Clinical Efficiency of Epigam in Patients with Exacerbation of Peptic Ulcer Disease of the Stomach and Duodenum

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Clinical efficiency and safety of Epigam containing antibodies to histamine in ultralow doses were studied during the therapy of patients with exacerbation of peptic ulcer disease of the stomach and duodenum associated with *Helicobacter pylori* infection. We examined 20 patients (18-50 years) with ulcerative lesions of the mucosal layer in the stomach and duodenum and *H. pylori* infection. Epigam (1 tablet, 6 times a day) or H_2 receptor blocker ranitidine (150 mg, 2 times a day) were given in combination with amoxicillin (500 mg, 3 times a day, 14 days) and metronidazole (500 mg, 2 times a day, 14 days) for 28 days. The efficiency of treatment was determined before and 1, 2, 3, and 4 weeks after the start of therapy. The symptoms of peptic ulcer disease and time of ulcer healing underwent similar changes in patients of both groups. However, after ranitidine therapy pain syndrome disappeared more rapidly than in patients receiving Epigam. Epigam did not cause undesirable side effects. Our results indicate that Epigam is an efficient and safe preparation that may be used for combination therapy of patients with peptic ulcer disease of the stomach and duodenum.

Key Words: *peptic ulcer disease; antiulcer therapy; antibodies against histamine; ultralow doses*

Peptic ulcer disease is characterized by polyetiology and complex pathogenesis. There are 50 medicinal preparations used for conservative therapy of this disorder. Despite an understanding of a key role of *Helicobacter pylori* in the pathogenesis of peptic ulcer disease [2] and successful eradication therapy, the incidence of recurrences and complications of this disorder constantly increases. Potent antiulcer preparations with antisecretory activity (H_2 receptor blockers and proton pump inhibitors) should maintain intragastric pH>4.0 for no less than 18 h a day.

These antisecretory preparations have several disadvantages. Prolonged inhibition of hydrochloric acid secretion impairs barrier functions of the stomach and promotes hypergastrinemia and dissemination of *H. pylori* in the gastric mucosa. The development of medicinal resistance is associated with antibody production after long-term treatment with selective M1 cholinoceptor blockers.

It is important to synthesize new highly potent drugs affecting the mechanisms of ulceration and not causing side effects and elaborate new approaches to the therapy of this disease. Epigam containing antibodies to histamine in ultralow doses and synthesized by the method of potentiation at the "Materia Medica Holding" Research-and-Production Company holds much promise in this respect.

Experiments on animals showed that intragastric pretreatment with Epigam produces the protective effect in various models of ulceration. I was hypothesized that antiulcer activity of Epigam is related to its protective effect on the mucosal layer of the stomach and duodenum. The preparation stimulates synthesis of glycosaminoglycans, improves regional blood flow, intensifies reepithelization of the mucosal layer, and activates antioxidant enzymes [3].

Epigam reduces pH and acidity of the gastric juice in experimental animals, which probably underlies its antiulcer activity. A correlation was found between histamine level, gastric pH, and proteolytic enzyme activity. It cannot be excluded that antibodies against histamine affect secretion and modulation of the effect produced by histamine, which plays a key role in the pathogenesis of peptic ulcer disease. There are no data on clinical studies of Epigam.

Here we studied clinical efficiency and safety of Epigam in patients with exacerbation of peptic ulcer disease of the stomach and duodenum associated with *Helicobacter pylori* infection.

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MATERIALS AND METHODS

Twenty patients with peptic ulcer disease of the stomach and duodenum associated with *H. pylori* infection were examined for 28 days. Endoscopic examination revealed 1 or several ulcerative lesions with a diameter of up to 20 mm. Infection with *H. pylori* was verified by rapid urease test or immunologic and molecular-and-genetic assays (polymerase chain reaction). The age of patients varied from 18 to 50 years (32.2 years). We examined 12 men (60%) and 8 women (40%). The medical history of most patients (n= 19, 95%) included peptic ulcer disease. In 5 patients (25%) the diagnosis of peptic ulcer disease was made for the first time. The average duration of this disease was 3.2 years.

Depending on treatment, the patients were divided into 2 groups. Group 1 patients received Epigam (1 tablet sublingually, 6 times a day, 28 days), amoxicillin (500 mg, 3 times a day, 14 days), and metronidazole (500 mg, 2 times a day, 14 days). Group 2 patients received ranitidine (150 mg, 2 times a day, 28 days), amoxicillin (500 mg, 3 times a day, 14 days), and metronidazole (500 mg, 2 times a day, 14 days). The therapy was considered to be ineffective when we observed complications of the disease, undesirable effects, or incomplete cicatrization of ulcerative lesions after 4-week treatment. These patients were excluded from further observations.

If necessary, the patients received symptomatic antacid therapy. The requirements for this treatment were taken into account. We evaluated the severity of major symptoms accompanying exacerbation of peptic ulcer disease, number and diameter of ulcerative lesions, endoscopic and histologic signs of inflammation in the gastroduodenal mucosa, and secretory activity. *H. pylori* were identified.

The patients subjectively evaluated undesirable reactions and tolerability of treatment. The incidence and severity of side effects were determined by blood test and biochemical assay that reflected functional state of the liver and kidneys. Treatment was performed by the fixed scheme. Parameters were recorded in a special medical history of patients. The patients were examined before and 1, 2, 3, and 4 weeks after the start of therapy. The program and scheme of examination were approved by the Ethical Committee of the Volgograd Medical Academy.

Clinical symptoms were evaluated by formalized scales 1 week before the start of therapy. We analyzed the incidence and severity of epigastric pain, incidence and severity of nocturnal pain in the epigastrium that caused awakening, incidence and severity of dyspepsia (nausea, vomit, heartburn, belching, and abnormal stool), complications of peptic ulcer disease (hematomesis and melena), requirements for symptomatic (situational) therapy (number of tablets/doses of antacid preparations taken daily to relieve symptoms of hyperacidity), number of asymptomatic days (no symptoms of peptic ulcer disease), episodes of missed therapy (type and dose of untaken tablets), and presence and severity of therapy-associated undesirable effects.

Symptoms of exacerbation, undesirable changes, requirements for additional treatment, and compliance of the regimen and scheme for treatment were analyzed using a formalized "dairy of symptoms". Besides this, we performed control examination of patients. The patients completed questionnaires before and 1, 2, 3, and 4 weeks after the start of therapy.

Endoscopic examination was performed using an Olympus-GIF-E fibrogastroscope before and 4 weeks after the start of therapy. Secretory state (high, normal, and low) was estimated in the Congo red test. Benignity of mediogastric ulcers was verified histologically. *H. pylori* were detected by invasive (histological and molecular-and-genetic assays and rapid urease test) and noninvasive diagnostic methods (indirect solid-phase enzyme immunoassay) [1,4,5]. Primary diagnostics of *H. pylori* was performed with rapid urease test (KhELPIL test, St. Petersburg). This test is based on measurements of urease activity in biopsy specimens of the gastric mucosa obtained during endoscopy.

The results were analyzed by nonparametric and correlation tests (Statistica and StatSoft softwares). The significance of differences was evaluated by Student's t test and Mann-Whitney U test.

RESULTS

Before treatment the patients felt pain in the epigastric and/or pyloroduodenal zone. The symptoms of dyspepsia included heartburn, belching, and nausea. We revealed no significant differences in the severity of gastroduodenal symptoms between patients of various groups. The period from manifestation of clinical symptoms for exacerbation of the disease to primary endoscopic examination and start of therapy was 2-14 days.

TABLE 1. Clinical Symptoms in Patients with Exacerbation of Peptic Ulcer Disease Receiving Therapy ($M\pm m$, days)

Disappearance, days	Group (n=10)	
	1	2
Pain syndrome	10.64±1.17	7.50±0.81
Heartburn	5.25±0.73	4.87±0.82
Belching	8.71±0.64	7.20±0.89
Nausea	2.0±0.17	3.80±0.54

TABLE 2. Major Clinical Symptoms of Peptic Ulcer Disease during Combination Therapy with 3 Preparations (*M*±*m*, points)

Symptom	Group 1		Group 2	
	before therapy	after therapy	before therapy	after therapy
Epigastric pain	2.81±0.40	0.78±0.04*	2.43±0.50	0.74±0.03*
Nocturnal pain	1.76±0.20	0.12±0.01*	1.56±0.10	0.21±0.01*
Heartburn	1.34±0.20	0.48±0.01*	1.62±0.10	0.32±0.01*
Belching	1.12±0.08	0.67±0.03	0.92±0.04	0.84±0.01
Vomit	0.94±0.07	0.55±0.02	1.23±0.06	0.41±0.02
Palpatory pain	2.87±0.20	0.65±0.03*	2.67±0.20	0.49±0.06*

Note. Here and in Table 4: *p<0.05 compared to symptoms before therapy.

Pain and dyspepsia were relieved over the same period of time in patients receiving various schemes of treatment (Table 1).

On days 3, 10, and 14 of therapy epigastric pain disappeared in 2 (20%), 6 (60%), and 10 patients of group 1 (100%), respectively. Pain and dyspepsia were relieved 10.64±1.17 days after the start of therapy (Table 1).

Epigastric pain disappeared in 5 (50%), 3 (30%), and 10 patients of group 2 (100%) on days 2, 10, and 14 of therapy, respectively. The average time to relieve pain and dyspepsia was 7.50±0.81 days after the start of therapy. The severity of gastrointestinal symptoms in patients of groups 1 and 2 decreased after 4-week therapy (p<0.001), which correlated with changes in endoscopic signs of damage to the gastroduodenal mucosa and gastric pH.

Clinical improvement was accompanied by a decrease in the requirements for symptomatic antacid therapy in patients of groups 1 (from 3.21±0.16 to 0.53±0.09 tablets/spoons per day, p<0.001) and 2 (from 2.96±0.11 to 0.22±0.04 tablets/spoons per day, p<0.001).

In group 1 patients the severity of epigastric pain (including nocturnal pain), heartburn, and nausea and requirements for symptomatic therapy markedly decreased after 4-week therapy (Table 2). The average time to relieve pain in most patients was 6-7 days (Table 1).

In group 2 patients pain syndrome and dyspepsia disappeared more rapidly than in group 1 patients. Pain in the epigastric and pyloroduodenal zone and dyspepsia were relieved over 3-11 and 2-14 days, respectively. In 53.8% patients pain syndrome disappeared on day 5 of therapy. The average time to relieve epigastric pain and dyspepsia in group 2 patients was lower than in group 1 patients (Table 1). Potency of the preparation did not depend on gastric pH.

After 4-week therapy the area of ulcerative lesions in the gastroduodenal mucosa markedly decreased in group 1 patients (p<0.001, Table 3). In 9 patients (90%) duodenal ulcers scarred after 4-week therapy. In 1 patient receiving Epigam the area of ulcerative lesions decreased by 75-80%. Group 1 did not include patients with gastric ulcers.

In 6 patients of group 1 with associated erosions of the stomach and/or duodenum, healing of ulcers was accompanied by epithelization after 4-week therapy. However, the severity of erosions in group 1 patients decreased insignificantly. We revealed no significant changes in the severity of gastroduodenitis (Table 4).

In group 2 patients the area of erosive and ulcerative lesions in the gastroduodenal mucosa and severity of macroscopic (endoscopic) signs of gastritis decreased after 4-week therapy (Table 4). The symptoms of erosive gastroduodenitis disappeared, and duodenal ulcers healed in all patients. It should be emphasized that mediogastric ulcers healed slower than duodenal ulcers.

Histological assay of biopsy specimens obtained from patients of groups 1 and 2 was performed 4 weeks after the start of therapy. *H. pylori* were not detected in the gastric mucosa in 64.3% patients of group 1. The degree of dissemination with *H. pylori* decreased in 21.4% patients and remained unchanged in 14.3% patients.

TABLE 3. Clinical Efficiency of Combination Therapy in Patients with Peptic Ulcer Disease of the Stomach and Duodenum (% of the Total Number of Patients in Group)

Parameter	Group 1 (n=10)	Group 2 (n=10)
Incidence of duodenal ulcer healing	9 (90)	10 (100)
Incidence of gastric ulcer healing	—	1 (75)
Incidence of epithelization of erosions	6 (60)	8 (80)

Note. n, number of patients; % of the total number of patients in group is shown in brackets.

TABLE 4. Reparative and Inflammatory Processes in the Mucosal Layer of the Stomach and Duodenum in Patients with Peptic Ulcer Disease (Endoscopic Examination, *M*±*m*, points)

Parameter	Group 1		Group 2	
	before therapy	after 4-week therapy	before therapy	after 4-week therapy
Area of ulcers	1.21±0.07	0.0*	0.96±0.02	0.0*
Number of ulcers	1.06±0.04	0.0*	1.45±0.04	0.07±0.01*
Erosions	0.90±0.03	0.46±0.02*	0.73±0.01	0.24±0.01*
Gastritis	1.29±0.06	1.05±0.01	1.17±0.06	1.03±0.03
Duodenitis	1.35±0.04	1.30±0.05	1.08±0.02	1.01±0.02
Duodenogastral reflux	0.18±0.01	1.17±0.04	0.35±0.01	0.27±0.01

H. pylori were not detected in 74.1% patients of group 2. The degree of dissemination with *H. pylori* decreased in 25.9% patients of this group.

We did not reveal considerable differences in the period of ulcer healing in patients receiving combination therapy with Epigam (group 1) and ranitidine in optimal doses (group 2). Changes in the symptoms of peptic ulcer disease and periods of healing were similar in patients of both groups. The severity and persistence of symptoms did not depend on the initial intensity of hydrochloric acid secretion and duration of the disease. The H_2 receptor blocker ranitidine was more potent than Epigam in affecting the duration of clinical symptoms in patients with peptic ulcer disease. These preparations relived pain in various periods after the start of therapy.

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