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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 Zeitlin apparatus 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 antagonists, inflammation, carageenin, Zeitlin apparatus

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INTRODUCTION

Angiotensin II (Ang II) is an octapeptide generated in plasma from a precursor plasma α2 globulin with variety of effects including alleviating vessel inflammation [1]. Ang II induces vascular inflammatory responses by activating macrophages and increasing their ability to attach to and invade into the vascular cells [2]. Ang II 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].COX -2 synthesis and release is also induced by Angiotensin II (A II) [4]. The aim of our study was to evaluate the anti inflammatory activity of Angiotensin II (A II) antagonists Losartan, Irbesartan and Valsartan and also wants to discuss the action of drugs on inflammation and their percentage 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.

Losartan potassium-USP (Simlan laboratories ltd., Mumbai), Irbesartan-USP(Hetero labs ltd., Andra Pradesh) valsartan - USP(Hetero labs ltd., Andra Pradesh), Diclomax (Diclofenac sodium 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 Zeitlin's method.

Zeitlin's method

Zeitlin's apparatus is a simple apparatus used to measure paw edema thickness in mm. Anti inflammatory activity was evaluated on the basis of the inhibition of the carageenin induced hind paw edema. Animals were divided into six 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 (10 ml/Kg i.p.)
Group II – positive control given with Diclofenac sodium (20 mg/Kg i.p.)
Group III – test group given with Losartan Potassium (10 mg/Kg i.p.)
Group IV – test group given with Irbesartan (10 mg/Kg i.p.)
Group V – test group given with Valsartan (10 mg/Kg i.p.)

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 thicknesses of the paw oedema were measured at 0,30,60,90 and 120 min (in cm) after the induction of inflammation using the apparatus Zeitlin.

Percentage inhibition were obtained for each group using the following ratio,

(V t-Vo)CONTROL - (V t-Vo) treated / (V t-Vo) CONTROL X100

Where V t is the average volumes for each group and V0 is the average volume obtained for each group before any treatment. [5-10]

RESULTS

Figure-1 shows the result of our findings in percentage of inhibition of paw edema at 120 min. The percentage inhibition of increase in paw thickness at 120 min is 92.3 for Diclofenac (20mg/kg) and for Losartan (10mg/kg), Irbesartan (10mg/kg) and Valsartan (10mg/kg) were 96.9, 93.8 and 95.4 respectively. Losartan (10mg/kg), Irbesartan (10mg/kg) and Valsartan (10mg/kg) possessed very significant anti inflammatory activity. The % inhibitions of increase in paw thickness at 120 min of all the three tested drugs were more than that of standard drug.

DISCUSSIONS

The anti inflammatory activity of the angiotensin antagonists Losartan, Irbesartan and Valsartan were evaluated using Zeitlin's apparatus using carageenin induced rat paw edema model.The tested drugs show 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 1st 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[11,12]. Angiotensin II is known to promote oxidative stress and to be proinflammatory. Leukocytes are known to express angiotensin II receptors [13]. 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 AT1 receptor by Valsartan may allow the activation of the AT2 receptor by angiotensin II [14]. This may, in turn, facilitate nitric oxide generation [15] 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 [16]. Ang II acts as an inflammatory and pro inflammatory factor, its blockage may provide beneficial effects in prevention and control of inflammation. The above results itself indicates that ARB may prevent inflammation and renal injury, vascular injury and progression of renal disease. The mechanism may be suppression of phase 1 and phase 2 or may be due to prevention of phase 3. If ACEI 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 ARB are used it

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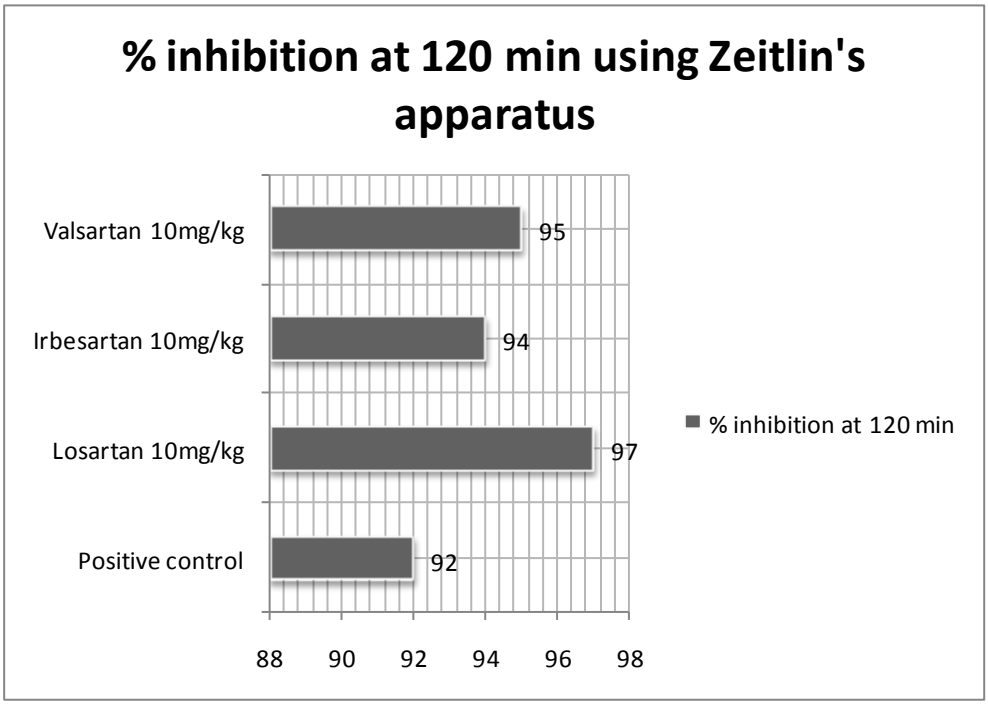
provide significant anti inflammatory activity by completing blocking the AT1 receptor and thus prevents action of Ang II on AT1 receptor.

Fig-1: anti-inflammatory activity of angiotensin antagonists



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