EXPERIMENTAL METHODS FOR CLINICAL PRACTICE

Gastroduodenal Mucosa Prostaglandins Participate in Realization of the Effect of the Antiulcer Drug Venter

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It is shown that in patients with ulcer disease endogenous biosynthesis of prostaglandins E and $F_{2\alpha}$ in gastric and duodenal mucosa is suppressed. In patients treated with Venter (sucralfat), ulcer healing is accompanied by enhanced prostaglandin production in both scar tissue and unaffected areas. Stimulation of prostaglandin E and $F_{2\alpha}$ synthesis in the gastroduodenal mucosa followed by activation of their cytoprotective effect in the gastrointestinal system is a key mechanism underlying the effect of Venter.

Key Words: *gastroduodenal mucosa prostaglandins; ulcer disease; Venter (sucralfat)*

In the digestive system prostaglandins (PG) produce cytoprotective and antiulcer effects [10]. The contribution of PG to the pathogenesis of ulcer disease is considerable; a correlation was demonstrated between PG content in the gastric (GM) and duodenal mucosa (DM) and functional state of these organs [1]. New pharmacological agents for therapy of ulcer disease are based on cytoprotective and antiulcer effects of PG. For instance, Venter (sucralfat, KRKA), a preparation for the treatment of the upper gastrointestinal erosions and ulcers, is a synthetic aluminum salt of sucrose octasulfate. Venter neutralizes gastric juice, adsorbs aggressive components such as pepsin and bile, and improves microcirculation in the upper gastrointestinal tract mucosa. It is assumed that Venter stimulates defense factors in the gastrointestinal mucosa [7]. However, the mechanisms underlying the effects of this preparation remain poorly understood.

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In the present study we investigate the role of PG produced by the gastroduodenal mucosa in the effects of Venter. To this end, the content of PG E and $F_{2\alpha}$ in GM, DM, and gastric juice was determined in patients with gastric and duodenal ulcer disease treated with Venter.

MATERIALS AND METHODS

A total of 95 patients with gastric and duodenal ulcer disease (33 and 62 patients, respectively) without complications (bleeding, perforation, or penetration) were examined. In all cases, ulcer disease was verified by X-ray, endoscopic and morphological examination. Endoscopy was also used for observation during treatment. Control group comprised 6 individuals without gastrointestinal pathologies. All patients received Venter (1 g 4 times per day, per os) for 1 month.

The content of PG E and $F_{2\alpha}$ in the mucosa samples and gastric juice was measured by radioimmunoassay. The samples were obtained from un-

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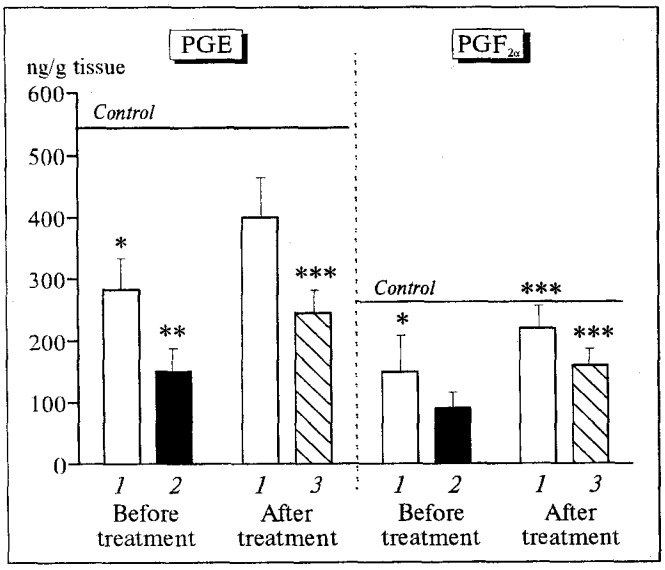

Fig. 1. Concentration of prostaglandins in gastric mucosa in patient with gastric ulcer treated with Venter. *1*) unaffected area; 2) ulcer edge, 3) scar. Here and in Fig. 2: $p<0.05$: *compared with the control, **compared with unaffected area, ***compared with the level before treatment.

affected areas (the duodenum or stomach fundus) and ulcer edges before treatment and from the corresponding unaffected areas and healed ulcer after treatment. Samples of GM and DM were also obtained from control subjects. Portions of basal and histamine-stimulated gastric juice were routinely obtained though a gastric tube. Prostaglandins E and $F_{2\alpha}$ were assayed using standard kits (Clinical Assays). The data were processed statistically using the Student *t* test.

RESULTS

It was shown that in patients with ulcer disease endogenous PG biosynthesis in gastric and duodenal mucosa is suppressed. This is confirmed by a marked decrease in the content of prostaglandins E and $F_{2\alpha}$ in comparison with the control (Fig. 1). These changes were most pronounced at the ulcer edges (3-3.5-fold in comparison with the control).

In GM from control subjects, the PGE/$PGF_{2\alpha}$ ratio was 2.15, which agreed with published data [4], while in patients with gastric ulcer this coefficient decreased to 1.8 in unaffected mucosa and to 1.6 at the ulcer edges.

Similar changes in the content of PG E and $F_{2\alpha}$ were found in DM of patients with duodenal ulcers (Table 1).

The intensity of PG synthesis in the gastric mucosa can be evaluated by PG secretion in gastric juice [2,9]. As seen from Table 1 and Fig. 2, in patients with duodenal and especially gastric ulcer, the concentrations of PGE and $PGF_{2\alpha}$ in basal and histamine-stimulated gastric juice were considerably lower (2-3-fold) than in healthy subjects. These data confirm the disturbances of PG biosynthesis in GM of patients with gastroduodenal ulcers.

Venter (1 g four times daily) relieved stomach aches in 76% patients (primarily within 7 days) irrespective of ulcer location; healing within 3-4 weeks was noted in 84% patients.

As seen from Table 1 and Fig. 1, healing was accompanied by a considerable increase in the PGE and $PGF_{2\alpha}$ production in GM and DM. These changes were noted both in gastric and duodenal ulcers and involved not only scars, but also unaffected (distant from the lesions) areas. This activation of PG synthesis in the gastric and duodenal mucosa correlated with enhanced (1.5-2-fold) PG secretion into basal and histamine-stimulated gastric juice (Fig. 2). These data confirm stimulating effect of Venter on PG biosynthesis in gastroduodenal mucosa.

TABLE 1. Content of PG in DM and Gastric Juice of Patients with Duodenal Ulcer Disease Treated with Venter (*M±m*)

Patients		PGE		$PGF_{2\alpha}$	
		before treatment	after treatment	before treatment	after treatment
DM, ng/g tissue					
Control		532.7±16.9	—	247.6±8.7	—
Duodenal	unaffected area	264.6±10.4*	331.6±21.7***	128.7±9.7*	185.4±8.9***
bulb ulcer	ulcer edge	144.3±8.9**	—	84.5±6.9**	—
	scar	—	220.4±14.6***	—	127.1±8.2***
Gastric juice, ng/ml					
Control		5.8±0.4	—	3.6±0.8	—
Duodenal	basal	1.9±0.5*	2.9±0.4*	1.1±0.2*	1.7±0.5
bulb ulcer	histamine-stimulated	2.1±0.3**	3.4±0.1***	0.95±0.4*	2.6±0.2***

Note. $p<0.05$: *compared with the control, **compared with unaffected area (mucosa) or basal secretion (gastric juice), ***compared with the level before treatment.

It has been shown that natural cytoprotectors PGE and $PGF_{2\alpha}$ [2] play an essential role in the maintenance of GM and DM integrity and resistance [3,6]. The stimulating effect of Venter on PGE and $PGF_{2\alpha}$ synthesis in the gastroduodenal mucosa promotes the recovery of PG-regulated defense factors such as production of alkaline component of gastric juice, mucus production, stimulation of trophic processes and circulation in affected area, etc. Normalization of these processes considerably improves ulcer healing [12]. The proposed mechanism of action and clinical effectiveness of Venter also agree with current concept on a principal role of impaired PG synthesis (defense factors opposing to aggressive factors such as acid, gastrin, pepsin etc.) in the pathogenesis of gastroduodenal erosions and ulcers [4].

The involvement of PG in the antiulcer effect of Venter is also proved by the fact that in addition to the gastric juice components (including hydrochloric acid) parietal cells of the GM produce considerable amounts of PG. Recent studies have shown that these cells express high-affinity PGE_2 and prostacyclin receptors involved in the regulation of mucus formation and hydrochloric acid production in the stomach [11]. Thus, our findings suggest that stimulation of suppressed PGE and $PGF_{2\alpha}$ biosynthesis in the gastroduodenal mucosa followed by their cytoprotective effects in the digestive system is a key mechanism underlying the antiulcer activity of Venter. Similar effects were attained with synthetic analogs of $PGF_{2\alpha}$ now used in the antiulcer therapy [8].

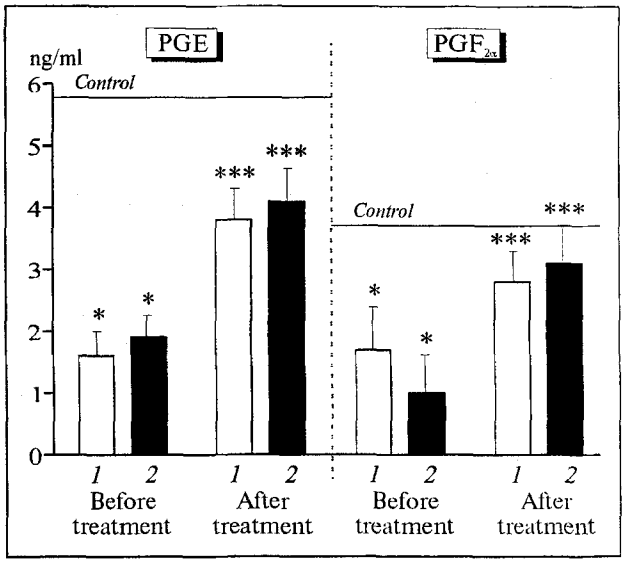

Fig. 2. Effect of Venter on the concentration of prostaglandins in gastric mucosa in a patient with gastric ulcer. *1*) basal secretion; *2*) histamine-stimulated secretion.

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