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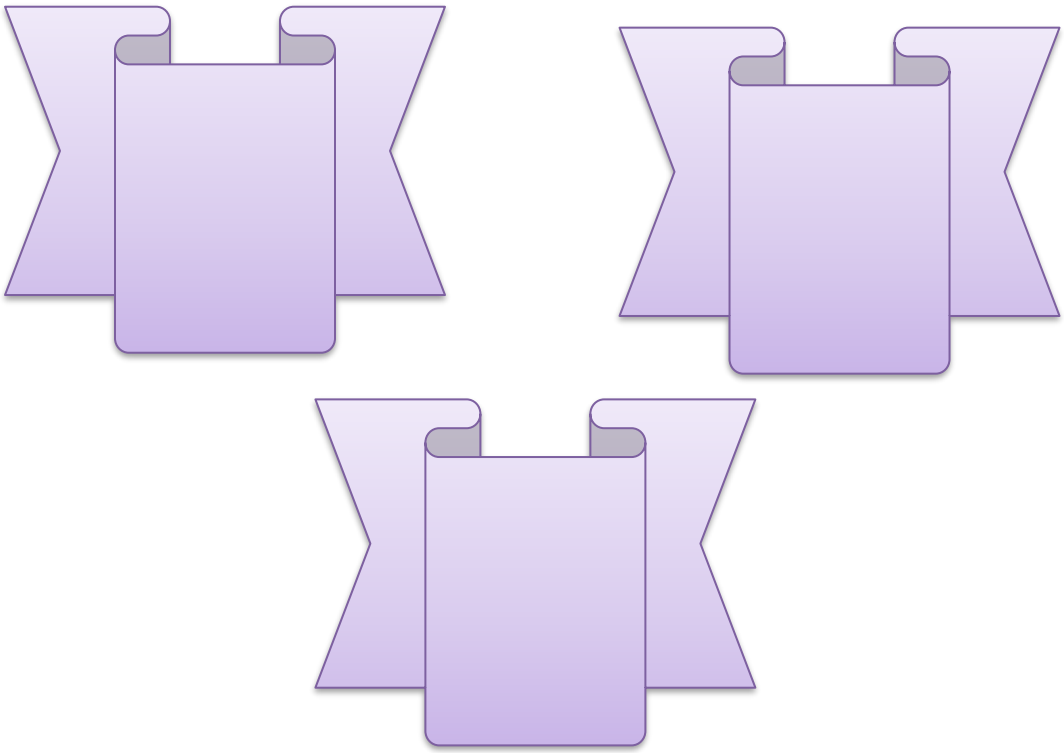

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Original Article

Assessment of Lisinopril Anti-Inflammatory Effect in Albino Rats

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ABSTRACT

Background: Renin-angiotensin-aldosterone system produces the hormone angiotensin II (Ang II). Vascular tension is regulated, pro-inflammatory cytokines are released, nuclear factor kappa B is activated, oxidative stress is increased, and angiotensin-II serves as an inflammatory mediator. Angiotensin-converted enzymes (ACE) inhibitor lisinopril works by preventing ACE, which lowers angiotensinogen II production. The purpose of the current study was to assess lisinopril's anti-inflammatory effect in albino rats

Aim of the work: To assess Lisinopril's anti-inflammatory effect in albino rats at different hour in carrageenan induced paw oedema using Vernier caliper as well as to evaluate the mean granuloma weight in Lisinopril and diclophenac potassium as compared to control group.

Materials and Methods: From a centralized animals' facility, 21 Wistar albino rats of both sexes, weighed between 150 and 200 g, were randomly chosen and categorized into three categories. The experimental group obtained lisinopril (1.8 mg/kg) orally for a period of six days, whereas the typical group got diclophenac potassium 5 mg/kg and the control group obtained standard saline 25 ml/kg. The rats underwent an experiment of cotton pellets-induced granuloma and carrageenan-induced paws oedema.

Results: As contrasted with controls and in cases of cotton pellets and carrageenan-induced granuloma, Lisinopril dramatically reduced the average paws oedema. Contrary to the control, Lisinopril lowered the average granuloma weight.

Conclusion: When administered orally to albino rats for a period of six days in a row, Lisinopril shown anti-inflammatory properties in an experiment for granuloma and paws oedema caused by cotton pellets and carrageenan.

Keywords: Reactive Oxygen Species, Nuclear Factor-kappa B, Cotton Pellet, Carrageenan, Angiotensin II.

INTRODUCTION

The body's response to numerous assaults, including infections, traumatic events, and allergies, is inflammation. Because of exogenous/endogenous stimuli, vascularized connective tissues undergo a complicated response [1]. Essentially, inflammation is a protective reaction, and its main objective is to clear the organism of both the original source of cellular harm and its effects [2]. Inflammation and pain are frequently linked. A typical reaction to any unpleasant stimuli that endangers the host is inflammatory processes, which can range from a localized to a generalized responses [3]. A number of agents of mediation, including prostaglandins, leuko-trienes, and platelets activating variables, as well as substances released from tissues and migratory cells are all involved in the intricate process [4]. Following the production of pro-inflammatory cytokines such tumors necrosis factors (TNF-α), IL-β, IL-6, and IL-8, tissues injury results in a cascade of inflammatory responses [5]. Prostaglandins like PGE1 and PGE2 are produced in greater amounts by damaged cells in inflammatory diseases like rheumatoid arthritis, which also increases local blood flows and amplifies the effects of agents like bradykinin which enhance vascular permeability [6].

One of the main byproducts of the renin-angiotensin-aldosterone systems (RAAS) is angiotensin II (Ang II). AT1 and AT2 terminals allow Ang II to trigger a physiological responses [7]. The majority of Ang II's effects are mediated via AT1 type. Ang II works and aids in the recruitments of inflammatory cells [8]. Monocyte chemoattractant protein-1 (MCP-1), macrophage colony stimulating factor, endothelium selectin, intercellular adherence molecule-1, vascular cells adhesions molecules-1 (VCAM-1), inducible nitric oxides synthases, and cyclooxygenase-2 are other genes whose transcription is induced by Ang II [9]. In mice lacking AT1, MCP-1 levels were reduced. Nuclear regulator kappa B (NF-B) is activated by angiotensin-II, which also modulates vascular tones, promotes the production of pro-inflammatory cytokines, enhances oxidative stress, and serves as inflammatory molecules [10]. The synthesis of proinflammatory genes, including nitric oxides synthesis, angiotensino-gen, cells adhesion proteins, and other genes related to inflammatory processes, is significantly regulated by NFκβ [11, 12]. Infiltration of inflammatory cells is caused by tissue NF κB concentrations. Production of the adhesion molecules MCP-1 and VCAM-1 was linked with increased tissues NF κB levels. Ang II boosts the DNA bound function in human neutrophils and increases the generation of reactive oxygen species (ROS) via stimulating NADPH oxidases [13, 14]. The gene expression of pro-inflammatory cytokines, adhesion molecule, and NADPH mediators is increased as a result of ROS activating the NFκβ. TNF-α, interleukin 6 (IL-6), and chemokines monocytes chemo attractant protein 1 are all produced in greater amounts and concentrations when exposed to Ang II. PPAR-γ and PPAR-α are suppressed by Ang II [15]. Elevated levels of Ang II are caused by increased angiotensin converting enzyme (ACE) activities. Nitric acid concentrations dropped and ROS production was boosted as a result of NADPH being stimulated by substantial quantities of Ang II [16].

Ang II's role in recruiting of inflammatory cells is its function. Investigations in numerous models have demonstrated that ACE inhibitors limit the number of invading cells via a variety of methods. As a result, Ang II is recognized as real cytokines that controls the inflammatory responses [17].

Lisinopril, an ACE inhibitor, enhances bradykinins and (met) enkaphalin levels while decreasing angiotensinogen II function. Management for heart failure, hypertension, nephropathy due to diabetes, non-diabetic kidney disorders, and post-myocardial infarction frequently involves the administration of ACE-inhibiting medications [18]. There are numerous pleotrophic pharmaceutical reactions that Lisinopril is believed to have. Numerous studies demonstrate the strong connection between localized vascular inflammation and RAAS activation, which results in the generation of Ang II [6, 19, 20]. There are various extra advantages of Lisinopril in addition to the blood pressure-lowering properties of anti-hyper-tensive medications.

Thus, the goal of the current investigation is to determine whether Lisinopril has any potential to reduce inflammation in albino rats.

Hypothesis: Theoretically, Lisinopril could regulate its anti-inflammatory effects by inhibiting the function of antigenic factor II (angiotensin II).

PATIENTS AND METHODS

Mature Wistar strains albino rats in either sex, weighed 150–200 g, and maturing at 3–4 months were chosen from the animals' center. Given ideal dwellings, temperatures, ventilations, and dietary circumstances, the rats were inbred in the animal house, Faculty of Medicine for Girls, Al-Azhar University, Egypt. Within standard circumstances, rats were kept in stainless cages at a ratio of two to three. They were maintained under a 12-hour dark/light cycles at a fixed temperature of 26 ± 2 °C and relative humid of 30–70%. The rats were given a regular food and unlimited access to water. Before the experiment, the animals were given a 7-day acclimatization period to the laboratory environment before being divided into the treatment group. According to **Barnes and Karin** [21], medication dosages which established on human's daily intake were adapted to those for animals [21].

Drugs and Chemicals

Diclophenac potassium (Cataflam, Novartis Egypt) lisinopril (Zesteril, Astra Zeneca Egypt), and carrageenan (TCI Chemicals, India). Seven rats (n = 7) were placed in each of the three categories containing rats (controls, standard, and experimental groups).

1. Group-1 (experimental): Lisinopril 1.8 mg/kg.
2. Group-2 (Standard): Diclophenac 5 mg/kg.
3. Group-3 (Control): Normal saline 25 ml/kg.

Rats Paw oedema caused by Carrageenan [12-14]:

Through injection of 0.1 ml of 1% carrageenan into the sub plantar tissues of the right hind paws in every animal in every group one hour after the medication was administered, paw oedema was generated. The size of the correct hind paw can be assessed both immediately (0-h-volume) and after 4 hours. Each group of rats given medication and the control group's average paw oedema were reported. When compared to the carrageenan control group, the proportion of oedema that was inhibited in the mice receiving Lisinopril treatment was used to determine the anti-inflammatory effects.

Utilizing the following equation, the percentages (%) inhibition of oedema is computed:

$$\text{Percentage inhibition} = \frac{V_C - V_t}{V_t} \times 100$$

Vc stands for paw volumes for controls. Vt is the experimental group drug's paw volumes.

Granulomas Caused by Cotton Wool Pellets [15, 16]:

The autoclave sterilized 10 ± 1 mg of cotton pellets at 120 °C for 30 minutes. With light ether anesthesia, four incisions were performed in the axilla and groynes 1 hour following the medication was administered on the first day. Two pellets on each side of the ventral area were subcutaneously inserted. It was filled with cotton woolen pellets and repaired with a dark silk suture. Subsequently, medication will be given orally once day for six straight days. The rats were gently sedated with ether on the eighth day, and the pellets and granuloma tissues were extracted. The dried pellets were weighed to estimate the constant dry weight after drying in an incubation chamber at 60 °C for 18 hours starting with the wet pellets, which were assessed to calculate the wet weights.

Exudate quantity (mg) = pellet's wet weight multiplied by its constant dry measurement.

Granulation tissues development (10 mg) = constant dry weight - weight of the cotton pellet (10 mg).

Ethical considerations

Upon receiving permission from the institutional ethical committee, the research project was carried out.

Statistical analysis

Following independent sample t-tests comparing the two categories, the findings were evaluated by computing the means, standard deviations, t-test, and analysis of variance (ANOVA) at various time intervals within a single category. Multiple comparative analyses were made using one-way ANOVA, and then post-hoc Tukey's test was applied to determine whether there was a statistically significant difference between the groups. For the statistical evaluation, IBM Corporation and Other(s) 1989,

2012 software called IBM SPSS statistics was employed. Significance was defined at P< 0.05.

RESULTS

Lisinopril and diclophenac's effects on carrageenan-induced paws oedema are shown in Table 1 employing vernier calipers. 1.8 mg/kg of lisinopril reduced carrageenan-induced paws oedema with a percentage reduction of 43.74%, whereas 5 mg/kg of diclophenac resulted in 63.34% as opposed to controls [table 1].

Lisinopril and diclophenac's impact on a model of granuloma caused by cotton pellets is shown in table 2 in comparison to the controls. Lisinopril's average weight of granuloma is 80.542 ± 3.31 mg lower than the controls, while the diclophenac group revealed 58.48±2.76 mg lower than the controls [table 2].

Table [1]: Comparing the effects of lisinopril and diclophenac to the controls at various times in carrageenan-induced paws oedema with a vernier caliper

Groups	Variation in paws oedema			Dosages
	Mean paws oedema (cm) at 0 h	Mean paws oedema (cm) at 4 h	Difference in mean paws oedema (cm)	
Lisinopril	1.65±0.34	7.64±0.68	5.99 ± 0.34*	1.8 mg/kg
diclophenac	1.47±0.04	5.19±0.26	3.72 ± 0.22	5 mg/kg
Control	1.35±0.35	12.65±0.55	11.3 ± 0.17	25 ml/kg

SD = Standard deviations. The outcomes are shown as mean ± SD, with n equal to 6 animals, and *P< 0.05.

Table [2]: Compares the control group's average granuloma weight to that of the lisinopril and diclophenac groups

Groups	Means weight of granuloma (mg) (mean ± SD)	Dosage
Lisinopril	80.542±3.31*	1.8 mg/kg
Diclophenac	58.48±2.76	5 mg/kg
Controls	146.93±3.29	25 ml/kg

SD = Standard deviations. The outcomes are shown as mean ± SD, with n equal to 6 animals, and *P< 0.05.

DISCUSSION

Since Carrageenan is known to trigger inflammation, it is utilized to test the effectiveness of nonsteroidal anti-inflammatory drugs. According to the current study, the difference between the Lisinopril sample's proportion suppression of paws oedema and the controls is significant. Lisinopril and diclophenac both show an overall reduction in the production of granulation tissues in comparison with controls. As contrasted to the controls, there is a statistically substantial reduction in the average granuloma weight of Lisinopril (P< 0.05). These findings agreed with another study which stated that Lisinopril has been shown to possess anti-inflammatory properties by suppressing the generation of pro-inflammatory cytokines such TNF-α in an investigation that tested the drug's hepatoprotective benefits against liver ischemia and injury caused by reperfusion in rats. Rats exposed to hepatocellular ischemia/reperfusions damage were protected by Lisinopril. The beneficial effect results from a decrease in the level of lipids peroxidation caused by oxidative stress and an increase in the accessibility of nitric oxides [22].

Acute inflammation can be screened using an animal model of paws oedema caused by carrageenan. Paws oedema builds up in two phases. The initial stage starts right away after the carrageenan injection and fades within one hour. Histamine and 5HT are the transmitters of inflammation in the initial stage. The following stage, which starts at the conclusion of the first hour and lasts until the third, is associated to the release of prostaglandins. A different investigation discovered that Lisinopril inhibits humans peripheral blood mononuclear cells' ability to produce interleukin-12 and interferon γ, which contributes to the drug's immunomodulatory influence and has a positive impact on inflammatory or autoimmune diseases that involve interleukin 12 [23].

As a result, the aforementioned results of our investigation show that Lisinopril has anti-inflammatory effects in albino rats. The

inflammatory properties of Lisinopril are evaluated using rat paw oedema caused by carrageenan and the cotton pellet generated granuloma technique.

Limitation of the study

Our research is restricted to ACE blockade. Additional investigations could examine various approaches by simultaneously acting on the ACE and AT1 receptors in order to strictly analyze the impact of RAAS blockade on inflammation. The study didn't provide sufficient data to support the effects of Lisinopril on pro-inflammatory cytokine signaling. The pro-inflammatory cytokines (especially MCP-1, IL-6, IL-12 and TNFα) should be measured in further studies.

Conclusion

As opposed to the controls, the experimental medication Lisinopril significantly reduced the average paws oedema and average granuloma weight. The idea indicated above is supported by the anti-inflammatory effects. Lisinopril, then, shown anti-inflammatory effect in albino rats by reducing Ang II, which in consequence reduces ROS and NF κB.

Conflict of Interest and Financial Disclosure: None.

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