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Short Communication

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ANTI INFLAMMATORY ACTIVITY OF ANGIOTENSIN ANTAGONISTS

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ABSTRACT

The angiotensin antagonists like Losartan, Irbesartan and Valsartan were evaluated for its action on inflammation using plethysmograph method i.e. carageenin induced paw edema model. It was reported that angiotensin II generated from plasma had various effects including inflammation. It stimulates the release of pro inflammatory cytokines, activates Nuclear factor kappa B (NF –kB), increases oxidant stress, suppress nitric oxide synthesis and behave as an inflammatory molecule. It also induces inflammation through the production of reactive oxygen species, adhesion molecules, and inflammatory cytokines such as chemo attractant protein-1(MCP-1).our study showed that the tested drugs of angiotensin antagonists at a dose of 10mg/Kg possessed significant anti inflammatory activity. The result was very comparable with standard drug Diclofenac sodium at a dose of 20mg/kg.

Keywords: Angiotensin Antagonist, Losartan, Irbesartan and Valsartan.

INTRODUCTION

Angiotensin II antagonists are class of drugs acts in the axis of Renin Angiotensin and Aldosterone and used for the treatment of hypertension. Angiotensin II is an octapeptide generated in plasma from a precursor plasma α_2 globulin with variety of effects including alleviating vessel inflammation.[1] It stimulates the release of pro inflammatory cytokines, activates Nuclear factor kappa B (NF –kB), increases oxidant stress, suppress nitric oxide synthesis and behave as an inflammatory molecule.[2] It also induces inflammation through the production of reactive oxygen species, adhesion molecules, and inflammatory cytokines such as chemo attractant protein-1 (MCP-1). MCP-1 act as a central mediator of inflammatory response in hypertensive vascular disease.[3] Cyclooxygenase-2(COX -2) synthesis and release is also induced by Angiotensin II.[4] The aim of the present study was to evaluate the effect of Angiotensin II antagonists like Losartan, Irbesartan and Valsartan on inflammation and their activity comparatively.

MATERIALS AND METHODS

Albino rats of both sex, adult ones (around 16 months old and weighing 150-200g) were selected and used. Animals were procured from the disease free small animal house. They were acclimatized to the laboratory to the laboratory conditions for 5 days. They were kept in sufficient poly propylene cages under controlled temperature and humidity. The animals had free access to food and water and were housed under standard light-dark cycle (12hr each). All the experiments were carried out during day time from 0900 to 1600hr.

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LOSARTAN POTASSIUM-USP (Simlan laboratories Ltd., Mumbai), IRBESARTAN-USP (Hetero labs Ltd., Andra Pradesh) VALSARTAN - USP (Hetero labs Ltd., Andra Pradesh), DICLOFENAC SODIUM (Diclomax) 25mg/ml-torrent pharmaceuticals, Thane. All the drugs were injected intraperitoneally; volume of injection was made 1ml/100g of body weight of the rat. All the drugs were dissolved in distilled water except Valsartan (made suspension with 0.5% CMC) and the anti inflammatory activity was evaluated using the apparatus Plethysmograph.

Plethysmograph method

Anti inflammatory activity was evaluated on the basis of the inhibition of the carageenin induced hind paw oedema. Animals were divided into five groups, each group composed of five animals. One group served as vehicle control, one group served as positive control and the other groups are served as test group.

Group I – vehicle control given with 0.5% CMC (10ml/Kg IP)
Group II – positive control given with Diclofenac sodium (20 mg/Kg IP)
Group III – test group given with Losartan (10 mg/Kg IP)
Group IV – test group given with Irbesartan (10 mg/Kg IP)
Group V – test group given with Valsartan (10 mg/Kg IP)

All the groups were injected with their control drug and test drug respectively. After 30 min of drug administration all the animals were challenged with 0.1 ml of 1%w/v of carageenin suspension in water in the plantar region of the left hind paw. The right paw served as reference non-inflammated paw. The volumes of paw were measured at 0, 15, 30, 60, 90 and 120 min (in ml) after the induction of

inflammation using the apparatus plethysmograph. Percentage inhibition were obtained for each group using the following ratio,

$$\%\ inhibition = \frac{(V_t - V_0)_{control} - (V_t - V_0)_{treated}}{(V_t - V_0)_{control}} \times 100$$

Where V_t is the average volumes for each group and V_0 is the average volume obtained for each group before any treatment.[5-7] (Table **1**)

TABLE 1. ANTI-INFLAMMATORY ACTIVITY OF ANGIOTENSIN ANTAGONISTS (Plethysmograph method)

Group	Treatment	Dose (IP)	Difference in paw volume at 120 mins	% inhibition at 120 mins
Group I	0.5% CMC	10 ml/Kg	0.09	-
Group II	Diclofenac Sodium	20mg/kg	0.01	88.9%
Group III	Losartan Potassium	10 mg/Kg	0.02	77.8%
Group IV	Irbesartan	10 mg/Kg	0.02	77.8%
Group V	Valsartan	10 mg/Kg	0.02	77.8%

RESULTS

Standard drug Diclofenac sodium (20mg/kg) shows significant reduction in paw oedema at 120 min. Losartan at a dose of 10mg/kg shows $p<0.001$ at 120min. Irbesartan (10mg/kg) shows $p<0.01$ and Valsartan (10mg/kg) shows $p<0.1$, when compared to control. The % inhibition of increase in paw volume at 120 min was 88.9% for Diclofenac (100mg/kg). And for test drugs Losartan, Irbesartan and Valsartan (10mg/kg) the % inhibition of increase in paw volume at 120 min were found to be 77.8%.

DISCUSSION

The tested drugs showed significant anti inflammatory activity. Losartan 10 mg/kg possessed very significant result which is comparable to vehicle control whereas Irbesartan and Valsartan at 10 mg/kg possessed significant activity comparable to vehicle control. It has been reported that various mediators are released by carageenin in rat paw. The initial phase is attributed to the release of histamine and 5-hydroxy tryptamine (5-HT). A second phase is mediated by kinins first few our after injection and finally more pronounced is the third phase ,the mediator suspected to be prostaglandins and PG like substances in 2 -3 hours.[8, 9] Angiotensin II is known to promote oxidative stress and to be proinflammatory. Leukocytes are known to express angiotensin II receptors.[10] Thus, angiotensin antagonists, which blocks angiotensin II, may be expected to inhibit inflammation and oxidative stress and, thus, the progression of atherosclerosis. The blockade of the AT_1 receptor by Valsartan may allow the activation of the AT_2 receptor by angiotensin II.[11] This may, in turn, facilitate nitric oxide generation[12] that may contribute to an anti-inflammatory effect. Ang II receptor antagonists could be benefit in atherosclerosis, diabetes mellitus, hypertension, myocardial infarction, Alzheimer's disease, dementia and schizophrenia, in which inflammation plays a significant role.[13] The mechanism may be suppression of phase 1 and phase 2 or may be due to prevention of phase 3. If Angiotensin converting enzyme inhibitors are used it prevents the formation of Ang II by renal pathway only. Non renal pathway may also enable the formation of Ang II by chymase. If Angiotensin II antagonists are used it provide significant anti inflammatory activity by completing blocking the AT_1 receptor and thus prevents action of Ang II on AT_1 receptor.

CONCLUSION

From the present finding it was concluded that angiotenin antagonists like Losartan, Irbesartan and Valsartan possessed significant anti-inflammatory activity in rat model. Further clinical studies have to be carried out to establish its action in hypertensive patients though it acts in the axis of Renin Angiotensin and Aldosterone and used as anti hypertensive agent.

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