PROPHYLACTIC AND THERAPEUTIC EFFECTS OF PROSTAGLANDIN E₁ ON THE DISEASE ACTIVITY IN ADJUVANT ARTHRITIC RATS

By
Gaballah, A. M.; El-Banna, F. M.; Abd El-Aziz, M. A.; Zeid, S. E. and Sirag, S. M.

From
Pharmacology and Pathology Departments,
Mansoura Faculty of Medicine
Received for Publication 5/12/1991

INTRODUCTION
Prostaglandin E₂ had been found to prevent and to improve adjuvant arthritis in rats (Aspinall and Cammarata, 1969). PGE₁ was found to affect other autoimmune phenomena in NZB/NZW mice (Zurier et al., 1977). Furthermore, Henriksson et al., (1988) reported that PGE₂ could decrease disease activity in patients with 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 Hellander et al., 1985).

The aim of the present study was to investigate the effect of oral PGE₁ 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 PGE₁ on serum cortisol level was also measured as a possible mechanism for it's potential effect on arthritis.

MAN S O U R A MEDICAL JOURNAL
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 average (Eckhardt et al., 1981). The arthritic rats were randomly divided into four equal groups. One group was given prostaglandin E1 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 PGE1 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 PGE1 administration.

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

1. Measurement of paw oedema thickness 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

PGE1 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, PGE1 treatment was found to produce a significant rise of the serum cortisol level either when given in prophylactic or therapeutic regimen 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 PGE1 (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 absent (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 PGE1 (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 PGE1 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 PGEI 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 threshold, 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 agreement with these findings Zurier & Quagliata (1971) reported that PGEI 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 arthritis 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 specialized glandular cells were decreased in number and focally absent. The intestinal mucosal thickness 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 E1 treatment given in ei-
ther prophylactic or therapeutic regimens produced marked increase in mucosal thickness, reduced incidence 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 PGE1 treated rats is in agreement 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, PGEI 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 PGEI may largely contribute to its prophylactic and therapeutic benefits in adjuvant arthritis, since strong association between joint disease and bowel disorders is well do-
## PROPHYLACTIC AND THERAPEUTIC EFFECTS etc...

### Table I: Prophylactic effect of PGE₁ on development of adjuvant arthritis in rats.

<table>
<thead>
<tr>
<th></th>
<th>Non arthritic control group (n = 8)</th>
<th>Arthritic control group given oral saline from the 1st day of adjuvant inoculation for 28 days (n = 8)</th>
<th>Arthritic group treated with PGE₁ 100 μg/m kg/m day orally for 28 days from the 1st day of adjuvant inoculation (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paw Thickness (Mean in mm ± S.E.)</td>
<td>2.29 ± 0.09</td>
<td>3.13 ± 0.13</td>
<td>2.15 ± 0.09</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.001</td>
<td>N.S.</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Analgesymeter test (Mean pressure weight in gm ± S.E.)</td>
<td>196 ± 12.5</td>
<td>118 ± 9.2</td>
<td>189 ± 15.7</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.001</td>
<td>N.S.</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

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 PGE₁ treated and the arthritic non treated groups.

### Table II: Therapeutic effect of PGE₁ on 1 adjuvant arthritis in rats.

<table>
<thead>
<tr>
<th></th>
<th>Non arthritic control group (n = 8)</th>
<th>Arthritic control group given oral saline daily for 2 weeks after development of arthritis, (n = 8)</th>
<th>Arthritic group treated with PGE₁ 100 μg/m kg/m day orally for 2 weeks after development of arthritis, (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paw Thickness (Mean in mm ± S.E.)</td>
<td>2.29 ± 0.09</td>
<td>3.21 ± 0.08</td>
<td>2.1 ± 0.06</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.001</td>
<td>N.S.</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Analgesymeter test (Mean pressure weight in gm ± S.E.)</td>
<td>196 ± 12.5</td>
<td>120 ± 8.9</td>
<td>201 ± 7.3</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.001</td>
<td>N.S.</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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 PGE₁ treated and the arthritic non treated groups.

---

*Volume 22, No. 1&2 Jan. & April, 1992*
Table III: Effect of prophylactic administration of PGE1 on serum C-reactive protein, albumin and cortisol levels in adjuvant arthritic rats.

<table>
<thead>
<tr>
<th></th>
<th>Non arthritic control group (n = 8)</th>
<th>Arthritic control group given oral saline from the 1st day of adjuvant inoculation for 28 days (n = 8)</th>
<th>Arthritic group treated with PGE1 100 ug/m kg / day orally for 28 days from the 1st day of adjuvant inoculation (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Serum C-reactive protein (Mean in ug/ml ± S.E.)</td>
<td>13.03±0.57</td>
<td>27.7±0.88</td>
<td>12.8±0.53</td>
</tr>
<tr>
<td>p</td>
<td>p</td>
<td>&lt;0.001</td>
<td>N.S.</td>
</tr>
<tr>
<td>p’</td>
<td>p’</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>* Serum albumin (Mean in g/ml/100 ml ± S.E.)</td>
<td>7.4±0.43</td>
<td>2.28±0.12</td>
<td>6.9±0.39</td>
</tr>
<tr>
<td>p</td>
<td>p</td>
<td>&lt;0.001</td>
<td>N.S.</td>
</tr>
<tr>
<td>p’</td>
<td>p’</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>* Serum cortisol (Mean in ug/100 ml ± S.E.)</td>
<td>1.58±0.09</td>
<td>0.74±0.052</td>
<td>4.83±0.28</td>
</tr>
<tr>
<td>p</td>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p’</td>
<td>p’</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table IV: Effect of therapeutic administration of PGE1 on serum C-reactive protein, albumin and cortisol level in adjuvant arthritic rats.

<table>
<thead>
<tr>
<th></th>
<th>Non arthritic control group (n = 8)</th>
<th>Arthritic control group given oral saline daily for 2 weeks after development of arthritis, (n = 8)</th>
<th>Arthritic group treated with PGE1 100 ug/m kg / day orally for 2 weeks after development of arthritis, (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Serum C-reactive protein (Mean in ug/ml ± S.E.)</td>
<td>13.03±0.57</td>
<td>27.7±0.88</td>
<td>12.8±0.53</td>
</tr>
<tr>
<td>p</td>
<td>p</td>
<td>&lt;0.001</td>
<td>N.S.</td>
</tr>
<tr>
<td>p’</td>
<td>p’</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>* Serum albumin (mean in g/ml/100 ml ± S.E.)</td>
<td>7.4±0.43</td>
<td>2.38±0.12</td>
<td>6.9±0.39</td>
</tr>
<tr>
<td>p</td>
<td>p</td>
<td>&lt;0.001</td>
<td>N.S.</td>
</tr>
<tr>
<td>p’</td>
<td>p’</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>* Serum cortisol (Mean in ug/100 ml ± S.E.)</td>
<td>1.58±0.079</td>
<td>0.74±0.052</td>
<td>4.83±0.28</td>
</tr>
<tr>
<td>p</td>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p’</td>
<td>p’</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P : Significance of the difference between the arthritic and non arthritic groups.
P’ : Significance of the difference between the PGE1 treated and the arthritic non treated groups.

MANSOURA MEDICAL JOURNAL
Fig. 1: Section of synovial membrane of arthritic rat showing cellular proliferation of synovium, dilated blood vessels and inflammatory cells (Hx. & E. X 160).

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

Fig. 3: Section of stomach of arthritic rat given PGEI prophylactically showing increased mucosal thickness and glandular cells (Hx. & E. X 160).

Fig. 4: Section of small intestine of arthritic rat showing 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).
REFERENCES


MANSOURA MEDICAL JOURNAL


دراسة التأثير الوقائي والعلاجي للبروساجلاندين
على نشاط المرضي في الفئران المصابة بالتهاب المفاصل

د/ علي جاب الله د/ فريدة البنا د/ محمد عبد الغنى
د/ صبري زيد د/ سهير سراج
من اقسام الفارماكولوجي والباثولوجي - بكلية الطب - جامعة النصرة

أجري هذا البحث على 40 فأر من الفئران البيضاء، مقسمة إلى خمسة مجموعات متساوية العدد. اتخذت المجموعة الأولى ضابطةً. أما المجموعات الأخرى الخمسة فقد حققت بها مادة الفرينيد لأحداث التهاب بالمفاصل بشاب الالتهاب المفصلي لمرض الروماتوند. وقد عولجت أعضاء المجموعات ببداية البروساجلاندين بـ 1 ملليغرام مجموعة (كرم / يوم) وذلك لاختبار تأثيرها الوقائي وعلاجية المجموعة الأخيرة. فضل الجرعة من البروساجلاندين بـ 1 ملليغرام، وذلك بعد 28 يوم من حقن مادة الفرينيد ولدته أسبوعين. وذلك لاختبار التأثير العلاجي للبروساجلاندين. أما المجموعات الخمسة فقد استخدمت كمجموعتين ضابطين للمقارنة. التأثير الوقائي والعلاجي للبروساجلاندين

وقد لوحظ عموما أن الفئران التي أعطيت البروساجلاندين بـ 1 ملليجرام دوجة توم المخلب وأظهرت درجة الألم وقياس بعض العاملات الكيميائية في مصل الدم التي تشير إلى نشاط الروماتوند للفور الصاعد وتظهر بعض الكيميائيات بمستويات برتين من المفاصل ونسبة الألبيومين وآخرين في درجة الأذى والاضطراب بالاغتصاب المخاطية في الفأر، ومع ذلك، أن الفئران المصابين بالالتهابات المصليتت يمكن أن يصبحوا أضعاف بما في ذلك الكورتيزول، بصل الدم.

ويعتبر مثل هذه الدراسة أن البروساجلاندين بـ 1 له تأثير فعال في علاج التهاب المفاصل الروماتوند والوقاية منه. وأن هذا التأثير يمكن أن يتضح حالياً في الأغذية المخاطية واللمعان، والتي غالبًا ما تصبح هذه الالتهابات المصليتت، وكذلك يمكن أن يكون بطرق غير مباشرة نتيجة زيادة مستوى الكورتيزول، بصل الدم.

Volume 22, No. 1 & 2 Jan. & April, 1992