

BY INVITATION

EFFECT OF PROSTAGLANDIN E₂ AND 15(R)15 METHYL PGE₂ ON DUODENAL ULCER

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SYNOPSIS

The efficacy of prostaglandin E₂, its synthetic analogue 15(R)15 methyl PGE₂ and a placebo was compared in a double blind trial in three groups of patients with duodenal ulcer. The treatment was given three times a day, half an hour before meals, for four weeks. Ulcer healing was assessed by endoscopy performed at the beginning and after four weeks of treatment. In the doses used, the two prostaglandins had no effect in reducing the symptoms nor in increasing the rate of healing of duodenal ulcer after four weeks when compared with the placebo group.

INTRODUCTION

In previous studies we have shown that 15(R)15 methyl PGE₂ (and its methyl ester) given orally inhibits basal and pentagastrin stimulated gastric acid secretion in healthy subjects as well as in those with duodenal ulcers (1-4). This compound also accelerates the healing of gastric ulcers (2, 5, 6). Whether the ulcer healing effect of 15(R)15 methyl PGE₂ is due to its gastric antisecretory effect or due to a cytoprotective effect (which is independent of effect on gastric secretion (7) is not known.

Naturally occurring prostaglandin E₂ also accelerates healing of gastric ulcers when given orally (2, 8). Since this compound has no effect on gastric secretion in man by the oral route (1), the ulcer healing effect may be due to a cytoprotective effect (7).

This double blind study was undertaken to assess the effect of orally administered PGE₂ and 15(R)15 methyl PGE₂ on the healing of duodenal ulcer.

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PATIENTS AND METHODS

Sixty ambulant patients with endoscopically proven duodenal ulcer initially entered the study. Excluded were those with other serious illnesses, those requiring hospitalisation after entering the study and those in whom satisfactory assessment of ulcer size could not be made. Fifty two patients completed the study (three did not return for repeat endoscopy, four returned too late and one patient was found to have constrictive pericarditis during the course of the study). All were treated on an outpatient basis. Patients were randomly allocated to three groups. One group was given prostaglandin E₂ 0.5 mg, the second 15(R)15 METHYL PGE₂ 100 µg and the third a lactose placebo. Prostaglandin E₂ tablets were supplied by the Upjohn Co..

UK; 15 (R) 15 methyl PGE₂ was dissolved in ethyl alcohol and 100 ug (0.1 ml) of this placed in an opaque gelatine capsule and evaporated to dryness in a vacuum desiccator. The capsule was then filled with lactose powder. Bioassay using guinea pig ileum and a study of the effect of these capsules in suppressing pentagastrin stimulated gastric acid secretion in a group of duodenal ulcer patients showed no loss of activity when compared with the standard stock solution. During the study patients were given these two prostaglandins or the placebo three times a day, half an hour before meals, for four weeks. A liquid antacid (magnesium trisilicate) was supplied, to be used as required for relief of ulcer pain. No other medication was given nor any dietary constraints made.

Fiberoptic endoscopies were performed by an experienced endoscopist using either the Olympus GIF-D3, the GIF-K or the GIF-Ps panendoscopes. Endoscopy was performed at the beginning and after a four week course of treatment. Patients who failed to return for endoscopy within 4 days of cessation of treatment were excluded from the study. Ulcer size was measured with the aid of an ACMI calibrated measuring device on colour photographs (Kodak Ektachrome EHB). Surface area of ulcers was calculated as $\pi(d/2)^2$ for round ulcers and $\pi(d1/2)(d2/2)$ for irregular shaped ulcers (d1 and d2 being the longest and shortest diameters). Multiple ulcers in the same patient were considered as a single ulcer by addition of their surface area. Symptomatic response was also assessed initially, after two weeks treatment and at the end of the study using a simple points system (Table 1). The X₂ test was applied for ulcer healing and Student's test for other results.

Table 1 Scoring for symptomatic assessment

Pain	Points	Tenderness	Points
Mild, occasional	1	Mild	1
Mild, daily	2	Moderate	2
Moderate, frequent, nocturnal	3	Intense	3
Severe, poorly relieved	4		

RESULTS

Of the fifty two patients who completed the study, 19 were in PGE₂ group, 17 in 15 (R) 15 methyl PGE₂ and 16 in the placebo group. The three groups were comparable in age, duration of disease and initial size of ulcer (Table 2). The patients were predominantly male (there were two

females in the PGE₂ group, one in the 15 (R) 15 me PGE₂ group and two in the placebo group). There were two Indian patients in the PGE₂ group, two in the 15 (R) 15 me PGE₂ group and one in the placebo group. The remainder were all Chinese. There were 6 patients who had multiple ulcers.

Ulcer Healing

The results of the endoscopic assessment were divided into 3 categories; ulcers showing complete healing after 4 weeks; those showing significant healing with a reduction of surface area by 80% or more and the rest with partial or no healing. There was no statistical difference either in complete healing or in the combination of complete and significant partial healing between the treated groups and the placebo group (Table 3).

Symptomatic Response

Patients in all three groups showed symptomatic improvement between the 1st and 28th day. There is no difference between the groups. As has been noted in another study (9) there was no correlation between symptomatic improvement and ulcer healing. There was no significant difference in the amount of antacid used by the patients in the three groups.

Side Effects

No adverse side effects were noted in any patient. A few patients on placebo as well as on prostaglandin commented on the laxative effective of the therapy but it was difficult to distinguish this from the effect of the antacid given. In any case, none of the patients considered the treatment unpleasant enough to discontinue the medication.

DISCUSSION

Since 15 (R) 15 methyl PGE₂ inhibits basal and pentagastrin stimulated gastric acid secretion and increases the rate of healing of gastric ulcers (1-8) it was anticipated that this compound would also increase the rate of duodenal ulcer healing. PGE₂ given orally does not have any effect on gastric secretion (1). However, this natural prostaglandin increases the rate of gastric ulcer healing in men (2, 8). This may be due to a cytoprotective effect of PGE₂ convincingly demonstrated against gastrointestinal ulcers induced by several drugs and procedures in laboratory animals (7).

Table 2 Characteristics of three groups of patient with duodenal ulcers

	No. of Patients	Mean Age ± SEM	Mean duration of Disease (Years) ± SEM	Mean Initial Ulcer size (mm ²) ± SEM
PGE ₂	19	36.9±14.2	5.6±3.3	24.1±17.3
15 (R) 15 me PGE ₂	17	46.5±15.2	6.0±5.2	26.0±14.5
Placebo	16	42.7±17.7	4.5±4.0	19.9±10.1

Table 3 Result of four weeks' treatment with prostaglandins or placebo in three groups of patients with duodenal ulcer

	(a) Complete healing	(b) Significant healing 80% reduction	Total a + b
PGE ₂ n = 19	7 X ² = 0.1 n.s.	7	14 X ² = 2.09 n.s.
15 (R) 15 me PGE ₂ n = 17	4 X ² = 0.25 n.s.	5	9 X ² = 0.03 n.s.
Placebo n = 16	4 —	4	8

Contrary to expectations, results of the present study show that neither PGE₂ nor 15 (R) 15 methyl PGE₂ given in doses which did not produce side effects had a significant effect in reducing the symptoms or in increasing the rate of healing of duodenal ulcers after 4 weeks of treatment when compared with a placebo.

Once formed the natural tendency of acute peptic gastrointestinal ulcer is to heal spontaneously. In a study of placebo treated ulcers. Scheurer et al (10) found that 53.3% of duodenal ulcers had healed by 3 weeks and 73.3% after 6 weeks. It is therefore conceivable that in our study the lack of difference in the prostaglandin and placebo groups may be due to the long time interval (4 weeks) between the two endoscopic examination. However, Gibinski et al (11) who treated their patients for 2 weeks with 15 (R) 15 me PGE₂ and carried out endoscopic examination at weekly interval could not demonstrate any significant difference in the healing of duodenal ulcers between prostaglandins and placebo treatment.

In conclusion the results of this study show that prostaglandin E₂ and its analogue given in doses which did not produce side effects, had no effect in reducing symptoms nor in increasing the rate of healing duodenal ulcer after 4 weeks when compared with a placebo.

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