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Dose-response Relationship of the Anti-inflammatory Activity of Pentoxifylline in Experimental Models of Chronic Inflammation

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Abstract: Background: The side effects of anti-inflammatory agents considered as a major problem during their clinical use; therefore, development of newer and more effective and safe anti-inflammatory drugs is necessary. The present study was designed to evaluate the dose-response relationship of the anti-inflammatory activity of pentoxifylline in experimental animal models of chronic inflammation. **Methods:** Seventy two rats were allocated into nine groups, each containing 8 rats, for the study of the anti-inflammatory activity of pentoxifylline in experimental animal model of formalin-induced chronic inflammation; another 16 rats were used, and allocated into two groups, for the study of the anti-inflammatory activity of pentoxifylline (4.0 mg kg^{-1}) when used in combination with dexamethasone or methotrexate. Fifty four rats were allocated into nine groups, each containing 6 rats, for the study of the anti-inflammatory activity of pentoxifylline in experimental animal model of cotton-pellet induced granuloma; another 12 rats were used and allocated into two groups, for the study of the anti-inflammatory activity of pentoxifylline (4.0 mg kg^{-1}) when used in combination with dexamethasone or methotrexate. **Results:** Pentoxifylline significantly suppress inflammation in experimental animal models of formalin-induced chronic inflammation and cotton-pellet induced granuloma. Pentoxifylline (4.0 mg kg^{-1}) in combination with dexamethasone significantly suppress inflammation in rat model of formalin-induced chronic inflammation and cotton pellet-induced granuloma which is significantly higher than all of the effects produced by other approaches of treatments. **Conclusion:** Pentoxifylline, in a dose dependent pattern, attenuates formaldehyde-induced chronic inflammation and cotton-pellet induced granuloma in rats and potentiates the anti-inflammatory activity of dexamethasone and methotrexate.

Key words: Pentoxifylline, chronic inflammation, granuloma

INTRODUCTION

Pentoxifylline (PTX), a methylxanthine derivative and phosphodiesterase inhibitor, has hemorheologic and immunomodulatory properties and is proposed to have a therapeutic role in the suppression of inflammatory reactions in different tissues (Korhonen *et al*., 2004). Other reported effects of PTX include inhibition of monocyte chemoattractant protein-1, interleukin-6 and -8, and macrophage inflammatory protein-1α and -1β, decreased expression of adhesion molecules on endothelial cells, decreased activation of neutrophils, decreased proliferation of lymphocytes and monocytes and decreased binding and transmigration of leukocytes (Sztrymf *et al*., 2004). Pentoxifylline is believed to attenuate inflammation by increasing intracellular cyclic adenosine monophosphate (cAMP) (Prescott and Johnson, 2005). However, it has major beneficial actions in Acute Lung Injury (ALI) and the Acute Respiratory Distress Syndrome (ARDS) which relates to its ability to raise cAMP levels, inhibition of free radical formation and antagonizing the production and actions of TNF-α (Raghavendran *et al*., 2008). Both *in vitro* and *in vivo* studies demonstrated its efficacy in the treatment of certain animal and human inflammatory diseases (Pollice *et al*., 2001). Pentoxifylline is an inhibitor of production of IL-1 and IL-6, an inhibitor of T and B cell activation and a suppressor of neutrophil degranulation (Zargari, 2008). It modulates the production/release of the pro-inflammatory cytokine (TNF-α) and inflammatory cells, in an experimental model of HCl-induced lung inflammation in rats (De Oliveira-Junior *et al*., 2008). Moreover, the antioxidant properties of the compound may be another explanation for the beneficial effects of PTX (Lee *et al*., 1997). The present study was designed to evaluate the dose-response relationship of the anti-inflammatory activity of pentoxifylline in animal models of chronic inflammation.

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MATERIALS AND METHODS

Animals: One hundred fifty four Sprague-Dawley rats weighing 180-240 g of both sexes were housed in the animal house of the College of Pharmacy/University of Baghdad and maintained on normal conditions of temperature, humidity and light/dark cycle. They were fed standard rodent pellet diet and have free access to water. The research protocol was approved by the Ethic Committee for Animal Care and Experiments at the College of Pharmacy, University of Baghdad.

Preparation of pentoxifylline solution: Pentoxifylline hydrochloride (Polpharm, Poland) powder was dissolved in distilled water to produce solution with concentration of 0.6 mg mL^{-1} which is used as a standard solution for the preparation of doses used in this study.

Study design: The study protocol were divided into 4 stages: First stage, 72 rats were allocated into 9 groups, each containing 8 rats, for the study of the anti-inflammatory activity of PTX in animal model of formalin-induced chronic inflammation; they represent control, standard drugs and test drugs groups. Second stage, 16 rats were allocated into two groups, each containing 8 rats, for the study of the anti-inflammatory activity of PTX (4 mg kg^{-1}) when used in combination with Dexamethasone (Dexa) and Methotrexate (MTX) as the standard anti-inflammatory agents in animal model of formalin-induced chronic inflammation. Third stage, 54 rats were allocated into 9 groups, each containing 6 rats, for the study of the anti-inflammatory activity of PTX in animal model of cotton pellet-induced granuloma. They represent control, standard drugs and test drugs groups. Fourth stage, 12 rats were allocated into two groups, each containing 6 rats, for the study of the anti-inflammatory activity of PTX (4 mg kg^{-1}) when used in combination with Dexa and MTX as the standard anti-inflammatory agents in animal model of cotton pellet-induced granuloma.

Formalin-induced chronic inflammation: The effect of PTX in chronic inflammation was evaluated utilizing formalin-induced paw edema (Chau, 1989). In this model, chronic inflammation was induced by injecting 0.1 mL of 2% formaldehyde into the sub planter area of the right hind paw of ether anaesthetized rat. All drugs including PTX (0.125, 0.25, 0.5, 1.0, 2.0 and 4.0 mg kg^{-1}), Dexa (1 mg kg^{-1}) and MTX (0.075 mg kg^{-1}), in addition to normal saline (0.1 ml/100 g) which is given to the control group, were administered 30 min prior to formalin injection and continued for seven consecutive days. All drugs and the vehicle were given as once daily intraperitoneal doses. In this model, the increase in paw edema was measured by standard vernier caliper. The paw thickness was measured before and 6 days after induction of inflammation and presented as mean increase in paw thickness (mm) (Joseph *et al*., 2005). The ability of the anti-inflammatory drug to suppress paw inflammation was expressed as a percentage of inhibition of paw edema and calculated according to the following equation (Khouzami *et al*., 2009):

$$\text{Percentage of inhibition (\%)} = \frac{(C - T)}{C} \times 100$$

where, C is mean increase in paw thickness of control group of rats and T is mean increase in paw thickness of treated group of rats.

Cotton pellet-induced granulomatous chronic inflammation: The cotton pellets-induced granuloma in rats was evaluated using the method of Winter and Porter (Winter and Porter, 1957). The cotton pellets weighing 10±1 mg were sterilized in an autoclave for 30 min at 120°C under 15 Ib pressure. Four pellets were implanted subcutaneously (s.c.), into the ventral region, two on either side, in each rat under light ether anesthesia (Lagishetty and Naik, 2008). PTX (0.125, 0.25, 0.5, 1.0, 2.0 and 4 mg kg^{-1}), Dexa (1 mg kg^{-1}), MTX (0.075 mg kg^{-1} and the vehicle (0.1 ml/100 g) were given intraperitoneally for seven consecutive days from the day of cotton pellet implantation. On 8th day, the animals were anaesthetized and the pellets together with the granuloma tissues were carefully removed and made free from extraneous tissues.

The wet pellets were weighed for wet weight and then dried in an incubator at 60°C until a constant weight was obtained (all the exudates was dried), after that the dried pellets were weighed again (Khouzami *et al*., 2009). The weight of exudate in mg was calculated by subtracting the constant dry weight of pellet from the immediate wet weight of pellet. Granulation tissue formation (dry weight of granuloma) was calculated after deducting the weight of cotton pellet (10 mg) from the constant dry weight of pellet and taken as a measure of granuloma tissue formation. The percent inhibitions of exudate and granuloma tissue formation were determined using the following formulas (Khouzami *et al*., 2009):

$$\text{Exudate inhibition (\%)} = \left(1 - \frac{\text{Weight of exudate in mg of treated group of rats}}{\text{Weight of exudate in mg of control group of rats}}\right) \times 100$$

$$\text{Granuloma inhibition (\%)} = \left(1 - \frac{\text{Weight of granuloma in mg of treated group of rats}}{\text{Weight of granuloma in mg of control group of rats}}\right) \times 100$$

All the results were expressed as mean±SD. The data were analyzed by using computerized SPSS program. The

significance of difference among the studied groups was determined using one-way Analysis of Variance (ANOVA). The p values less than 0.05 are considered significant.

RESULTS

In the 1st part, the suppressive effects of different doses of PTX, when used alone and in combination with standard anti-inflammatory agents (Dexa and MTX) on formalin-induced chronic inflammation were shown in Table 1. All doses of PTX (0.125, 0.25, 0.5, 1.0, 2.0 and 4.0 mg kg^{-1}) significantly reduced the increase in paw thickness (in a dose-dependent pattern) compared to controls, with maximum effect produced by the dose 4.0 mg kg^{-1} (29.33%) and all doses of PTX are significantly different when compared with each other. Meanwhile, both 1 mg kg^{-1} Dexa and 0.075 mg kg^{-1} MTX significantly inhibit the increase in paw thickness compared controls, with maximum effect produced by Dexa (36.36%). PTX (4.0 mg kg^{-1}) in combination with Dexa (1 mg kg^{-1}) produce 37.54% inhibition in paw edema, which was significantly higher than all of the effects produced by others; while combination of the same dose of PTX with MTX (0.075 mg kg^{-1}) produce 34.90% inhibition in paw edema, an effect comparable to that produced by Dexa alone and significantly different from those produced by other approaches of treatment. In Fig. 1, the dose-response relationship of the anti-inflammatory activity of pentoxifylline was found to be linear within the dose ranges utilized in the study.

In the 2nd part, the suppressive effect of different doses of PTX and combination of its highly effective dose with standard anti-inflammatory agents (Dexa or MTX) on exudate formation was shown in Table 2. PTX significantly decreased formation of the inflammatory exudate started in the dose of 0.25 mg kg^{-1} compared to controls, with maximum effect produced by 4.0 mg kg^{-1} (38.17%). Meanwhile, both 1 mg kg^{-1} Dexa and 0.075 mg kg^{-1} MTX significantly inhibited the formation of inflammatory exudate compared to controls, although their effects are not significantly different in this respect, maximum effect was produced by Dexa (45.62%). PTX (4.0 mg kg^{-1}) in combination with Dexa (1 mg kg^{-1}) produce 47.28% decrease in the formation of exudate, which was significantly higher than all of the effects produced by others; while PTX (4.0 mg kg^{-1}) in combination with MTX (0.075 mg kg^{-1}) produce 44.78% decrease in exudate formation, an effect significantly lower than that produced by the combination of PTX with Dexa and comparable to those produced by Dexa or MTX when used alone. In Fig. 2, the dose-response relationship of the anti-inflammatory activity (in term of attenuation of exudate formation) of PTX was found to be linear within the dose range of 0.25-4.0 mg kg^{-1}. Additionally, the suppressive effect of different doses of PTX and combination of its highly effective dose with standard anti-inflammatory agents (Dexa or MTX) on granuloma

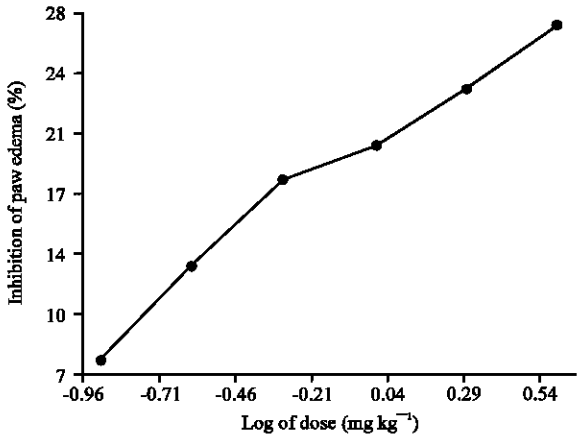

Fig. 1: Dose-response relationship of the effect of pentoxifylline on inhibition of paw edema (%) in formalin-induced chronic inflammation in rats

Table 1: Effects of different doses of pentoxifylline and its combination with dexamethasone or methotrexate on paw thickness and inhibition of paw edema (%) in formalin-induced chronic inflammation in rats

	Mean paw thickness (mm)		Mean increase in paw thickness (mm)	
Treatment groups	At zero time	After 7 days	after 7 days	Inhibition of paw edema (%)
Normal saline (0.1 mL/100 g)	4.01±0.06	7.42±0.05	3.41±0.04	-
PTX (0.125 mg kg^{-1})	4.06±0.06	7.25±0.05	3.19±0.05^{*a}	6.45
PTX (0.25 mg kg^{-1})	4.02±0.08	6.99±0.07	2.97±0.05^{*b}	12.90
PTX (0.5 mg kg^{-1})	3.95±0.09	6.72±0.05	2.77±0.07^{*c}	18.77
PTX (1 mg kg^{-1})	4.10±0.06	6.79±0.08	2.69±0.06^{*d}	21.11
PTX (2 mg kg^{-1})	4.09±0.06	6.65±0.07	2.56±0.05^{*e}	24.93
PTX (4 mg kg^{-1})	4.08±0.10	6.49±0.09	2.41±0.09^{*f}	29.33
PTX (4 mg kg^{-1}) +dexamethasone (1 mg kg^{-1})	4.11±0.08	6.24±0.09	2.13±0.09^{*i}	37.54
PTX (4 mg kg^{-1}) + methotrexate (0.075 mg kg^{-1})	4.01±0.08	6.23±0.07	2.22±0.07^{*h}	34.90
Dexamethasone (1 mg kg^{-1})	4.02±0.08	6.19±0.09	2.17±0.07^{*h}	36.36
Methotrexate (0.075 mg kg^{-1})	4.09±0.07	6.41±0.08	2.32±0.08^{*g}	31.96

Data were expressed as Mean±SD; number of animals = 8 in each group; *p<0.05 with respect to control group; values with non-identical superscripts (a, b, c, d, e, f, g, h and i) are considered significantly different (p<0.05)

Table 2: Effects of different doses of pentoxifylline and its combination with dexamethasone or metotrexate on exudation in cotton pellet-induced granuloma in rats

Treatment groups	Mean weight of exudates (mg)	Exudates inhibition (%)
Normal saline (0.1 mL/100 g)	107.20±7.13	-
PTX (0.125 mg kg^{-1})	100.54±6.97	6.21
PTX (0.25 mg kg^{-1})	96.87±4.71*[a]	9.64
PTX (0.5 mg kg^{-1})	89.35±5.74*[a]	16.65
PTX (1 mg kg^{-1})	78.55±7.32*[b]	26.72
PTX (2 mg kg^{-1})	70.59±6.50*[b]	34.15
PTX (4 mg kg^{-1})	66.28±8.52*[c]	38.17
PTX (4 mg kg^{-1}) +dexamethasone (1 mg kg^{-1})	56.52±4.97*[d]	47.28
PTX (4 mg kg^{-1}) +methotrexate (0.075 mg kg^{-1})	59.20±10.97*[c]	44.78
Dexamethasone (1 mg kg^{-1})	58.29±9.34*[c]	45.62
Methotrexate (0.075 mg kg^{-1})	60.43±5.83*[c]	43.63

Data were expressed as Mean±SD; number of animals = 6 in each group; *p<0.05 with respect to control group; values with non-identical superscripts are considered significantly different (p<0.05); PTX: Pentoxifylline

Table 3: Effects of different doses of pentoxifylline and its combination with dexamethasone or metotrexate on granular tissue formation in cotton pellet-induced granuloma in rats

Treatment groups	Mean dry weight of granuloma (mg)	Granuloma inhibition (%)
Normal saline (0.1ml/100g)	27.62±1.54	-
PTX (0.125 mg kg^{-1})	24.54±3.68*[a]	11.15
PTX (0.25 mg kg^{-1})	23.03±3.49*[a]	16.62
PTX (0.5 mg kg^{-1})	21.50±3.01*[b]	22.16
PTX (1 mg kg^{-1})	18.97±2.58*[b]	31.32
PTX (2 mg kg^{-1})	17.11±3.08*[c]	38.05
PTX (4 mg kg^{-1})	15.82±2.64*[c]	42.72
PTX (4 mg kg^{-1})+dexamethasone (1 mg kg^{-1})	13.20±1.46*[d]	52.21
PTX (4 mg kg^{-1})+methotrexate (0.075 mg kg^{-1})	14.21±2.57*[c]	48.55
Dexamethasone (1 mg kg^{-1})	14.16±2.37*[c]	48.73
Methotrexate (0.075 mg kg^{-1})	14.40±2.05*[c]	47.86

Data were expressed as Mean±SD; number of animals = 6 in each group; *p<0.05 with respect to control group; values with non-identical superscripts are considered significantly different (p<0.05)

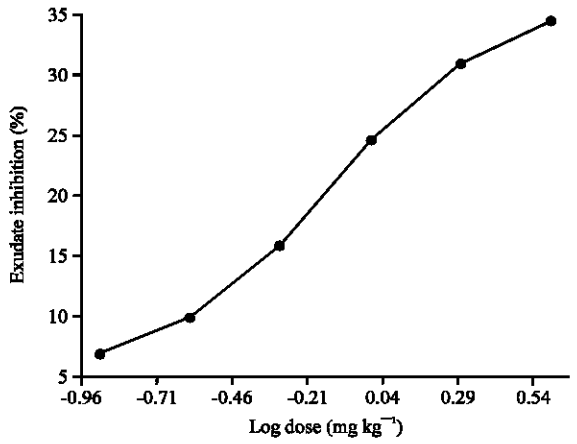

Fig. 2: Dose-response relationship of the effect of pentoxifylline on exudate inhibition (%) in cotton pellet-induced granuloma in rats

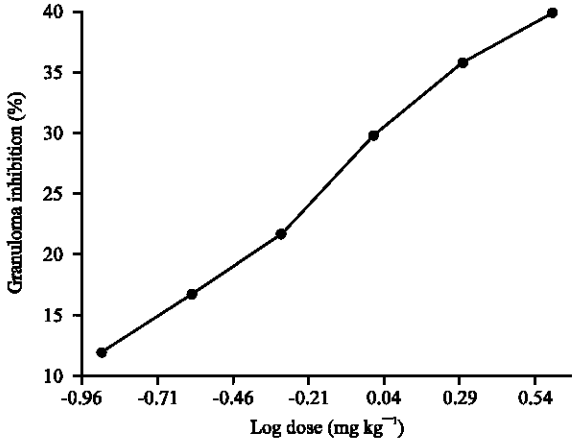

Fig. 3: Dose-response relationship of the effect of pentoxifylline on granuloma inhibition (%) in cotton pellet-induced granuloma in rats

formation was shown in Table 3. All PTX doses (0.125, 0.25, 0.5, 1.0, 2.0 and 4.0 mg kg^{-1}) significantly decrease formation of granuloma (in a dose-dependent pattern) compared to controls, with maximum effect produced by 4.0 mg kg^{-1} (42.72%). Meanwhile, both 1 mg kg^{-1} Dexa and 0.075 mg kg^{-1} MTX significantly inhibit the formation of granuloma compared to controls, although their effects are not significantly different in this respect. PTX (4.0 mg kg^{-1}) in combination with Dexa (1 mg kg^{-1}) produce 52.21% decrease in formation of granuloma, which was significantly higher than those produced by others; while PTX (4.0 mg kg^{-1}) in combination with MTX (0.075 mg kg^{-1}) produce 48.55% decrease in granuloma formation, an effect comparable to that produced by Dexa

and MTX when each of them used alone. In Fig. 3, the dose-response relationship of the anti-inflammatory activity (in term of attenuation of granuloma formation) of PTX was found to be linear within the dose ranges utilized in the study, with best linearity between 0.125-2.0 mg kg^{-1}.

DISCUSSION

The already reported biological activities of PTX, including anti-inflammatory, make it a good candidate to be evaluated for the exact dose-response relationship for the suspected anti-inflammatory activity. The definite mechanisms by which PTX exerts its beneficial effects during inflammation are not fully known but it may include blocking the production and release of pro-inflammatory cytokines (TNF-α, IL-6), attenuated LPS-induced leukocyte-endothelial adhesion/emigration and macromolecular extravasation, altered PMN chemotaxis, reduced superoxide production, improved microperfusion and microbicidal activity (Boldt *et al*., 2001). PTX at the dose of 15 mg kg^{-1} reduced TNF-α levels by 50% in an endotoxin-induced shock rat model, where administration of the drug to rats before intra-plantar injection of carrageenan reduced paw edema by 50-70% (Chen *et al*., 1994). Pentoxifylline inhibits Th1 cytokine production during allergen sensitization and lead to attenuation of airway hyper-responsiveness in a murine model of allergic pulmonary inflammation (Fleming *et al*., 2001). Moreover, PTX injected at doses of 1 and 2 mg intraplantarly (i.p) before (but not after) formaldehyde was effective in antagonizing formalin-induced pain behavior (Dorazil-Dudzik *et al*., 2004). These results explain the reported anti-inflammatory activity in the present study where similar model was utilized. In spontaneously hypertensive stroke-prone rats, an animal model that develops an inflammatory condition that precedes the appearance of brain abnormalities, treatment with high dose of PTX (200 mg/kg/day) completely protected the brain from abnormal development; drug treatment prevented the accumulation of macrophages or CD^{4+} positive cells, the activation of glia in brain tissues and the appearance of inflammatory proteins and thiobarbituric acid-reactive substances in body fluids (Banfi *et al*., 2004). Another suggested mechanism for of PTX effects probably includes the inhibition of the generation of oxygen radicals; it has been documented that PTX protects against lipid peroxidation in *in vitro* and *in vivo* models of ischemia (Bhat and Madyastha, 2001; Tanito *et al*., 2004). Because TNF-α and other cytokines have a crucial role in the development of different inflammatory diseases, PTX may be considered as a potential drug for the treatment of many inflammatory disorders like glomerulonephritis, leprae, diabetes mellitus and sepsis. It has been evaluated for its anti-inflammatory activity in different models of inflammatory nociception such as the writhing response induced by acetic acid and zymosan, zymosan-induced articular hyper-nociception in rats, and carrageenan-, bradykinin- and TNF-α-induced mechanical hyper-nociception (Verri *et al*., 2007) but the dose-response relationship is not elucidated. Pentoxifylline alone or when combined with low doses of corticosteroids has achieved significant improvement in respiratory function in patients with pulmonary sarcoidosis (Fazzi, 2003). TNF-α was inhibited by using PTX (10 mg/kg/day) for 5 days in rats with cirrhosis induced by common bile duct ligation (Sztrymf *et al*., 2004b). It inhibits proliferation and synthesis of collagen, fibronectin and glycosaminoglycans in normal, hypertrophic scar and keloid skin fibroblasts. PTX inhibited collagen synthesis in mesangial cells by over 50% on the mRNA level and attenuated the course of experimental mesangial proliferative glomerulonephritis (Strutz *et al*., 2000).

Moreover, PTX can decrease MMP activity by affecting the synthesis of inflammatory mediators (Siwik *et al*., 2000; Mann, 2002). Glucocorticoids dramatically reduce the manifestations of inflammation due to their profound effects on the concentration, distribution and function of peripheral leukocytes and their suppressive effects on the inflammatory cytokines, such as TNF-α or interleukin-6 (IL-6) and chemokines or other lipid and glycolipid mediators of inflammation. In addition to these effects, glucocorticoids influence the inflammatory response by reducing the prostaglandin synthesis that results from activation of phospholipase A_2 (Ardestani *et al*., 2007). Of the disease modifying anti-rheumatic drugs (DMARDs) commonly used in RA, Researchers reported that only methotrexate, sulfasalazine and aurothioglucose significantly slowed the rate of joint destruction and methotrexate, generally the DMARD of choice (Close, 2001). The mechanism by which MTX mediates its immunosuppressive and anti-inflammatory effects is still elusive. Down-regulation of inflammatory cytokines, adenosine release, modulation of release of metalloproteases and expression of cell surface adhesion molecules have been used to explain the effects of MTX in RA (Majumdar and Aggarwal, 2001). So, the effects of combination of pentoxifylline with dexamethasone or methotrexate may be related to pharmacodynamic impacts of these combinations. In conclusion, pentoxifylline, in a dose dependent pattern, attenuates formaldehyde-induced chronic inflammation and cotton-pellet induced granuloma in rats and potentiates the anti-inflammatory activity of dexamethasone and methotrexate.

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