PROPHYLACTIC AND THERAPEUTIC EFFECTS OF PROSTAGLANDIN E_1 ON THE DISEASE ACTIVITY IN ADJUVANT ARTHRITIC RATS

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INTRODUCTION

Prostaglandin E2 had been found to prevent and to improve adjuvant arthritis in rats (Aspinall and Cammarata, 1969). PGE_1 was found to affect other autoimmune phenomena in NZB/NZW mice (Zurier et al., 1977). Furthermore, Henriksson et al., (1988) reported that PGE_2 could decrease disease activity in patients with rheumatoid arthritis.

The association of joint diseases with a variety of bowel disorders is well documented (Neumann & Wright,1983; Bourne et al., 1985 and Segal et al., 1986). This has inevitably led to much speculation as to a possible aetiopathogenetic role for gut in rheumatoid arthritis (Henriksson et al., 1986 and Bjarnason & Peters, 1987). PGs are known to have trophic action on gastrointestinal mucosa and to protect it against various injurious factors (Miller & Jacobsson, 1979 and Helander et al.,1985).

The aim of the present study was to investigate the effect of oral PGEl when given in prophylactic or therapeutic regimen on the disease activity of adjuvant induced rheumatoid like arthritis in albino rats and it's relation to the trophic action of PGs on gastrointestinal mucosa. The effect of PGE_1 on serum cortisol level was also measured as a possible mechanism for it's potential effect on arthritis.

MATERIAL AND METHODS

Fourty male albino rats (mean weight 150 gm) were housed under similar conditions and diet. Eight rats were left as non-arthritic control group. The other 32 rats were rendered arthritic by single intradermal inoculation with 0.1 ml complete Freud's adjuvant (Difco Laboratories Inc., Detroit U.S,A.) into the base of the rat tail. Systemic arthritis was fully developed within 28-days in avarge (Eckhardt et al., 1981). The arthritic rats were randomly divided into four equal groups. One group was given prostaglandin El saline suspension by intragastric intubation in a dose of 100 ug/ kg/day (Reinhart et al.,1983) from the first day of adjuvant inoculation till the full development of arthritis(i.e.28 days) to test it's prophylactic action. The second group was given PGEI 100 ug/ kgm/day orally for 2 weeks after full development of arthritis to test it's potential therapeutic action. The other two arthritic groups served as controls and they were given daily normal saline orally for the duration corresponding to the prophylactic or therapeutic PGE_1 administration.

At the end of medication of each group , the animals were subjected to the following experimental procedures:

1. Measurement of paw oedema thickeness and pain threshold (by analgesymeter) to assess the severity of inflammation as an indicator for disease activity. or adjuvant arthritis.
2. Animals were sacrificed and blood samples were taken for determination of:
   * Serum C-reactive protein (Kindmark, 1972 and-Dego et al., 1980) and serum albumin (Doums & Blggs,1972) as biochemical inflammatory markers.
   * Serum cortisol by enzyme radioimmunassay method (Farmer & Priece, 1974).
3. Specimens from. joints, stomach and small intestine were taken, fixed in 10 % neutral formalin and processed later as .paraffin sections stained with Haemtoxylin & Eosin for histopathological examination.

RESULTS

PGE_1 was found to produce a significant prophylactic and therapeutic effects on adjuvant arthritis in rats a.q

evidenced by the significant reduction in paw oedema thickness ($P<0.001$), significant elevation of pain-threshold measured by analgesymeter (tables I & II) and the significant correction of the biochemical changes in serum C-reactive protein and serum albumin (Tables III & IV).

In addition, PGE_1 treatment was found to produce a significant rise of the serum cortisol level either when given in prophylactic or therapeutic re gimen as compared to the corresponding arthritic control group (Tables III & IV).

Histopathological Findings :

Joints :

The arthritic group showed cellular proliferation of the synovium together with dilated blood vessels and infiltration by acute and chronic inflammatory cells. Both groups treated with PGEI (prophylactic and therapeutic) revealed no significant histopathological changes in comparison to the control (Fig. 1).

Stomach

The gastric mucosa of arthritic group showed atrophic changes, it was decreased in thickness and was focally ulcerated as compared to the control group. The specialized cells of the gland were degenerated, decreased in both number and size and focally abscent (Fig.2). Infiltration of the lamina propria by cellular infiltrate composed mainly of lymphocytes was seen. On the other hand, an increase in thickness of gastric mucosa was seen in animals given PGEI (prophylactically or therapeutically) as compared to arthritic group. The specialized cells of the glands were increased in number in both groups, being formed mainly of parietal and mucous cells (Fig. 3). The lamina propria still showed chronic inflammatory cells but distributed focally. This trophic changes were more pronounced in gastric antrum than gastric corpus.

Small Intestine :

In arthritic group, the small intestine revealed mucosal atrophy, the villi appeared shorter and broader than normal (Fig. 4). There was increased cellular infiltration mainly lymphocytes in the lamina propria. Both groups given PGEI showed increased mucosal

thickness as indicated by relatively longer villi and deeper crypts (Fig. 5).

The improvement of small intestine on histopathological examination was less evident than the marked correction in gastric pathological changes.

DISCUSSION

The present study demonstrated that PGEl had a significant prophylactic and therapeutic effects on adjuvant arthritis in rats as evidenced by the significant reduction of paw oedema thickness,the increase of pain thereshold,the absence of inflammatory reaction in the joints of treated animals , the reduction of serum C-reactive protein and the elevation of serum albumin as biochemical inflammatory markers commonly used to assess the activity of inflammatory rheumatic diseases (Amos et al., 1977 & Henriksson et al., 1988). In aggreament with these findings Zurier & Quagliata (1971) reported that PGEl had therapeutic effects on adjuvant arthritis in rats but they did not investigate it's prophylactic value. Similary, PGE was found to have both prophylactic and therapeutic effect on adjuvant arth-ritis in rats (Aspinall & Cammarata, 1969) and on rheumatoid arthritis in man (Henriksson et al., 1988).

Histopathological examination revealed that all the non treated adjuvant arthritic rats had an atrophic gastrointestinal mucosa with focal ulcerations and chronic inflammatory cells infiltration. The thickness of gastric mucosa was decreased and the speciallized glandular cells were decreased in number and focally absçent. The intestinal mucosal thickaness was also decreased with short wide villi as compared with the control non arthritic rats. These findings are in accord with those described by Main and Whittle (1977) who assumed that the cause of these atrophic changes may be an increased sensitivity of the parietal cell to secretory stimuli coupled with the reduction in mucosal blood flow and accompanying ischaemia resulting from depletion of endogenous prostaglandines. In support to the present findings clinical studies had demonstrated the prevalence of atrophic changes in gastric, jejunal and colonic mucosa in patients with rheumatoid arthritis (Marcolongo et al., 1979 and Anonymous, 1986). Prostagrandin El treatment given in ei-

ther prophylactic or therapeutic regimens produced marked increase in mucosal thickness, reduced incidance of mucosal ulcerations and decreased density of chronic inflammatory cells infiltration. This trophic effects were more pronounced in the gastric antrum than in gastric corpus or small intestine. A similar trophic actions of EPGs on gastrointestinal mucosa were well documented in the rats (Helander et al., 1985) as well as in man (Henriksson et al., 1988).

The observed increase in number of mucous cells in PGE_1 treated rats is in aggreement with Helander et al., (1985) who stated that mucous cells are capable of production of both mucous and bicarbonates which seem to be of importance in the phenomenon of cytoprotection of prostaglandins . However, other cytoprotective actions of PGs should be considered viz:increased mucosal blood flow to prevent tissue ischaemia (Whittle, 1977),inhibition of acid secretion seems to play a minor role , since PGs in doses that do not suppress acid secretion can confer protection (Miller, 1983 and Vapaatalo & Ylikorala, 1984), also PGs may correct the increase in permeability to H ions and the inhibition of sodium & chloride transport, such factors which have been accused to be involved in the pathogenesis of mucosal damage (Bowen et al.,1975), stimulation of macromolecular (i.e. DNA, RNA and protein) synthesis could be another factor that may play a role in chronic forms of mucosal injury (Konturek et al,, 1981), stimulation of C-AMP production in gastric epithelium (Terano et al., 1982). Again, PGEl was found to stabilize lysosomal membranes and prevent their breakdown (Ferguson et al., 1973). However , the magnitude of the role the lysosomal stabilization played in prostaglandins cytoprotection is still not identified (Miller, 1983). In addition, Robert (1976) suggested that PGs may act as trophic hormones for gastrointestinal mucosa in much the same way as gastrin has been shown to be a trophic hormone for gastric fundus.

The gastrointestinal cytoprotective action of PGEl may largely contribute to it's prophylactic and therapeutic benefits in adjuvant arthritis, since strong association between joint disease and bowel disorders is well do-

Table I : Prophylactic effect of PGE_1 on development of adjuvant arthritis in rats .

	Non arthritic control group (n = 8) .	Arthritic control group given oral saline from the 1st day of adjuvant inoculation for 28 days (n = 8) .	Arthritic group treated with PGE_1 100 ugm/ kgm / day orally for 28 days from the 1st day of adjuvant inoculation (n = 8) .
Paw Thickness (Mean in mm ± S . E .)	2.29 ± 0.09	3.13 ± 0.13	2.15 ± 0.09
P	-	<0.001	N . S .
P'	-	-	<0.001
Analgesymeter test (Mean pressure weight in gm ± S . E .)	196 ± 12.5	118 ± 9.2	189 ± 15.7
P	-	<0.001	N . S .
P'	-	-	<0.01

SE : Standard Error n= Number of Rats in each group .

P : Significance of the difference between the arthritic and non arthritic groups .

P ' : Significance of the difference between the PGE_1 treated and the arthritic non treated groups .

Table II : Therapeutic effect of PGE_1 on f adjuvant arthritis in rats .

	Non arthritic control group (n = 8) .	Arthritic control group given oral saline daily for 2 weeks after development of arthritis, (n = 8) .	Arthritic group treated with PGE_1 100 ugm/ kgm / day orally for 2 weeks after development of arthritis, (n = 8) .
Paw Thickness (Mean in mm ± S . E .)	2.29 ± 0.09	3.21 ± 0.08	2.1 ± 0.06
P	-	<0.001	N . S .
P'	-	-	<0.001
Analgesymeter test (Mean pressure weight in gm ± S . E .)	196 ± 12.5	120 ± 8.9	201 ± 17.3
P	-	<0.001	N . S .
P'	-	-	<0.001

SE : Standard Error n= Number of Rats in each group .

P : Significance of the difference between the arthritic and non arthritic groups .

P ' : Significance of the difference between the PGE_1 treated and the arthritic non treated groups .

Table III : Effect of prophylactic administration of PGE_1 on serum C-reative protein , albumin and cortisol levels in adjuvant arthritic rats .

	Non arthritic control group (n = 8) .	Arthritic control group given oral saline from the Ist day of adjuvant inoculation for 28 days (n = 8) .	Arthritic group treated with PGE_1 100 ugm/ kgm / day orally for 28 days from the Ist day of adjuvant inoculation (n = 8)
* Serum C- reative protein (Mean in ug / ml ± S.E.)	13.03± 0.57	27.7 ± 0.88	12.8 ± 0.53
P	-	<0.001	N.S.
P'	-	-	<0.001
* Serum albumin (mean in gm/100 ml ± S.E)	7.4 ± 0.43	2.28 ± 0.12	6.9 ± 0.39
P	-	<0.001	N . S .
P'	-	-	<0.001
* Serum cortisol (Mean in ug/ 100 ml ± S.E.)	1.58 ± 0.09	0.74 ± 0.052	4.83 ± 0.28
P	-	<0.001	<0.001
P'	-	-	<0.001

Table IV : Effect of therapeutic administration of PGE_1 on serum C- reative protein, albumin and cortisol level in adjuvant arthritic rats .

	Non arthritic control group (n = 8) .	Arthritic control group given oral saline daily for 2 weeks after development of arthritis, (n = 8)	Arthritic group treated with PGE_1 100 ugm/ kgm / day orally for 2 weeks after development of arthritis, (n = 8) .
* Serum C-reative protein (Mean in ug / ml ± S.E.)	13.03 ± 0.57	27.7 ± 0.88	12.8 ± 0.53
P	-	<0.001	N.S.
P'	-	-	<0.001
* Serum albumin (mean in gm/100 ml ± S.E)	7.4 ± 0.43	2.38 ± 0.12	6.9 ± 0.39
P	-	<0.001	N . S .
P'	-	-	<0.001
* Serum cortisol (Mean in ug/ 100 ml ± S.E.)	1.58 ± 0.079	0.74 ± 0.052	4.83 ± 0.28
P	-	<0.001	<0.001
P'	-	-	<0.001

P : Significance of the difference between the arthritic and non arthritic groups .
P ' : Significance of the difference between the PGE_1 treated and the arthritic non treated groups .

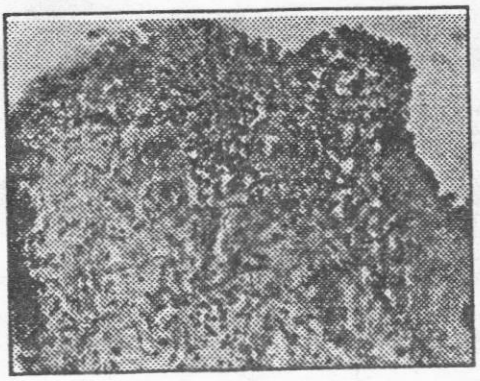

Fig. 1 : Section of synovial membrane of arthritic rat showing cellular proliferation of, synovium, diluted blood vessels and inflamatory cells (Hx. & E. X 160).

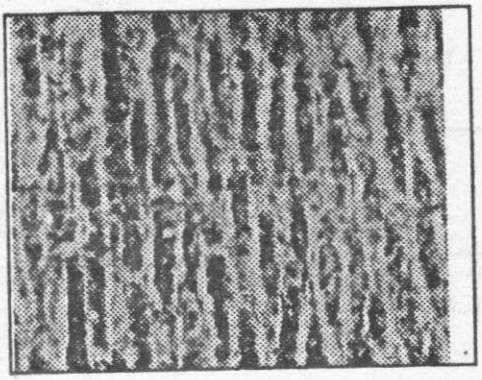

Fig. 3 : Section of atomaoh of arthritic rat given PGEI prophylaotically showing increaged mucosal thickness and glandular . cells (Hx. & E. X 160).

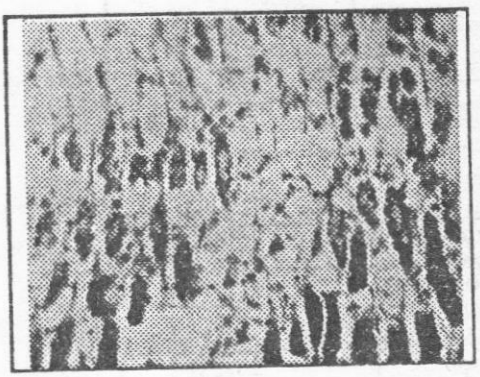

Fig. 2 : Section of stomach of arthritic rat ahowing mucosal atrophy and degeneration of the glandular cells . (Hx . & E. X 160).

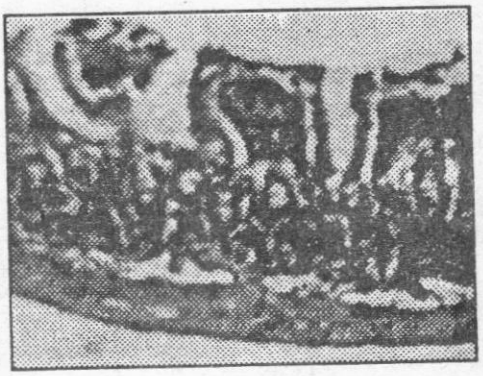

Fig. 4: Section of small intestine of arthritic rat ahowing short and broad villi (Hx. & E. X 160).

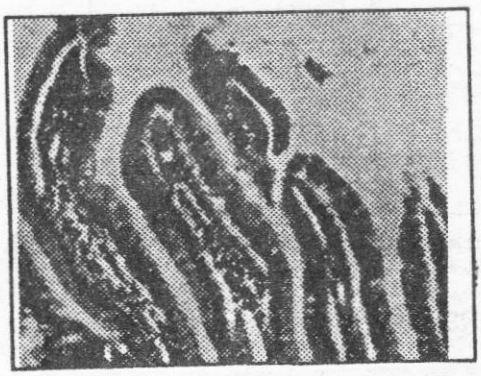

Fig. 5 : Section of small intestine of arthritic rat given PGE prophylactically showing relatively longer villi and deeper crypts (Hx. & E. X 160).

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دراسة التأثير الوقائى والعلاجى للبروستاجلاندين إ ١ على نشاط المرضى فى الفئران المصابه بالتهاب المفاصل

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اجرى هذا البحث على ٤٠ فأر من الفئران البيضاء مقسمة الى خمسة مجموعات متساويه العدد .

اتخذت المجموعة الاولى ضابطه . اما المجموعات الاربعة الاخرى فقد حقنت بها مادة الفريند لاحداث التهاب بالمفاصل يشابه الالتهاب المفصلى لمرضى الروماتويد . وقد عولجت احدى المجموعات بمادة البروستاجلاندين إ ١ عن طريق الفم منذ اليوم الاول لحقن الفئران بمادة الفريند ولمدة ٢٨ يوما (بجرعة ١٠٠ ميكروجرام / كجم / يوم) وذلك لاختبار تأثيرها الوقائى واعطيت المجموعة الاخرى نفس الجرعة من البروستاجلاندين إ ١ ولكن بعد ٢٨ يوم من حقن مادة الفريند ولمدة اسبوعين وذلك لاختيار التأثير العلاجى للبروستاجلاندين إ ١ . أما المجموعتان الاخيرتان فقد استخدمتا كمجموعتين ضابطين لمقارنة التأثير الوقائى والعلاجى للبروستاجلاندين إ ١ .

وقد لوحظ عموما أن الفئران التى اعطيت البروستاجلاندين إ ١ بطريقة وقائية أو علاجية حدث بها تحسن ملموس فى التهاب المفاصل كما أوضح ذلك قياس درجة تورم المخلب واختبار درجة الالم وقياس بعض المعاملات الكيمائيه فى مصل الدم التى تميز وجود النشاط الروماتيزمى بالمفاصل مثل مستوى بروتين س المتفاعل ونسبة الالبيومين واظهر الفحص الباثولوجى تحسن فى درجة الاذيه والضمور بالاغشية المخاطية فى المعده والامعاء التى تصاحب حدوث الالتهاب المفصلى ولكن هذا التحسن كان بصوره اوضح فى المعده . وقد وجد أن البروستاجلاندين إ ١ يسبب زياده ذات دلاله احصائيه هامه فى مستوى الكورتيزول بمصل الدم .

ويستخلص من هذه الدراسة ان البروستاجلاندين إ ١ له تأثير فعال فى علاج التهاب المفاصل الروماتيزمى والوقايه منه . وأن هذا التأثير يمكن تفسيره بتحسن حاله الاذيه فى الاغشيه المخاطيه بالمعده والأمعاء والتى غالبا ما تصاحب هذه الالتهابات المفصليه وكذلك يمكن ان يكون بطريقة غير مباشره نتيجه زياده مستوى الكورتيزول بمصل الدم .