EFFECT OF PENTOXIFYLLINE ON ADJUVANT-INDUCED ARTHRITIS IN ALBINO RATS

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ABSTRACT

Rheumatoid arthritis (RA) is a common inflammatory autoimmune disorder. Non-steroidal anti-inflammatory drugs (NSAIDs) have become an integral part of RA therapy. Adverse effects of these drugs are widely expanding. Data implicate the cytokine tumor necrosis factor- α (TNF- α) in the pathophysiology of RA as well as involved in the indomethacin induced gastrointestinal damage. Pentoxifylline (PTX), a methylxanthine derivative is documented to possess anti-inflammatory and anti-TNF- α properties.

The present study was conducted to investigate the effect of PTX on edema, serum malondialdehyde (MDA) and TNF- α in experimentally

induced collagen II adjuvant arthritis in albino-rats. Forty-two male albino rats weighing 200-250 grams were used throughout the study. The animals were divided into seven equal groups. Group (1): Non-arthritic control rats received daily 0.5 ml intragastric isotonic saline for 6 weeks. Group (2): Arthritic control rats received daily 0.5ml isotonic saline intragastrically for 6 weeks. Group (3): Arthritic rats treated intragastrically with indomethacin (1.3 mg/kg/day) for 6 weeks. Group (4): Arthritic rats treated with daily intragastric PTX (50 mg/kg) for 6 weeks. Group (5): Arthritic rats treated with PTX (100 mg/kg/day), intragastrically for 6 weeks. Group (6): Arthritic rats treated with PTX (50 mg/kg/day) given 30 minutes before administration of indomethacin

(1.3 mg/kg/day), intragastrically for 6 weeks. Group (7): Arthritic rats treated with PTX (100 mg/kg/day) administered 30 minutes before administration of indomethacin as above.

It was found that administration of collagen II and complete freund's adjuvant to rats produced a significant arthritic changes as assessed by paw edema thickness, analgesmetric pressure and C-reactive protein, arthritic rats developed a significant increase in serum MDA and TNF- α . Daily intragastric administration of either indomethacin, PTX alone or in combination induced a significant decrease in paw edema thickness, CRP, MDA as well as induced increase in analgesmetric pressure tolerance. Administration of PTX (50 mg or 100mg/kg) to arthritic rats produced significant decrease in TNF- α . Mean while administration of indomethacin alone to arthritic rats produced significant increase in TNF- α . Administration of PTX (50 or 100 mg/kg/day) 30 minutes before indomethacin induced a significant decrease in TNF- α as compared to administration of indomethacin alone. These findings suggest that PTX is effective in treatment

of collagen-II induced adjuvant arthritis. In addition the present work support the concept that antagonizing TNF- α is successful in treating inflammatory disorders as RA. PTX may have to be used as adjuvant therapy in RA.

INTRODUCTION

RA is a common inflammatory autoimmune disorder with a widely varying degree of severity (1). NSAIDs have become an integral part of the rheumatological disorders therapy (2). The gastro-intestinal and renal toxicity of these medications are well known (2,3).

Collagen II induced arthritis (CIA) is an experimental model of autoimmune disease that can be induced in rats by immunization with type II collagen (1,4). Many features of CIA resemble those of RA in human. It has been shown that both cellular and humoral immune responses to collagen II are involved in pathogenesis of CIA (4). Data implicates the cytokine TNF- α in the pathophysiology of RA (5). In vitro data suggest that PTX may possess anti-TNF- α properties (7). PTX has been used for more than 20 years in the treatment

of peripheral vascular disease because of its potent hemorrhheological properties (6) subsequently, PTX was found to have anti-inflammatory properties mediated via inhibition of phosphodiesterases (7).

In vitro, PTX inhibits monocyte production of TNF- α (8) that thought to play a central role in the pathogenesis of many diseases like RA. Modest clinical effects have also been observed in RA (5,34). Beneficial effects of PTX have been reported in idiopathic dilated cardiomyopathy (9), childhood type I diabetes (10), and systemic vasculitis (11). Furthermore, PTX inhibits lipopolysaccharide induced production of TNF- α by monocytes and T-cells as well as interleukin-2 induced (IL-2) adherence to leukocytes (12,13). Substantial evidence indicates that inflammatory cytokines subserve a crucial role in joint destruction and disease propagation in RA (14). Among these cytokines, TNF- α has been considered as the pivotal factor to induce and sustain tissue damage by activating the inflammatory mediator cascade, stimulating the mechanism of angiogenesis and up-regulating the vascular endo-

thelial adhesiveness (15). TNF- α is found in elevated level in sera of RA patients (15). Thus this study was carried out to examine whether treatment with PTX ameliorates edema and, inflammation in rats with CIA. Furthermore this study aimed to test the hypothesis that PTX inhibits pro-inflammatory cytokine (TNF- α) production in CIA in rats.

MATERIALS AND METHODS

Drugs used :

- Pentoxifylline (PTX) powder is supplied by Sigma Co, dissolved in sterile isotonic saline. Control rats received an equivalent volume of the vehicle.
- Indomethacin, Sigma Co, dissolved in sterile isotonic saline.

Statistical Analysis :

One-way analysis of variance (ANOVA) was done to compare between the studied groups followed by Student's "T" test according to Pipkins (17) to compare statistically the significant changes between control group and test group. P values ≤ 0.5 were considered to be statistically significant.

Animals used :

Forty-two male albino rats aged 3-4 months and weighing 200-250 grams each were used throughout the experiment. They were put under similar housing conditions; kept on diet of milk and bread, and liberally supplied with water.

Animal grouping :

This experiment comprised 7 equal groups (n=6), received medications daily intragastric for 6 weeks.

Group (1) : Non-arthritic control rats treated with daily intragastric isotonic saline (0.5 ml).

Group (2) : Arthritic control rats treated with 0.5 ml isotonic saline.

Group (3) : Consisted of arthritic rats treated with indomethacin [single daily dose of 1.3mg/kg(18)].

Group (4) : Arthritic rats treated with daily intragastric PTX (50 mg/kg) (19).

Group (5) : Arthritic rats treated with PTX (100 mg/kg/day) (19).

Group (6) : Arthritic rats treated with (50 mg/kg/day) PTX

which administrated 30 minutes before indomethacin (1.3 mg/kg/day).

Group (7) : Consisted of arthritic rats treated with PTX (100 mg/kg/day) administered 30 minutes before indomethacin.

INDUCTION OF ARTHRITIS

CIA was produced in albino rats according to the method of Eckhardt et al (20). Collagen II (C11) was dissolved overnight at 4°C in 0.1M acetic acid (prepared by addition of 5.7 ml glacial acetic acid to one litre of distilled water at a concentration of 4mg/ml). The solution was clarified by centrifugation, diluted when necessary with 0.1M acetic acid. The previously prepared C11 was emulsified in an equal volume of complete freund's adjuvant (CFA) which composed of dried heat killed mycobacterium in mineral oil (this was supplied by Difo laboratories, Detroit, Michigan). This emulsification was done by using Virtis 23 homogenizer (Gardmer, New York). Centrifugation was done at 300 r.p.m for 5 minutes. A total volume of 0.1 ml of the cold emulsion was injected intradermally (ID) into the tail

base of each rat. A booster dose was given after 3 weeks. After 45 days the systemic arthritis was manifest in both hind paws. Inflammatory and anti-inflammatory effects (pain tolerance and edema development and suppression) were assessed by using the analgesimeter and paw edema tests respectively (21,22). At the end of the experiment, all rats were sacrificed by knife. Trunk blood of each rat was collected and centrifuged at 1000 r.p.m for 15 min. the unhaemolyzed serum samples were separated carefully and stored at -70°C until used for assay. Serum CRP was measured by using latex particles of agglutination (23,24). Lipid peroxidation was assessed spectrophotometrically by measuring serum MDA using thiobarbituric acid method (25). In addition to measurement of serum tumor necrosis factor- α according to Carti et al (26).

RESULTS

Induction of collagen-II adjuvant arthritis produced a significant decrease in analgesmetric pressure tolerance, significant increase in paw edema thickness as well as significant increase in serum CRP, MDA

and TNF- α (Tab.1).

Daily administration of indomethacin (1.3 mg/kg) for 6 weeks produced significant increase in analgesmetric pressure tolerated by the arthritic rats, significant decrease in serum CRP and MDA but significant increase in serum TNF- α (tab. 2&3).

Intragastric administration of PTX in a dose of 50 or 100 mg/kg/day produced significant improvement of arthritic rats. This improvement was indicated by significant decrease in serum CRP and MDA as well as increase in analgesmetric pressure tolerated by the rats . Also of PTX in either doses produced significant decrease in TNF- α as compared to the arthritic control (Tab.2 &3). Moreover, administration of PTX in either daily dose 50 mg/kg or 100 mg/kg 30 minutes before administration of indomethacin (1.3 mg/kg/day, intragastrically for 6 weeks) induced significant increase in analgesmetric pressure tolerated by the arthritic rats and significant decrease in paw edema thickness as well as significant decrease in serum TNF- α as compared to administration of indomethacin alone (tab. 2 &3).

Table (1): Analgesmetric pressure, paw edema thickness, serum c-reactive protein (CRP), malondialdehyde (MDA) and tumor necrosis factor- alpha (TNF- α) in non-arthritis and arthritis control rats (Mean $\pm$ SE).

Animal group N = 6	Analgesmetric pressure (grams)		Paw edema thickness (cm)		CRP (mg/L)	MDA (n mol/L)	TNF- α (pg/ml)
	Right paw (R)	Left paw (L)	R	L			
Non-arthritis rats	205 $\pm$ 3.2	208 $\pm$ 3.1	1.8 $\pm$ 0.1	1.9 $\pm$ 0.1	No agglutination < 6 mg/L	0.13 $\pm$ 0.002	1.2 $\pm$ 0.1
Arthritis rats	128 $\pm$ 9.5*	120 $\pm$ 10.1*	3.1 $\pm$ 0.12*	3.3 $\pm$ 0.15*	105 $\pm$ 6.7*	0.52 $\pm$ 0.01*	5.9 $\pm$ 0.32*

SE = standard error

* = significant difference between arthritis and non arthritis control groups ($p \leq 0.05$).

Table (2): Effect of intragastric administration of indomethacin and pentoxifylline (PTX) for 6 weeks on analgesmic pressure, paw edema thickness and serum c-reactive protein (CRP) in arthritic rats.. (Mean $\pm$ SE).

group n = 6	Analgesmic pressure (grams)		Paw edema thickness (cm)		Serum CRP (mg/L)
	Right paw (R)	Left paw (L)	R	L	
Arthritic control	128 $\pm$ 9.5	120 $\pm$ 10.1	3.1 $\pm$ 0.12	3.3 $\pm$ 0.13	105 $\pm$ 6.7
Indomethacin treated (1.3mg/kg/day)	350 $\pm$ 12.3*	348 $\pm$ 11.6*	2.0 $\pm$ 0.2*	2.1 $\pm$ 0.17*	No agglutination ($<$ 6 mg/L) *
PTX-treated (50 mg/kg/day)	209 $\pm$ 10.1**	203 $\pm$ 8.9**	2.5 $\pm$ 0.3*	2.3 $\pm$ 0.1*	No agglutination*
PTX-treated (100 mg/kg/day)	215 $\pm$ 12.3**	212 $\pm$ 10.5**	2.3 $\pm$ 0.2*	2.6 $\pm$ 0.1*	No agglutination *
Indomethacin (1.3 mg/kg/day) + PTX (50 mg/kg/day)	352 $\pm$ 3.4*	345 $\pm$ 11.5*	2.2 $\pm$ 0.1*	2.2 $\pm$ 0.1*	No agglutination
Indomethacin (1.3 mg/kg/day) + PTX (100mg/kg/day)	343 $\pm$ 4.1*	358 $\pm$ 6.7*	2.3 $\pm$ 0.2*	2.1 $\pm$ 0.14*	No agglutination*

SE = standard error

* = significant difference between arthritic treated versus arthritic control groups ($p \leq 0.05$).

** = significant difference between PTX or PTX+ indomethacin treated versus indomethacin

Tab (3): Effect of intragastric administration of indomethacin and or pentoxifylline (PTX) for 6 weeks on serum MDA and TNF- α in arthritic rats (Mean $\pm$ SE).

	Arthritic control	Indomethacin (1.3 mg/kg/day)	PTX (50 mg/kg/day)	PTX (100 mg/kg/day)	Indomethacin + PTX (50 mg/kg)	Indomethacin + PTX (100 mg/kg)
MDA (n mol/L)	0.52 $\pm$ 0.01	0.15 $\pm$ 0.005*	0.14 $\pm$ 0.001*	0.130 $\pm$ 0.002*	0.15 $\pm$ 0.005*	0.145 $\pm$ 0.003*
TNF- α (pg/ml)	5.9 $\pm$ 0.32	7.2 $\pm$ 0.01*	3.5 $\pm$ 0.2*	1.5 $\pm$ 0.01*	4.7 $\pm$ 0.02*	2.2 $\pm$ 0.01*

SE = standard error

TNF- α = tumor necrosis factor alpha.

* = significant difference between drug treated groups and arthritic control group ($p \leq 0.05$).

▲ = significant difference between PTX or PTX + indomethacin treated group versus indomethacin

DISCUSSION

Collagen induced arthritis (CIA) is an experimental model of autoimmune disease (27). It can be induced in mice(27), rats(28), and monkeys(29) by immunization with type II collagen (C11). Many features of CIA resemble those of RA in human (30).

In the present study CIA developed within 45 days after ID injection of C11 in CFA as evidenced by significant decrease in pain threshold and increase the mean hind paw edema thickness accompanied by increase in serum CRP, MDA and TNF- α . These results are in accord with those observed by Rodinguez et al (31) and Yamaki et al (32).

Intragastric administration of indomethacin in a dose of 1.3mg/kg/day for 6 weeks to rats with CIA produced a potent anti-inflammatory activity as assessed by decrease paw edema thickness, increased analgesmetric pressure tolerance, and serum CRP. These findings are in agreement with Yamaki et al (32). Furthermore, administration of indomethacin to CIA rats resulted in significant increase in TNF- α . This finding is supported by

the study of Reuter and Wallace and by the study of Souza et al (19,33). Also, they suggested that PTX prevented acute gastric mucosal damage and neutrophil migration induced by indomethacin and reduced indomethacin induced release of TNF- α . TNF- α acting via tumor necrosis factor- α receptors-1 (TNF- α . R1) is involved in indomethacin induced gastric damage and granulocyte infiltration. In present study administration of indomethacin to arthritic rats induced a significant decrease in serum MDA. This findings is consistent with Twoney and Dale (16) as they have been documented that NSAIDs can either attenuate or depress the neutrophil respiratory burst that occurs when cells become activated by specific stimuli. The respiratory burst generates the superoxide anion which give rise to tissue damaging oxygen metabolites.

In the present study, administration of PTX to the arthritic rats in a dose of 50 mg/kg/day or 100 mg/kg/day, intragastrically for 6 weeks resulted in significant improvement as indicated by decreased serum CRP, MDA as well as increase in an anal-

gesmetric pressure tolerated by the arthritic rats. These results are supported with clinical studies (34,35,45) which found that PTX exerted modest beneficial effects in RA. Neutrophils enter the affected joint in RA and become activated to secrete tissue damaging granule enzymes and reactive oxygen metabolites. Synovial fluid contains oxidatively altered components and neutrophil derived proteins such as myeloperoxidase that are detected within joints in RA suggesting that degranulation has occurred (36). Interestingly low doses of PTX have been associated with suppression of neutrophil function such as chemotaxis, superoxide anion production, hydrogen peroxide production, deformability, phagocytosis and degranulation (37). Furthermore, PTX has been shown in human and animal studies to have a variety of physiological effects at the cellular and vascular levels (38). Administration of PTX (50 or 100 mg/kg/day) for 6 weeks to arthritic rats produced significant decrease in TNF- α . This results could be explained on the light of the study done by Porter et al (39) as they reported that PTX in a dose of 100 mg induced a significant decrease in

lipopolysaccharide (LPS) induced production of TNF- α , but administration of PTX in a dose of 50mg/kg/day resulted in a non-significant change in TNF- α levels induced by LPS (39,40). PTX prevents the degradation of cAMP leading to an increase in the intracellular concentration of cAMP, which suppresses TNF- α production (41). Increased cAMP activates protein kinase A (PKA) which catalyzes the phosphorylation of protein, altering their conformation and activity. Perhaps increased PKA activity alters factors such as activation of phospholipase C, PKC and protein tyrosine kinase which play role in cytokine synthesis (39,41). In present study CRP was reduced in arthritic rats treated by PTX. CRP was proved to have direct pro-inflammatory effects on endothelial cells, including the expression of adhesion molecules and monocyte chemotactic protein-1 (43). Furthermore CRP is implicated in the synthesis of TNF- α (42). Hence, a reduction in serum CRP by PTX could have beneficial effect on RA by decreasing TNF- α .

Administration of PTX either in a dose of 50mg/kg/day or 100mg/kg/

day, 30 minutes before administration of indomethacin produced significant increase in analgesmetric pressure tolerated by the arthritic rats and a significant decrease in paw edema thickness, as well as of significant decrease in serum TNF- α , as compared to administration of indomethacin alone. These results could be explained on the light of study of Coururier et al (44). Those authors reported that the intestinal damage produced by indomethacin could be significantly attenuated by pretreatment with specific type IV phosphodiesterase (PDE)inhibitor (RO-20-1724) by decreasing TNF- α . On the other hand Reuter and Wallace (19), reported that PDE inhibitor (PTX) had its protective effect against NSAID enteropathy through a mechanism independent of TNF- α synthesis inhibition. So the present study support the concept that antagonizing the action of TNF- α is successful in treating inflammatory disorders (RA) and for optimal effect in treating RA, PTX may have to be used as adjuvant therapy.

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الملخص العربى

تأثير عقار البنتوكسيفلين على التهاب المفاصل الروماتيزمى المحدث معملياً فى الفئران البيضاء (دور معامـل تحلل الأورام - ألفا)

كروان محمد عبد الرحمن

قسم الفارماكولوجيا الإكلينيكية - كلية الطب - جامعة المنصورة

أجرى هذا البحث لدراسة مدى تأثير عقار البنتوكسيفلين على معامـل تحلل الأورام _ ألفا والشقوق الحرة فى الفئران المصابة بمرض الالتهاب المفصلى. استخدم فى اجراء هذا البحث عدد ٤٢ فأراً أبيضاً وقسمت إلى ٧ مجموعات متساوية كالتالى:

المجموعة الأولى: مجموعة ضابطة عادية لم يحدث بها التهاب مفصلى روماتيزمى وأعطيت يومياً محلول ملح متعادل بمقدار ٢/١ ملم عن طريق الفم وذلك لمدة ٦ اسابيع متتالية. المجموعة الثانية: احدث بها التهاب مفصلى وأعطيت محلول الملح كما سبق (مجموعة ضابطة للالتهاب المفصلى).

المجموعة الثالثة: احدث بها التهاب مفصلى وعولجت بدواء الاندوميثاين بجرعة تعادل ١,٣ مجم/كجم يومياً عن طريق الفم لمدة ٦ أسابيع متتالية.

المجموعة الرابعة: مصابة بالتهاب مفصلى وأعطيت دواء البنتوكسيفلين بجرعة مقدارها ٥٠ مجم /كجم يومياً ولنفس المدة السابقة.

المجموعة الخامسة: تكونت من فئران مصابة بالتهاب المفصلى وعولجت بدواء البنتوكسيفلين بجرعة ١٠٠ مجم/كجم يومياً عن طريق الفم ولمدة ٦ اسابيع.

المجموعة السادسة : فئران مصابة بالتهاب المفاصل وعولجت بدواء البنتوكسيفلين بجرعة ٥٠ مجم /كجم يومياً ثم أعطيت بعد ٣٠ دقيقة دواء الاندوميثاين بجرعة ١,٣ مجم/كجم يومياً ولمدة ٦ اسابيع متتالية.

المجموعة السابعة: مثل السابقة ولكن تختلف عنها فى جرعة البنتوكسيفلين حيث أعطى

بجرعة ١٠٠ مجم/كجم وتم تقييم الالتهاب المفصلي بواسطة المعايير الآتية :

- ١- قياس حجم الورم فى المخلب الخلفى للفئران بواسطة جهاز الاديما متر.
- ٢- قياس مدى تحمل الألم بإحداث ضغط على المخلب الخلفى بواسطة جهاز الانلجزميتر
- ٣- قياس مستوى البروتين ج المتفاعل فى المصل.
- ٤- قياس معدل المألونديالديهايد فى المصل.
- ٥- قياس معدل معامل تحليل الأورام ألفا فى المصل.

ويمكن تلخيص نتائج هذه الدراسة فى النقاط التالية.

اعطاء كلا من دواء الاندوميثاين والبنتكوكسيفلين كلا على حده او معاً أحدث تأثيراً مسكناً للألم ومثبط لتورم المفاصل ، كما أحدثت هذه الأدوية نقص ذو دلالة إحصائية فى مستوى بروتين ج المتفاعل فى المصل وكذلك معدل المألونديالديهايد بينما أحدث دواء البنتكوكسيفلين نقص ذو دلالة إحصائية فى معامل تحليل الأورام ألفا وذلك عند اعطائه يومياً لمدة ٦ أسابيع بينما أحدث اعطاء الاندوميثاين منفرداً زيادة ذات دلالة إحصائية فى معامل تحليل الأورام- ألفا وعندما اعطى دواء البنتكوكسيفلين قبل دواء الاندوميثاين بنصف ساعة يومياً حدث نقص ذو دلالة إحصائية فى مستوى تحليل الاورام الفا.

وعلى ضوء هذه الدراسة يمكن استخلاص ان دواء البنتكوكسيفلين له تأثير مسكن للألم ومقلل لتورم المفاصل وايضاً يقلل من ارتفاع معامل تحليل الأورام ألفا المصاحب لحدوث الأتهاب المفصلي المصاحب للعلاج بدواء الاندوميثاين ولذلك يمكن اضافة البنتكوكسيفلين كعامل مساعد فى علاج الالتهاب المفصلي الروماتيزمى.