STUDY OF THE EFFECT OF VALSARTAN ON ADJUVANT-INDUCED ARTHRITIS IN ALBINO RATS

By
Somaia A. Mokbel,

From
department of clinical pharmacolog Mansoura
Faculty of medicine, Egypt.

ABSTRACT

The present work was conducted to investigate the influence of valsartan (a highly selective antagonist on angiotensin II type-1 receptors (AT₁-R blocker) in rats with experimentally - induced inflammation in the form of collagen II- induced adjuvant arthritis.

Thirty two, healthy male albino rats were used throughout this study. Rats were divided into 4 equal groups, each comprised 8 rats. The first group consisted of non-arthritic animals (normal control). This group received intra-gastrically normal saline (the vehicle used to dissolve drugs), for 2 weeks. The second group consisted of arthritic rats that received intra-gastrically saline for 2 weeks & served as an arthritic control. The

third group consisted of arthritic rats treated with indomethacin (non-steroidal anti-inflammatory drug, NSAID) in a daily dose of 1.3 mg/kg for the same previously mentioned duration & by the same route of administration. The fourth group consisted of arthritic rats treated with a daily intra-gastric dose of valsartan (20 mg/kg) for 2 weeks.

It was found that administration of collagen II & complete freund's adjuvant to rats produced a significant arthritic changes as assessed by paw oedema thickness, analgesmetric pressure & C-reactive protein (CRP). Furthermore arthritic rats showed a significant increase in fibronectin (fn) & malondialdehyde (MDA) ; an indicator of free oxygen radical. Daily in-

tra-gastric administration of either indomethacin or valsartan induced a significant decrease in the paw oedema thickness, CRP, MDA as well as induced increase in analgesmetric pressure tolerance, these results suggested that valsartan has a potential anti-inflammatory effect in collagen II induced adjuvant arthritis (this is in addition to its known anti-hypertensive effect).

INTRODUCTION

Angiotensin II (Ang II) has emerged as an important growth factor for vascular, cardiac & renal cells. Depending on the specific cell type & presence of other growth factors, Ang II induces hypertrophy (increase cell size, cell protein & mRNA content without DNA replication), proliferation (replication of DNA with subsequent successful division of cells), apoptosis (programmed cell death) or differentiation. Such Ang II-mediated modulation of growth process may underlie various pathophysiological processes such as atherosclerosis, vascular & cardiac remodeling, and progression of chronic renal disease (1). It is widely accepted that Ang II-1 receptors

(AT₁R) account for the majority of cardiovascular effects evoked by Ang II, such as contraction / pressor activity and growth-promoting effects leading to cardiac and vascular hypertrophy. However, there has been increasing evidence indicating that Ang II type-2 receptors (AT₂R) may exert pharmacological action per se as well as play a role in pathophysiological processes. In addition Ang II increases expression & production of Fn & collagen type 1, chondroitin / dermatan sulphates & proteoglycans (2). In particular it has been suggested that AT₂R may exert a beneficial vasodilator & anti-growth effects, as well as contribute to the efficacy of AT₁R antagonists (2).

Rheumatoid arthritis (RA) is a common inflammatory autoimmune disorder with a widely varying degree of severity (3). Non-steroidal anti-inflammatory drugs have become an integral part of the rheumatological disorders therapy (4). Patients who are at risk of adverse effects of these drugs are rapidly exposed to well known gastro-intestinal & renal toxicity (5).

Valsartan **LOSARTAN**

Losartan monopotassium salt

Losartan carboxy acid HCl

Valsartan is a highly selective, orally available antagonist of AT_1 receptors. Valsartan is a non-heterocyclic antagonist in which the imidazole of losartan has been replaced with an acylated amino-acid (see the above figure). Valsartan doesn't need to be metabolized to be effective, and it is excreted both by the bile (70%) & the kidney (30%). There is only one inactive metabolite for Valsartan. Food decreased drug absorption by 40% like losartan, valsartan lacks affinity for adrenergic, histamine, substance P, muscarinic & serotonin receptors (6). It has been

suggested that Valsartan had beneficial effects in patients with hypertensive end-organ damage such as renal disease and left ventricular hypertrophy. Furthermore, the drug is evaluated for its efficacy in heart failure and patients with myocardial infarction (7).

Siragy et al., (8) reported that AT_1R blockade with Valsartan induced a potential anti-inflammatory effect through prevention of the increase in tumor necrosis factor alpha in diabetic rats. This finding of Valsartan is new in addition to its known anti-hypertensive effects

Stoboda et al., (9) reported that type II collagen -induced adjuvant arthritis in rats is an experimental model of RA that simulating RA in humans.

The aim of the present work is to study the effect of valsartan in collagen II - induced adjuvant arthritis in rats to declare the above finding in diabetic rats & to study its mechanism. Such possible finding of exerting anti-inflammatory action may be of future benefit to many patients suffering RA in association with cardiovascular diseases (e.g. hypertension) & in need for the use of valsartan to control such problems.

MATERIAL AND METHODS

Drugs used :

- Diovan tab. (Valsartan, 160 mg), supplied by Novartis Co.
- Indocid tab. (indomethacin, 25 mg) supplied by Cairo Co.

Animals used :

Thirty two, healthy, male albino rats aged 3-4 months & weighing 150-200 grams were used throughout the experiment. They were put under similar housing conditions, kept on diet of milk & bread. They liberally supplied with water.

Animals grouping :

The experiment included 4 equal animal groups, each consisting of 8 rats. They were divided as the following :

- **Group (1) :** non-arthritic control rats treated with intra-gastric saline for 2 weeks (normal control).
- **Group (2) :** arthritic rats treated with intra-gastric saline (the vehicle) & Served as non-treated arthritic control.
- **Group (3) :** arthritic rats treated with indomethacin in a single daily intra-gastric dose of 1.3 mg/kg for 2 weeks (10).
- **Group (4) :** consisted of arthritic rats treated with valsartan in a daily dose of 20 mg/kg/ day by the same previously mentioned route & for the same duration (11).

Adjuvant induced arthritis was produced in albino rats according to Eckhardt (12). Inflammatory & anti-inflammatory effects (pain tolerance & oedema development and suppression) were assessed by using analgesymeter (Fig. 4) & paw oedema tests (Fig. 3) respectively (13,14). CRP was measured by using latex particles agglutination (15). CRP may be the parameter of choice among acute phase proteins that reflects inflamma-

tion (16). Lipid peroxidation was assessed spectrophotometrically by measuring (MDA) using the thiobarbituric acid method (17). Estimation of (Fn) by single radial immuno-diffusion plates. These plates were obtained from Behring werke, AG, Marburg, w. Germany (18). In addition to assessment of serum creatinine according to seeling & wust (19).

STATISTICAL ANALYSIS

Student "t" test according to Pipkins (20), was used to determine the degree of significance between samples. The difference was regarded as significant when $P =$ or < 0.05 .

RESULTS

Inducation of collagen II – adjuvant arthritis produced a significant decrease in analgesmetric pressure tolerance, significant increase in paw

oedema thickness as well as a significant increase in CRP & Fn. (table 1).

Furthermore, arthritic rats showed increase in free oxygen radical as indicated by MDA (Table 2).

Daily administration of either valsartan (20 mg/kg/day) or indomethacin (1.3 mg/kg/day), for 2 weeks produced a significant increase in analgesmetric pressure tolerated by arthritic rats. In addition these rats showed a significant decrease in paw oedema thickness as well as decrease in CRP & MDA, but without changes in serum creatinine. As regards, Fn, there was no significant changes produced by indomethacin.. In contrast administration of valsartan to arthritic rats produced significant decrease in Fn. These findings are in comparison to arthritic non-treated control rats; table (1 & 2) & Fig. (1,2,5,6 & 7).

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Table (1): Inflammatory reaction as assessed by analgesmetry, paw oedema thickness, CRP & fn.levels in arthritic & non-arthritic rats (Mean±SE):

Group, n= 8	Analgesmetric pressure (grams)		Paw oedema thickness (mm)		Fibronectin fn. (mg/L)	c-reactive protein CRP, (mg/L)
	Right paw (R)	Left paw (L)	Right paw (R)	Left paw (L)		
Non-arthritic control rats	210±8.1	201±3.3	23±0.12	24.6±0.22	21.8±1.88	<6.ng/L no agglutination
Arthritic control rats	130±10.5	115±1.3	40.2±0.19	40.8±0.19	36.4±1.09	85.5±6.09
P	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

SE= Standard error.

P = Test of significance between the test group (arthritic rats) & non-arthritic control.

Table (2): Serum Malondialdehyde (MDA) & serum creatinine in arthritic & non-arthritic control rats (mean ±SE):

Group n=8	Malondialdehyde (MDA) (nmol/L)	Serum creatinine (mg/dL)
Non-arthritic control rats	0.12±0.007	0.98±0.02
Arthritic control rats	0.408±0.02	0.99±0.03
P	P < 0.001	P > 0.05 (NS)

SE= Standard error.

NS= non significant

p = Test of significance between non-arthritic & arthritic control group

Fig (1) : Effect of either indomethacin or valsartan treatment on analgesia (gms).

Fig (2) : Effect of either indomethacin or valsartan treatment on paw oedema thickness (cm).

Fig (3) : Paw oedema meter.

Fig (4) : Analgesymeter.

Fig (5) : Fibronectin immunodiffusion plate of the standard and arthritic control No 1,2,3 = standard, from 4-12, arthritic control.

Fig (6) : Fibronectin immunodiffusion plate of arthritic rats treated with indomethacin.

Fig. (7) : Fibronectin immunodiffusion plate of arthritic rats treated with valsartan.

DISCUSSION

Inflammatory collagen polyarthritis developed in rats within 45 days after intradermal injection of type II collagen in complete freund's adjuvant (CFA) as evidenced by a significant decrease in pain threshold & increase in mean hind paw oedema accompanied by increase in serum CRP, fibrinectin & free oxygen radical. These results are in accord with that obtained by (21) as they reported that immunization with type II collagen in (CFA) induced polyarthritis & immunity. The immunological mechanisms involved in the pathogenesis of type II collagen induced arthritis was initially suggested by dense polymorphnuclear (PMN) infiltration of synovium of arthritic joint (22&23). Stoboda et al., (9) had been reported that type II collagen induced arthritis in rats considered as an experimental model of rheumatoid arthritis occurring in humans. In this model it was speculated that anti-type II collagen antibodies contributed to the incidence of arthritis (24).

Oral administration of indomethacin in a daily dose of 1.3 mg/kg for 2 weeks to rats with adjuvant-induced arthritis produced a significant anti-inflammatory effect as indicated by

improvement of paw oedema thickness, pain tolerance, serum CRP & MDA but without a statistically significant changes in serum fibronectin (Fn) or serum creatinine. These findings are in accord with (25). These effects contribute to the analgesic- anti-inflammatory actions of indomethacin. Furthermore it was reported that indomethacin didn't affect renal function (26).

Administration of valsartan in a daily intragastric dose of 20 mg/kg for 2 weeks to rats with adjuvant arthritis produced significant improvement of paw oedema thickness, pain tolerance as well as a significant decrease in elevated serum CRP, MDA & Fn, but without significant changes in serum creatinine as compared to arthritic non-treated rats table (1&2). These findings could be explained on the light of previous studies which reported that AngII is responsible for production of O_2^* & $H_2O_2^{**}$ free radicals in cardiac, vascular smooth muscle, endothelial adventitial, and mesangial cells (27,28,29). Furthermore, rantes (regulated upon activation, normal Tcells expressed and secreted) which is a member of C-C chemokine subfamily with chemoattractant properties for monocytes / macrophages

(M/M), eosinophils, granulocytes & basophils to T-lymphocytes. Rantes induction is mediated by Ang II. Angiotensin converting enzyme inhibitors (ACEIs) & Ang II-receptor antagonists may be effective in prevention of chemokine induction (30). In addition, it was found that AT1-receptor blockade with valsartan prevented the increase in TNF α in diabetic rats by acting on the Ang II at AT1 receptor levels. TNF α is (M/M) derived cytokine that activates transcription factors such as nuclear factor kappa B (NFkB) which induces expression of genes involved in inflammation & cell growth (31). Fiebeler et al., & Muller et al., (32,33), had been found that valsartan suppressed the nuclear factor KB DNA binding activity & reduced collagen 1 & Fn in the heart. In addition, it was reported that valsartan's beneficial effect in transgenic rats overexpressing the human renin and angiotensinogen genes (dTGR) are mediated by the inhibition of nuclear factor KB & activator protein-1 (AP-1) (34). Furthermore valsartan protected the kidney from inflammation. This anti-inflammatory effect is not a result of lowering blood pressure, but is a result of direct action on cytokine TNF α at the level of the kidney. This finding made valsartan of

a potential anti-inflammatory effect(8).

Conclusions :

From this study, it could be concluded that valsartan has comparable anti-inflammatory action as it attenuated the inflammatory response associated with collagen II induced adjuvant arthritis. Clearly, further studies are necessary to declare if this potential anti-inflammatory effect of valsartan occurs in humans.

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دراسة تأثير دواء الفالسرطان على إلتهاب المفاصل الروماتيزمى المحدث معملياً فى الفئران البيضاء

د. سوميه عبد اللطيف مقبل

قسم الفارماكولوجيا الإكلينيكية - كلية الطب

جامعة المنصورة - جمهورية مصر العربية

أجرى هذا البحث لدراسة احتمال وجود تأثير مضاد للإلتهاب لدواء الفالسرطان فى الفئران البيضاء المصابة بمرض الإلتهاب المفصلى المحدث معملياً.

استخدام لإجراء هذا البحث عدد ٣٢ فأراً أبيضاً وقسمت إلى أربعة مجموعات متساوية كل مجموعة تكونت من ٨ فئران كالتى:

المجموعة الأولى : مجموعة ضابطة عادية - لم يحدث بها التهاب مفصلى روماتيزمى، أعطيت محلول ملح عادى بنفس الكمية المستخدمة لإذابة الدواء وذلك لمدة أسبوعين متتاليين

المجموعة الثانية : عبارة عن فئران مصابة بالتهاب المفاصل أعطيت أيضاً محلول الملح عن طريق الفم (مجموعة ضابطة للإلتهاب) وذلك بنفس الجرعة ولنفس المدة.

المجموعة الثالثة : أحدث بها معملياً التهاب مفصلى وعولجت بدواء الاندوميثاين بجرعة ١٣ر١ مجم/كجم يومياً وذلك عن طريق الفم لمدة أسبوعين متتاليين أيضاً.

المجموعة الرابعة : أحدث به معملياً التهاب مفصلى وعولجت بدواء الفالسرطان بجرعة ٢٠ مجم/كجم يومياً وذلك عن طريق الفم لمدة أسبوعين متتاليين أيضاً.

وتم تقييم الإلتهاب المفصلى الروماتيزمى بواسطة المعايير الآتية :

- قياس حجم الورم فى المخلب الخلفى للفئران بواسطة جهاز الاديامتير.
- قياس مدى تحمل الألم بإحداث ضغط على المخلب الخلفى بواسطة جهاز الأنلجيمتر.
- قياس مستوى البروتين - ج المتفاعل فى المصل.

- قياس معدل الشقوق الحرة فى المصل.

- قياس معدل الفيبرونكتين فى المصل.

- قياس معدل الكرياتينين فى المصل.

وكانت نتائج هذا البحث كالتالى :

- احدث الالتهاب المفصلى نقص ذو دلالة إحصائية فى مدى تحمل الألم بإحداث ضغط على المخلب الخلفى.

- أحدث الالتهاب المفصلى زيادة ذات دلالة إحصائية فى حجم الورم فى المخلب الخلفى للفران.

- احدث الالتهاب المفصلى زيادة ذات دلالة إحصائية فى كل من مستوى البروتين - ج المتفاعل فى المصل وكذلك فى معدل الشقوق الحرة فى المصل ومعدل الفيبرونكتين فى المصل مع عدم تغيير فى معدل الكرياتينين فى المصل.

- إعطاء دواء الاندوميثاين للفران المصابة بالتهاب المفاصل بالجرعات السابق ذكرها أحدث زيادة ذات دلالة إحصائية فى مدى تحمل الألم. وكذلك أحدث نقص ذو دلالة إحصائية فى حجم الورم فى المخلب الخلفى وأيضاً أحدث نقص ذو دلالة إحصائية فى كل من مستوى البروتين - ج وفى معدل الشقوق الحرة فى المصل بينما ظل معدل الفيبرونكتين فى المصل دون تغيير وكذلك معدل الكرياتينين فى المصل. وذلك بالمقارنة بالمجموعة الضابطة المصابة بالتهاب المفاصل.

- إعطاء دواء الفالسرتان للفران المصابة بالتهاب المفاصل بالجرعات السابق ذكرها أحدث زيادة ذات دلالة إحصائية فى مدى تحمل الألم. وكذلك أحدث نقص ذو دلالة إحصائية فى حجم الورم فى المخلب الخلفى. وأيضاً أحدث نقص ذو دلالة إحصائية فى كل من مستوى البروتين - ج وفى معدل الشقوق الحرة فى المصل وأيضاً معدل الفيبرونكتين فى المصل - بينما ظل معدل الكرياتينين فى المصل دون تغيير. وذلك بالمقارنة بالمجموعة الضابطة المصابة بالتهاب المفاصل.

وعلى ضوء هذه الدراسة يمكن استخلاص ان دواء الفالسرتان له تأثير مشبط للإلتهاب المفصلى الروماتيزمى فى الفران البيضاء المصابة بهذا المرض معملياً وذلك بالمقارنة بدواء الاندوميثاين المشبط للإلتهاب المفصلى.

وبناء على ذلك نوصى بدراسة هذا التأثير فى مرضى الالتهاب الروماتيزمى وخصوصاً المرضى منهم المصابين فى نفس الوقت بارتفاع ضغط الدم الشريانى وفى حاجة الى علاج وذلك لتقليل الأعراض الجانبية وتقليل نفقات العلاج.