008**	69.29	17.35	0.0001
3 hr	1.458 \pm 0.020	1.092 \pm 0.008**	84.15	1.033 \pm 0.010**	98.74	273	<0.0001
4 hr	1.325 \pm 0.051	0.983 \pm 0.021**	98.32	1.067 \pm 0.016**	91.60	28.44	<0.0001
5 hr	1.200 \pm 0.022	0.975 \pm 0.021**	95.54	1.033 \pm 0.016**	97.86	33.09	<0.0001

Post hoc analysis by Dunnett's Test: * $p < 0.05$, ** $p < 0.01$

Table 2: Effect of telmisartan treatment on carrageenan induced paw edema when compared with aspirin group.

Time after carrageenan injection	Control	Aspirin	Percentage inhibition	Telmisartan	Percentage inhibition	ANOVA result	
	Paw edema in ml (Mean \pm SEM)	Paw edema in ml (Mean \pm SEM)		Paw edema in ml (Mean \pm SEM)		F _{2,15}	p value
½ hr	0.991 \pm 0.041	1.108 \pm 0.020	30.24	1.233 \pm 0.024*	24.77	15.93	0.0002
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5 hr	1.200 \pm 0.022	0.975 \pm 0.021	95.54	1.033 \pm 0.016	97.86	33.09	<0.0001

Post hoc analysis by Bonferroni's Test: * $p < 0.05$

Recently, various in vitro studies have suggested that ARBs may possess anti-inflammatory activity. TNF- α and angiotensin II play important roles in atherogenesis through enhancement of vascular inflammation.¹³ ARBs have been found to decrease TNF- α and IL-6 levels in a dose dependent manner.¹⁴ Telmisartan has been found to inhibit TNF- α induced IL-6 expression at the transcriptional level through the activation of peroxisome proliferator-activated receptor- γ (PPAR- γ). The transrepression effects of telmisartan on NF- κ B and C/EBP β activity are responsible for the IL-6

suppression.¹⁵ Also telmisartan has been shown to modulate pleiotropically, TNF- α induced vascular cell adhesion molecule-1 (VCAM-1) expression and oxidative damage in vascular endothelium, possibly by acting as a hydroxyl radical scavenger. These anti-inflammatory and antioxidant properties may contribute to the therapeutic effect.¹⁶ This suggests that telmisartan may attenuate the inflammatory process induced by TNF- α in addition to the blockade of angiotensin II type 1 receptor. ARBs have been found to antagonize the effect of angiotensin by blockade of angiotensin II binding to

the macrophage receptors and therefore may also exert anti-inflammatory effects.¹⁷ In our study also telmisartan showed significant anti-inflammatory activity which is comparable with that of aspirin. There is further need to do the study of inflammatory markers in hypertensive patients who are on telmisartan therapy.

CONCLUSION

Present study clearly showed anti-inflammatory effect of telmisartan in acute model of inflammation in male Wistar rats. This anti-inflammatory effect of telmisartan beyond its class effects as angiotensin II receptor blocker might make this compound a very powerful inhibitor of atherosclerosis. This study shows that in addition to antihypertensive property, telmisartan may also possess anti-inflammatory properties that could be of additional benefit in the treatment of atherosclerosis and hypertension and their complications like coronary heart diseases, congestive heart failure, ischemic and haemorrhagic stroke, renal failure and peripheral arterial diseases.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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