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EXPERIMENTAL USE OF PROSTAGLANDIN E_2 (DINOPROST) IN THE TREATMENT OF DUODENAL ULCER IN HUMANS

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SUMMARY

Oral administration of 20 mg PGE_2/day/patient (5 mg every 4 hours, 4 times a day) promptly relieved pain in 10 patients suffering from duodena ulcer. After 3 days of treatment, the ulceration - observed by radiologic and gastrofibroscopic means - diminished by 30% in dimensions, and after 10 days, it almost disappeared. The results were compared with those observed in a placebo-group, who recieved 20 mg lactose/day/patient and with those in another group treated by sodium bicarbonate.

INTRODUCTION

Five thousand years ago, Chinese reports mentioned the favourable effect of human semen in the treatment of gastric ulcers. Today it is known that semen contains at least 13 different types of prostaglandins (14). Robert (32,33,34) demonstrated by experiments on dogs, that PGL_1, E_2 and A_1, administered intravenously, diminish gastric secretion, hydrochloric acid concentration, pepsin, fucose and sialic acid secretion both in the basal state as well as after stimulation by histamine or pentagastrin. A large body of experience has confirmed those observations (1,2,7,8,9, 10,11,13,17,20,23,26,40) in other species also (2,3,21,22,35,37,39). In addition to the effects of PGs on gastric secretion, an independent "cytoprotective" action against ulcerogenic agents has also been described.

Karim (12,14,15) was the first to use PGs in the treatment of human gastric and duodenal ulcers. The present work extends these observations and offers a new point of view.

MATERIALS AND METHODS

30 male patients aged between 20 and 40 years were studied. The following selection criteria were used: confirmation of the duodenal ulcer by gastro-duodenal seriogaphy and gastrofibroscopy, failure for about one month of conventional treatments (alkali, neutralising and

antisecretory agents, blockers of H_2 - receptors), no other treatment, no other concomitant disease and written acceptance of the experiment. Three groups each of 10 patients were studied.

For all the patients free (FA), combined (CA), and total acidity (TA), acid output have been measured in basal as well as in stimulated conditions (BAO and SAO). Stimulation was induced by 0.04 mg/kg body weight histamine injected subcutaneously. Gastric juice samples were obtained every 15 minutes by means of an Einhorn tube: three samples before injecting histamine (evaluation of basal secretion) and another four samples after.

The test group received 2.5 mg PGE_2 (Dinoprost)/patient dissolved in 50 ml water by the tube, after the first two samples of gastric juice, and 2.5 mg PGE_2/patient in 50 ml water after the fourth sample. The placebo-group received 2.5 mg lactose/patient dissolved in 50 ml water also by the tube after the first two samples and other 2.5 mg lactose/patient in 50 ml water after the fourth sample. The third group received the same amount of sodium bicarbonate dissolved in water, by the same route. For each sample, the above mentioned parameters were calculated.

The test group received further, every 4 hours (4 times a day), one tablet containing 5 mg PGE_2/patient, for 10 days. The patients of the placebo-group received every 4 hours one 5 mg tablet of lactose/patient, also for 10 days. The third group of subjects received the same amount of sodium bicarbonate, following the same protocol.

PGE_2, lactose and sodium bicarbonate tablets were identical in appearance. Clinical assessment was made daily. After 3 and 10 days of treatment, gastrofibroscopy and gastro-duodenal seriography were repeated.

RESULTS

Measuring the free (FA), combined (CA) and total acidity (TA) as well as the acid output in basal and histamine-stimulation conditions (BAO, SAO), no significant modification of these parameters could be observed following PGE_2 administration (Table I and Graph 1).

Basal FA and TA remained within normal limits before and after the administration of 2.5 mg PGE_2. CA was measured by the difference between TA and FA (mean value 10 ± 2 m Eq/l). BAO remained constant at the level of 25 ± 1.5 m Eq/l. Stimulation by histamine (0.04 mg/kgbw) increased FA to 52 ± 1 m Eq/l, CA to 23 ± 2 m Eq/l and TA to 75 ± 0.5 m Eq/l. SAO reached the value of 43 m Eq/l. All the parameters returned to basal values after 105 minutes. Post-stimulation values showed practically no effects of PGE_2 administration.

Similar observations were made in the placebo-group (Table II and Figure 2).

Table I

min.	TIME *	15	30	45	60	75	90	105
m Eq/l	FREE ACIDITY	20 ± 2	22 ± 1	23 ± 0	30 ± 2,5	52 ± 1	51 ± 0,5	30 ± 1
	TOTAL ACIDITY	30 ± 2	32 ± 0,5	33 ± 0	40 ± 2	75 ± 0,5	74 ± 0	53 ± 0,3
	ACID OUTPUT	25 ± 2	25 ± 2	25 ± 2	36 ± 0,5	43 ± 1,5	41 ± 0	30 ± 0

* Time of sample prelevation from the beginning of the test (see also grafic 1)

GRAPHIC 1

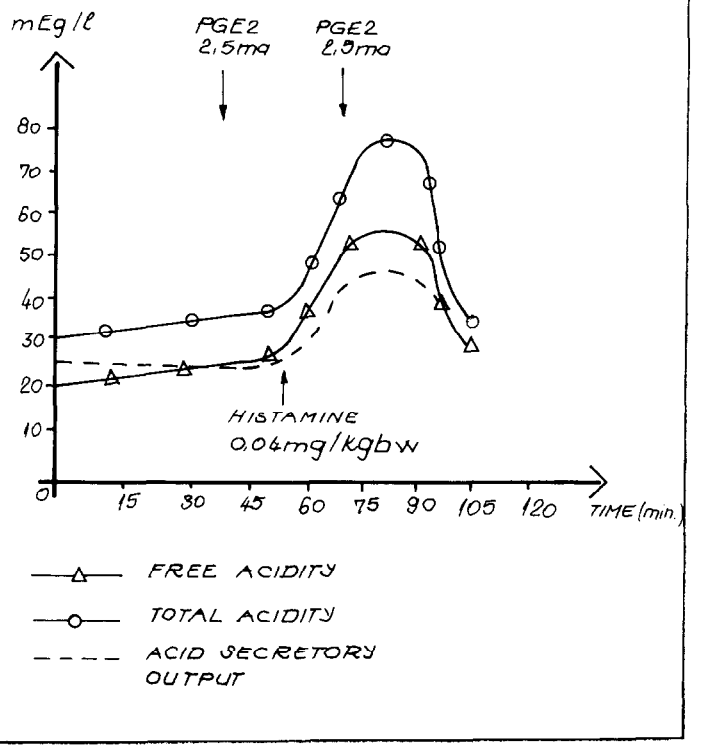
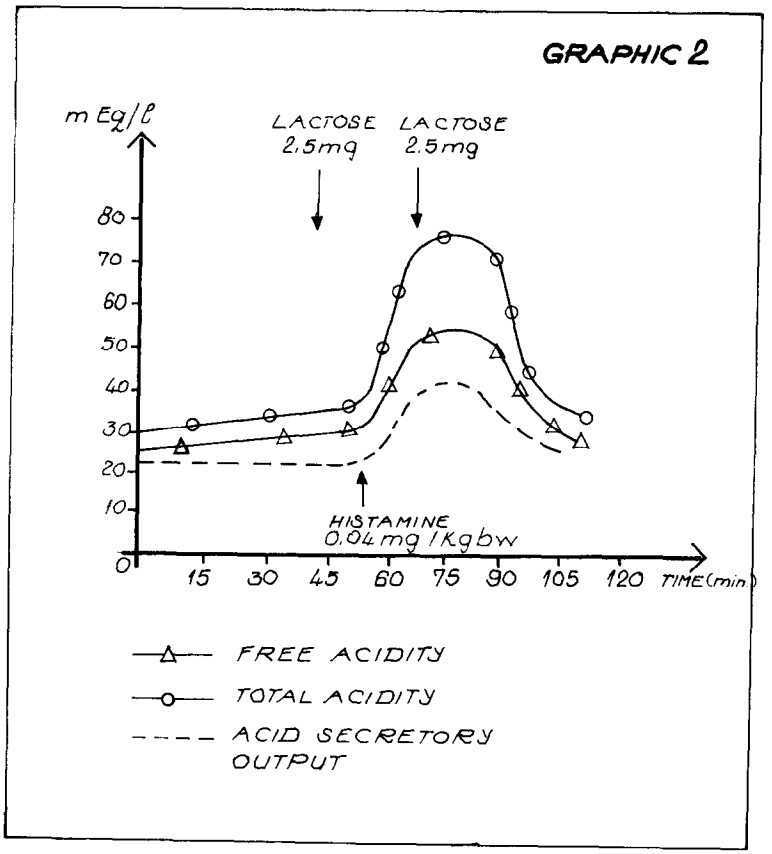


Table II

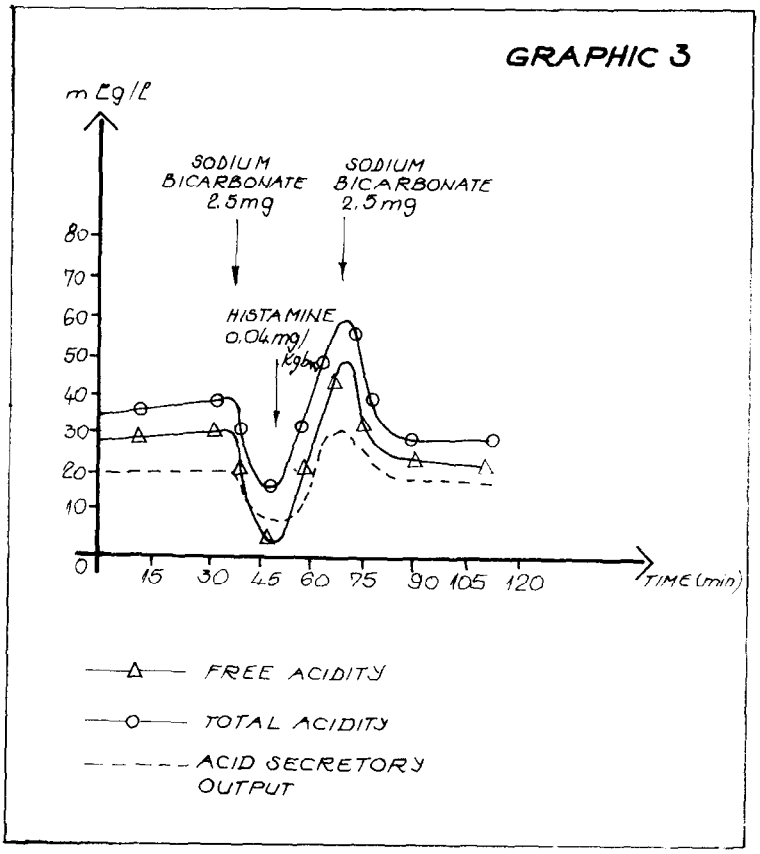
min.	TIME	15	30	45	60	75	90	105
m Eq/l	FREE ACIDITY	30 ±1,5	33±0,5	35±0,5	45± 0	56±0,5	50±0,5	25± 1
	TOTAL ACIDITY	25±0	28±0,5	30± 1	35±1,5	53±0,5	44±0	30±0
	ACID OUTPUT	22±0,1	22±0,1	22±0,1	30±0,5	42± 1	33±0,1	23±0



In contrast in the third group (Table III and Figure 3), a significant fall in the FA and TA values was observed after the administration of sodium bicarbonate.

Table III

min.	TIME	15	30	45	60	75	90	105
mEq/l	FREE ACIDITY	28 ± 0,3	29 ± 0,2	3 ± 0,5	30 ± 2	48 ± 1	29 ± 0,5	28 ± 1
	TOTAL ACIDITY	35 ± 0	36 ± 1	18 ± 0,5	28 ± 1,2	60 ± 1,5	30 ± 0	31 ± 1,5
	ACID OUTPUT	20 ± 0	20 ± 0	10 ± 1,3	15 ± 0,2	30 ± 1,5	20 ± 2,5	20 ± 0



In the test-group, all the patients mentioned the disappearance of epigastric pain, 10 minutes after receiving the PGE_2 tablet, the favourable effect lasting for about 4 to 5 hours. After 3 days of treatment gastro-duodenal seriopgraphy and gastrofibroscopy, revealed a diminution in ulcer size of approximately 30%. At the end of the treatment, investigations revealed the complete disappearance of the duodenal ulceration in 8 cases. In the other 2 cases, the ulcerations were reduced by 80% in size. As side effects, only in 1 case were nausea and vomiting observed, not severe enough to interrupt treatment.

In the placebo-group, neither epigastric pain nor ulcer dimensions were influenced substantially. Epigastric pain was slightly reduced in only 2 cases. Radiologic and endoscopic investigations showed unchanged appearances in 8 cases and enlargement of ulceration in the other 2.

The patients of the third group mentioned mild reduction of pain in 4 cases. The other 6 patients mentioned no influence of the treatment. Investigations revealed no changes in lesion size.

DISCUSSION

The results show the favourable effect of PGE_2 in selected cases of duodenal ulcer resistant to conventional therapy.

Ulcer pain appears to be produced by the irritative action of hydrochloric acid on the submucosal pain receptors. The mechanism of action of all conventional drugs on this cardinal symptom is the same: they reduce the gastric hydrochloric acid output, so reducing the degree of irritation. Previous observations of Karim, et al. (14,15) confirmed by our conclusions show that, contrary to its effect in animals PGE_2 induces no significant decrease of gastric acidity in humans. Two other explanations should be considered: the stimulating effect of PGE_2 on gastric mucus secretion (4,24,27,32); and a mild analgesic action observed in animals (42). Although this second mechanism is uncertain in humans, it could explain the rapid effect of PGE_2 on ulcer pain. More difficult to explain is the observation that the effect lasted for over 4 hours, since PGE_2 is considered to be rapidly inactivated when used by the oral route. Probably PGE_2 prior to inactivation induces some persistent changes responsible for this favourable effect.

The healing effect on duodenal ulceration probably has a complex explanation. It has been suggested that between local PGE concentration and the H^+ - concentration within the parietal gastric cell there is a negative feed-back relation (16,30). PGE_2 administration restores this equilibrium which seems to be affected in duodenal ulcer patients (30). The still unelucidated mechanism of cytoprotection probably plays also an important role, efficient also when PGE_2 is administered orally (18,28,29,37,38).

Of particular significance is the ability of PGE_2 to stimulate the regeneration of epitelia since it has been demonstrated that PGE_1 and PGE_2 stimulate the synthesis of DNA, RNA, and cellular proteins in epithelial cells (19).

Mucosal blood flow increase may also contribute to a favourable outcome, since the Virchowian concept states the pathogenic role of local ischaemic factors in ulcers (3,7,21).

It is worth mentioning that PGE_2 reduces considerably the H^+ retrodiffusion in the gastric mucosa and also has an antigastrinic effect (17).

All these points suggest a reevaluation of PGE_2 as a potent therapeutic agent in human duodenal ulcer.

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