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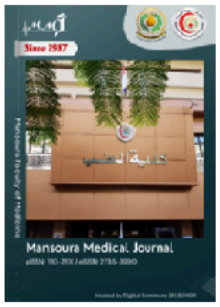

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EFFECT OF PENTOXIFYLLINE ON ADJUVANT-INDUCED ARTHRITIS IN ALBINO RATS

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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-alpha (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 hemorrheological 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 endothelial 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 stastistically the significant changes between control group and test group. P values ≤ 0.5 were considered to be stastistically 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 boaster 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 analgesmeter 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 unhaemalyzed 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-arthritic and arthritic control rats (Mean ± 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-arthritic rats	205 ± 3.2	208 ± 3.1	1.8 ± 0.1	1.9 ± 0.1	No agglutination < 6 mg/L	0.13 ± 0.002	1.2 ± 0.1
Arthritic rats	128 ± 9.5•	120 ± 10.1•	3.1± 0.12•	3.3± 0.15•	105 ± 6.7•	0.52 ± 0.01•	5.9 ± 0.32•

SE = standard error

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

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

group n = 6	Analgesmetric pressure (grams)		Paw edema thickness (cm)		Serum CRP (mg/L)
	Right paw (R)	Left paw (L)	R	L	
Arthritic control	128±9.5	120 ± 10.1	3.1 ±0.12	3.3±0.13	105±6.7
Indomethacin treated (1.3mg/kg/day)	350±12.3•	348±11.6•	2.0±0.2•	2.1±0.17•	No agglutination (< 6 mg/L) •
PTX-treated (50 mg/kg/day)	209±10.1•▲	203±8.9•▲	2.5±0.3•	2.3±0.1•	No agglutination•
PTX-treated (100 mg/kg/day)	215±12.3•▲	212±10.5•▲	2.3±0.2•	2.6±0.1•	No agglutination •
Indomethacin (1.3 mg/kg/day) + PTX (50 mg/kg/day)	352±3.4•	345±11.5•	2.2±0.1•	2.2±0.1•	No agglutination
Indomethacin (1.3 mg/kg/day) + PTX (100mg/kg/day)	345±4.1•	358±6.7•	2.3±0.2•	2.1±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 ± 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± 0.01	0.15 ± 0.005•	0.14 ± 0.001•	0.130± 0.002•	0.15 ± 0.005•	0.145 ± 0.003•
TNF-α (pg/ml)	5.9 ± 0.32	7.2 ± 0.01•	3.5 ± 0.2•▲	1.5 ± 0.01•▲	4.7±0.02▲●	2.2 ± 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 Rodringuez 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 aggreement 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- alpha 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 metabolities. 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 Couturier et al [44]. Those authers 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.

REFERENCES

1) **Trentham DE (1982) :** Collagen arthritis as a relevant model for rheumatoid arthritis. Arthritis Rheum; 25:911.

2) **David M, Clive MD and Jeffrey S (1984) :** Renal syndromes associated with non-steroidal anti-inflammatory changes. N Engl J Med; 310:9.

3) **Somerville K, Faulkner G and Langman M (1986) :** Non steroidal anti-inflammatory drugs in bleeding peptic ulcer. Lancet; 1: 462.

4) **Trentham DE, Dynesius RA and David JR (1978) :** Passive transfer by cell of type II collagen induced arthritis in rats. J clin Invest. 11:539.

5) **Maksymowych WP, Anva-Zubieta AWong MH and Russel AS (1995) :** An open study of pentoxifylline in treatment of severe refractory rheumatoid arthritis. J Rheumatology; 22 (4) : 625.

6) **Frampton JE and Brogden RN**

(1995) : Pentoxifylline (oxpentifylline): A review of its therapeutic efficacy in the management of peripheral vascular and cerebrovascualr disorders. Drugs Aging; 7:480.

7) Semnler J, Gebert U, Eisenhut T, Moeller J and Schonharting M (1993) : Xanthine derivatives : comparison between suppression of tumor necrosis factor-α production and inhibition of CAMP phosphodiesterase activity. Immunology; 78:520.

8) Mandell GL (1995) : Cytokines, phagocytes, and pentoxifylline. J Cardiovasc Pharmacol; 25 (supp 2): S20.

9) Sliwa k, Skudicky D, Condy G, Wisenbaugh T and Sareli P (1998) : Randomised investigation of effects of pentoxifylline on left ventricular performance in idiopathic dilated cardiomyopathy. Lancet; 351:1091.

10) Mac Donald MJ, Skahidi NT, Allen DB, Lusting RH, Mitchell TL and Cornwell ST (1994) : Pentoxifylline in the treatment of children with new onset type-1 diabetes mellitus. TAMA; 271:27.

11) Yasui K, Ohta K, Kobayashi M, Aizawa T and komiyama A (1996) : Successful treatment of Behcet's disease with pentoxifylline. Ann Intern Med; 124:891.

12) Gomez Cambronero L, Camps B, Asuncion JG, Cerda M, Pellin A and Pallardo FV (2000) : Pentoxifylline ameliorates cerulein induced pancreatitis in rats: Role of glutathione and nitric oxide. J Pharmacol Exp Therap; 18:670.

13) Choy EH and Panayi G S (2001) : Cytokine Pathways and joint inflammation in rheumatoid arthritis . N Engl J Med; 344:907.

14) Lee MD and Weinblatt ME

(2001) : Rheumatoid arthritis, Lancet; 358:903.

15) **Manicourt DH, Triki R, Fukuda K, Devogelaer JP and De Deuxchaisenes C (1993) :** Levels of circulating TNF-α and IL-6 in patients with rheumatoid arthritis. Arthritis Rheum; 36:490.

16) **Towney BM and Dale MM (1992) :** Cyclooxygenase independent effects of non-steroidal anti-inflammatory drugs on the neutrophil respiratory burst. Biochem Pharmaco; 43:413.

17) **Pipkins FB (1984) :** Statistical analysis of the obtained data. Descripitive and comparative analysis in :"Medical statistics made ease" Churchill living stone publication. London, Mellarisis, New York.

18) **Rhymer A and Gengos D (1983) :** Anti-rheumatic drugs; ed. By Husskinson EC, Prager publication, New York. P.P 265.

19) **Reuter BK and Wallace JL (1999) :** Phosphodiesterase inhibitors prevent NSAID enteropathy independently of effects on TNF-α release. Am J Physiol. Gastrointestinal liver physiol; 277:G847.

20) **Eckhardt S, Mitchell N and Ceil PA (1981) :** Collagen II induced arthritis in rats. J Pharmacol. Exp Therap; 220 (2):417.

21) **Randall IO and Selitto JJ (1957) :** Analgesmeter. Arch Int Pharmacodyn; 111 : 409.

22) **Winter CA, Risely EA and Nuss GW (1992) :** Paw edema test in experimentally induced arthritis. Pros Sco Exp Biol Med; 11:544.

23) **Kindmark CO (1972) :** The concentration of C-reactive protein in sera from healthy in-

dividuals. Scand J Clin LAB Invest; 29 (Supp 124):407.

24) **Wilcher J T (1985) :** Interleukin-1 and acute phase proteins. J Rheumatol; 24:21.

25) **Draper. W and Hadley M (1990) :** Indirect determination of oxygen free radicals. Methods Enzymol; 186 : 421.

26) **Carti A, Fassina G, Marcucci F, Barbanti E and Cassani G (1992) :** Oligomeric tumor necrosis factor (slowly converts into inactive forms of bioactive level). Biochem J; 284:165.

27) **Counrtenay JS, Dallnan MJ, Dayan AD, Martin A and Mosedale B (1980) :** Immunization against heterologours type II collagen induces arthritis in mice. Nature; 283:666.

28) **Trentham DE, Townes AS and Kang AH (1977) :** Autoimmunity to type II collagen: an experimental model of arthritis. J Exp Med; 146:857.

29) **Yoo TJ Kim S, Stuart JM, Floyd RA, Olson GA, Cremer MA and Hang AH (1988) :** Induction of arthritis in monkeys by immunization with type II collagen. J Exp Med; 168:777.

30) **Stwart J, Townes AS and Kang AH (1981) :** The role of collagen auto immunity in animals and human disease .J Clin Invest; 62:359.

31) **Rodriguez RM, Pitzalis C and Henderson E (1992) :** T-lymphocyte adhesion to fibronectin; a possible mechanism for T-cell accumulation in rheumatoid Joint. Clin Exp Immunol; 89 (3): 439.

32) **Yamaki K, Nakagawa H and Truru Fujj S (1987) :** Inhibitory effects of anti-inflammatory drugs on type II collagen-induced arthritis

in rats. Ann Rheum Dis; 46:543.

33) **Souza MH, Plemos H, Oliver RB and Cunha FQ (2004) :** Gastric damage and granulocyte infiltration induced by indomethacin in TNF- receptor-1 (TNF-R1) or inducible nitric oxide synthase (IONS) deficient mice. Gut; 53(6):791.

34) **Dubost JJ, Soubrier M, Ristori JM, Beaujon G, Oualid T, Bussiere JL and Sauvezie B (1997) :** An open study of the anti-TNF-alpha agent pentoxifylline in the treatment of rheumatoid arthritis. Rev Rheum Engl; 64:789.

35) **Huizinga TW, Dijkmans BA, Vander Velde EA, Vande Pouw Krann TC, Verweij CL, Breedveld FC (1996) :** An open study of pentoxifylline and thalidomide as adjunct therapy in the treatment of rheumatoid arthritis. Ann Rheum Dis; 55:833 .

36) **Nurcombe HL, Bucknall RC and Edwards SW (1991) :** Neutrophils isolated from the synovial fluid of patients with rheumatoid arthritis: Priming and activation in vivo. Ann Rheum Dis; 50:147.

37) **Mah Mp, Aeberhard EF and Gillian MB (1993) :** Effects of pentoxifylline on vivo leukocyte function and clearance of group B streptococcal disease. Immune; 62:4997.

38) **Fang CC, Yen CJ and Chen YM (2000) :** Pentoxifylline inhibits human peritoneal mesothelial cell growth and collagen synthesis: Kidney Int; 57:2626.

39) **Porter MH, Hrupka BJ, Altreuther G, Arnold M and Langhams W (2000) :** Inhibition of TNF-α production contributes to the attenuation of lipopolysaccride induced hypophagia by pentoxifylline. Am J Physiol Regul In-

tegr Comp physiol; 279: R2113.

40) **Huizinga TW, Brinkman BM and verweij CL (1996) :** Regulation of tumor necrosis factor alpha production: basic aspects and pharmacological modulation. J Rheumatol; 23:416.

41) **Sinha B, Semmler J, Eisenhut T, Eigler A and Endres S (1995) :** Enhanced tumor necrosis factor suppression and cyclic adenosine monophosphate accumulation by combination of phosphodiesterase inhibitors and prostanoids. Eur J Immunol; 25:147.

42) **Pasceri V, Willerson J Tandye ET (2002) :** Direct proinflammatory effect of c-reactive protein on human endothelial cells. Circulation; 1022165.

43) **Silwa K, Woodiwiss A, Konev K, Badenharst D, Norton G, Zambakides C, Peters F and Essop R (2004) :** Therapy of ischemic cardiomyopathy with the immunomodulating agent pentoxifylline. Circulation; 109 : 750.

44) **Couturier L, Chauvelot Mand chaussade S (1998) :** Role of tumor necrosis factor alpha and inducible nitric oxide synthase in the prevention of nitro flurbiprofen small intestine toxicity. Eur J Pharmacol; 356:245.

45) **White House M (2005) :** Tumor necrosis factor-α inhibitors for the treatment of adult rheumatoid arthritis. Prescr; 28:5.

الملخص العربى

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

كروان محمد عبد الرحمن

قسم الفارماكولوجيا الإكلينيكية - كلية الطب - جامعة المنصورة

أجرى هذا البحث لدراسة مدى تأثير عقار البنتوكسيفلين على معامل 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 ١/٢ملم 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 الاندومثياثين بجرعة تعادل ١,٣ مجم/كجم يومياً عن طريق الفم لمدة ٦ أسابيع متتالية.

المجموعة الرابعة: مصابة بالتهاب مفصلى وأعطيت دواء البنتوكسيفلين بجرعة مقدراها 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 اعطيت بعد ٣٠ دقيقة دواء الاندومثياثين 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 تقيم الالتهاب المفصلى بواسطة المعايير الآتية :

١- قياس حجم الورم فى المخلب الخلفى للفئران بواسطة جهاز الاديمامتر.

٢- قياس مدى تحمل الألم بإحداث ضغط على المخلب الخلفى بواسطة جهاز الانلجزميتر

٣- قياس مستوى البروتين ج المتفاعل فى المصل.

٤- قياس معدل المالونديألديهايد فى المصل.

٥- قياس معدل معامل تحلل الأورام ألفا فى المصل.

ويمكن تلخيص نتائج هذه الدراسة فى النقاط التالية.

اعطاء كلا من دواء الاندوميثاسين والبنتوكسيفلين كلا على حده او معاً احدث تأثيراً مسكناً للألم ومثبط لتورم المفاصل ، كما احدثت هذه الأدوية نقص ذو دلالة إحصائية فى مستوى بروتين ج المتفاعل فى المصل وكذلك معدل المالونديألديهايد بينما احدث دواء البنتوكسيفلين نقص ذو دلالة احصائية فى معامل تحلل الأورام ألفا وذلك عند اعطائه يومياً لمدة ٦ أسابيع بينما احدث اعطاء الاندوميثاسين منفرداً زيادة ذات دلالة إحصائية فى معامل تحلل الأورام- الفا وعندما اعطى دواء البنتوكسيفلين قبل دواء الاندوميثاسين بنصف ساعة يومياً حدث نقص ذو دلالة إحصائية فى مستوى تحلل الاورام الفا.

وعلى ضوء هذه الدراسة يمكن استخلاص ان دواء البنتوكسيفلين له تأثير مسكن للألم ومقلل لتورم المفاصل وأيضاً يقلل من ارتفاع معامل تحلل الأورام ألفا المصاحب لحدوث الأتهاب المفصلى المصاحب للعلاج بدواء الاندوميثاسين ولذلك يمكن اضافة البنتوكسيفلين كعامل مساعد فى علاج الالتهاب المفصلى الروماتيزمى.