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Omeprazole is More Effective than Famotidine for Preventing Acute Gastritis in Rats

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Abstract

Purpose. Acute gastric mucosal lesions, which can develop within a few hours after polytrauma, shock, major operations, central nervous system lesions, or severe infection, cause about 33% of cases of gastrointestinal bleeding. We analyzed and compared the effectiveness of famotidine and omeprazole on acute gastric mucosal lesions.

Methods. Thirty male albino Wistar rats were given ketalar anesthesia after 12 h fasting, then immobilized and exposed to stress according to Brodie's protocol, without restricting their respiration. We divided the rats into three groups of ten according to whether they were given famotidine, omeprazole, or normal saline (control group). All rats were ulcer-indexed according to the diameter of their ulcers. The stomach contents were aspirated for acid output and pH analysis, and sent to the laboratory. The total number of mast cells was also counted.

Results. Omeprazole was more effective than famotidine in keeping gastric pH high and lowering the total gastric acid output. Lower ulcer indexes in acute gastric mucosal erosions and better protected mucosal integrity were found in the omeprazole-treated rats.

Conclusion. Omeprazole prevents acute gastric mucosal erosions in rats more effectively than famotidine.

Key words Gastric mucosal lesion · Gastric acid output · PH · Famotidine · Omeprazole

Introduction

About one third of all gastrointestinal bleeds are caused by acute gastric mucosal lesions which, unlike true gastric ulcers, do not generally invade beyond the muscularis mucosa. The other stress-related mucosal disease is caused by stress ulcers, which are deeper lesions that tend to be more focal and present a greater risk of severe bleeding.¹ It is known that both humans and experimental animals undergo changes in gastrointestinal motor and secretory functions when subjected to stress.² The major mechanism in this process is the breakdown of splanchnic microcirculation, which results in ischemia of the stomach mucosa, with the release of pepsin and hydrochloric acid (HCl) into the lumen. The stress-related gastric ulcer is a serious complication of exposure to extreme stress. These ulcers usually develop within a few hours after burns, central nervous system lesions, polytrauma, shock, major operations, or severe infection.³ Once acute gastric mucosal lesions form, their medical and surgical treatment will extend the hospitalization and delay the patient's recovery. Prophylactic medication is the most effective way of managing these gastric lesions. Famotidine is a histamine H₂ receptor blocker and omeprazole is a hydrogen-pump inhibitor that inhibits gastric acid secretion by blocking adenosine triphosphate (ATP).^{4,5} We conducted this study to analyze and compare the effects of famotidine and omeprazole treatments on acute gastric mucosal lesions.

Materials and Methods

We conducted these experiments at the Haydarpaşa Teaching Hospital Animal Laboratories, using 30 male Wistar albino rats, under the supervision and approval of the local ethics committee. The European Union guidelines for the handling and care of laboratory

animals were followed throughout the study. We divided the rats into a control group ($n = 10$), a famotidine group ($n = 10$), and an omeprazole group ($n = 10$). The rats were kept at room temperature, and fed standard food and water ad libitum. Anesthesia was induced with 100 ml/kg intraperitoneal ketamine hydrochloride (ketalar, Eczacıbası, Istanbul, Turkey) after 12 h fasting. They were later subjected to extreme stress, according to Brodie's protocol, by immobilizing them on T-rods 20 cm high and gently strapping their four feet, without interfering with their breathing.^{6,7}

In all three treatment groups, we inserted a 24-gauge (0.7×19 mm) needle into the right femoral vein under aseptic conditions, before the stress and while the animals were under ketalar anesthesia. In group 1 (control group), 1 ml/100 g physiological saline was given at the beginning of immobilization, then 12 h later. In group 2, 1.14 mg/kg famotidine (Nevofam-inject 40 mg; Mustafa Nevzat, Gayrettepe, Istanbul, Turkey) was injected intravenously before the stress and 12 h later. In group 3, 1.14 mg/kg omeprazole (Losec-inject 40 mg; Eczacıbası, Levent, Istanbul, Turkey) was injected intravenously before the stress and 12 h later. An SPSS statistical package program (SPSS, Cary, NC, USA) was used for data analysis. First, the data were ascertained for normal distribution with the one-sample Kolmogorov-Smirnov test, followed by analysis of variance with Tukey's post hoc analysis. $P < 0.05$ was considered significant.

Biochemical Analysis

After inflicting stress under ether anesthesia, a median laparotomy was performed in all rats, followed by concomitant ligation of the esophagus and the second portion of duodenum at 1-h intervals. The abdomen was closed with 3/0 silk, and a relaparotomy was done 1 h later. The contents of the stomach were collected and sent to the biochemistry laboratory for acid output and pH analysis. Whatman (pH 1-14) papers were used for pH measurement.

Pathologic Investigation

Following gastrectomy and partial jejunectomy, all of the animals were killed. The stomachs were incised along the longer-curvature and examined macroscopically by an independent pathologist, in a single-blind fashion. Petechias were counted and a group of five petechias was considered to be a 1-mm ulcer. Mucosal ulcers were measured along the widest diameter. The sum of the ulcers in each rat was recorded. All three groups were indexed according to the diameter of their ulcers.⁸ Samples taken from the stomach and the mesenteric section of jejunum were fixed in a 10% formaldehyde solution. Cross sections of 5- μ m thickness were prepared from blocks after routine paraffin processing, and dyed with hematoxylin-eosin plus 1% toluidine blue dye. Preparations were examined under the light microscope at 400 \times magnification, and positive-stained cells were evaluated. The total number of mast cells was counted at ten different sites and averages were calculated.

Results

The groups pretreated with omeprazole or famotidine had lower mean ulcer indexes than the control group (Table 1). The control group had the highest index, whereas the omeprazole group had the lowest ($P < 0.05$). The total acid output in the famotidine- and omeprazole-pretreated groups was lower than that in the control group. Biochemical analysis showed the highest total acid output in the control group and the lowest in the omeprazole group ($P < 0.05$) (Table 1). Similarly, the pH value was lowest in the control group and highest in the omeprazole group ($P < 0.05$) (Table 1).

Histopathologic Examination

Histopathologic examination of gastric mucosa in the control group revealed widespread mucosal and submucosal hyperemia related to the obliteration of gastric

Table 1. Mean (\pm SD) values of ulcer index, total acid, pH, and mast cell number in the three groups

Group	Ulcer index (mm)	Total acid (mEq/l)	pH	Mast cell number
Control	25.8 \pm 3.01	14.1 \pm 1.98	1.1 \pm 0.6	39.7 \pm 21.08
Min., max.	21.6, 29.7	10.80, 16.50	0.40, 2.0	0, 70
Famotidine	12.1 \pm 2.02	6.8 \pm 2.39	4.31 \pm 0.35	49.4 \pm 25.08
Min., max.	9.9, 15.3	3.70, 9.90	3.80, 4.80	18, 101
Omeprazole	6.4 \pm 2.84	2.9 \pm 1.40	5.2 \pm 0.46	66.7 \pm 20.94
Min., max.	3.6, 10.0	0.80, 5.20	4.5, 5.9	39, 96
<i>F</i>	140.65	81.417	179.108	3.648
<i>P</i>	0.0001	0.000	0.000	0.040

Table 2. Tukey multiple comparisons of different variables in the three groups

Variable	(I) Group	(J) Group	Mean difference (I – J)	SE	<i>P</i>	95% CI
UI	Control	Famotidine	13.70	0.951	0.001	(10.75–16.65)
	Control	Omeprazole	19.40	0.898	0.001	(16.45–22.35)
	Famotidine	Omeprazole	5.70	0.638	0.001	(2.75–8.65)
Total acid	Control	Famotidine	7.30	0.882	0.000	(5.11–9.48)
	Control	Omeprazole	11.07	0.882	0.000	(8.88–13.25)
	Famotidine	Omeprazole	3.77	0.882	0.001	(1.58–5.95)
pH	Control	Famotidine	–3.11	0.221	0.000	(–3.66––2.55)
	Control	Omeprazole	–4.00	0.221	0.000	(–4.55––3.44)
	Famotidine	Omeprazole	–0.89	0.221	0.001	(–1.44––0.33)
No. of mast cells	Control	Famotidine	–9.70	10.127	0.609	(–34.81–15.41)
	Control	Omeprazole	–27.0	10.127	0.033	(–52.11––1.88)
	Famotidine	Omeprazole	–17.30	10.127	0.221	(–42.51–7.81)

UI, ulcer index; CI, confidence interval

mucosal integrity, neutrophil accumulation in the submucosa, increased number of lymphocytes and leukocytes, epithelial destruction, and areas of petechial bleeding and necrosis. The number of mast cells was decreased in damaged areas. The mucosa in the famotidine group had minimal mucosal desquamation, muscularis mucosal congestion, and edema. Mast cells were seen. The omeprazole group had increased epithelia thickness with normal subepithelial glands, and minimal polymorphonuclear leukocyte infiltration and edema. The mast cells were decreased in number in the damaged tissues, but more abundant in the undamaged mucosal tissues. There were more mast cells in the omeprazole group than in the other two groups (Table 1). The only significant difference in the number of mast cells was found between the omeprazole group and the control group ($P < 0.05$) (Table 2).

Post hoc analysis showed significant differences among the three groups in ulcer index, total acid output, and pH values. According to all these measurements, omeprazole was more effective than famotidine, and famotidine was more effective than the placebo (Table 2).

Discussion

Acute mucosal erosions usually occur as a consequence of certain drugs, severe burns, and crush injuries, which cause acid hypersecretion, the loss of mucosal integrity, or both. Before stress ulcers develop in the stomach, an inflamed infiltration composed of hyperemia, edema, lymphocytes, macrophages, and aggregation of a few neutrophils and eosinophils can be seen in a superficial section of the lamina propria. Although focal foliation is seen in the mucosa, it is usually located superficially and seldom extends further than the mucosal layer. These changes always accompany bleeding.⁹ Generally, exami-

nation of the gastric mucosa reveals an increase in polymorphonuclear leukocytes, lymphocytes, plasma cells and eosinophils, congestion and edema, petechial bleeding, focal erosion, focal necrosis, ulceration, and bleeding in the erosion crater. Although the exact mechanism of stress in the rat is unclear, it is speculated that a decrease in gastric mucosal contractility and gastric hemoperfusion could play a role.¹⁰ In the absence of an effective mucosal barrier or repair process, exposure to gastric acid causes gastrointestinal mucosal injury and represents the most important factor in stress-related mucosal disease. However, even small amounts of acid can cause mucosal injury and therefore, the inhibition of acid secretion is the primary goal of any treatment aimed at preventing stress-related mucosal disease. Clinical trials have clearly shown that maintaining an intragastric pH above 3.5–5.0 can prevent injury^{9,11} and that a gastric pH below 4.0 increases the risk of stress ulceration.¹² The gastric pH in our study was around these values. When given intravenously, omeprazole maintains the total acid value at the lowest possible level and preserves the mucosa in rats. Famotidine is an H₂-receptor blocker, which competitively blocks the binding of histamine to H₂-receptors, thereby inhibiting the secretion of gastric acid. Famotidine was found to decrease gastric acidity to pH 6.4 in rats.¹³

Several studies have investigated how different methods of delivering proton pump inhibitors help to prevent stress ulcers and increase intragastric pH levels. One method involved breaking open a capsule and crushing the granules to form a suspension of omeprazole, which was subsequently given via a nasogastric tube.^{14,15} In another study, investigators gave intact lansoprasole granules together with orange juice through a gastrostomy tube and reported positive effects on intragastric pH levels.¹⁶ Similarly, we found that omeprazole, when given intravenously, maintains a pH above 4.

The acute gastric superficial hemorrhagic lesions in rats are similar to those in humans. Ogle et al. found that the amine release from gastric mast cells was decreased, the gastric wall was distended, and gastric secretion was diminished,¹⁷ but showed verapamil to be effective for decreasing the mucosal lesions, reducing stomach contractions, and inhibiting mast cells. Another experimental study found that the number of mast cells in damaged gastric tissues was reduced.¹⁸ In our study, there were more mast cells in the omeprazole group than in the other two groups. Many investigators believe that mast cells play an important role in protecting the mucosa. This effect was not evident in the control group in the present study, and was more prominent in the omeprazole group than in the famotidine group, although the exact mechanism remains unclear. The mucosal mast cells of the stomach are the major source of synthesized mediators. Mast cells are located around the postcapillary venules, from where they can influence local tissue reactions. Histamine plays an essential role in the development of acute mucosal lesions and the histamine derived from these mast cells may be essential in this process.¹⁹ Further studies are warranted to clarify this issue. Levy et al. published a prospective and randomized study on the prophylaxis of stress ulcers and gastrointestinal bleeding.²⁰ They randomly gave omeprazole 40mg/dl per day via a nasogastric catheter or ranitidine 150mg/dl per day intravenously, and found omeprazole to be safer and more effective, in accordance with our findings.

Alarcon de la Lastra et al. studied the antiulcerogenic effects of cisapride, a potent benzamide-stimulating gastrointestinal motility agent, on cold-restraint and pylorus-ligated gastric ulcers in rats, and compared these effects with those of ranitidine and omeprazole. They found that cisapride and omeprazole assisted gastric mucus production and quality more effectively than ranitidine.²¹ Warzecha et al.³ studied the effects of histamine on the prophylaxis of stress ulcers in rats. They found that giving ranitidine or omeprazole before the stress reduced the area of gastric lesions remarkably, and that adding histamine to ranitidine or omeprazole caused a further significant reduction in the ulcer area evoked by water immersion and restrained stress. Moreover, the effects of histamine plus omeprazole were better than those of ranitidine plus omeprazole.

Melatonin protects against stress-induced gastric lesions by cleaning the hydroxyl radical. When compared with antiulcer drugs, such as ranitidine or omeprazole, melatonin was more effective than ranitidine, but less effective than omeprazole in preventing stress ulcers.²² The objective of omeprazole is to reduce HCl secretion so as to promote mucosal regeneration and the healing of ulcers under less acidic conditions.²³

In conclusion, omeprazole was more effective than famotidine for maintaining a high gastric pH and lowering total gastric acid output. The omeprazole-treated rats had lower ulcer indexes in acute gastric mucosal erosions and better protected mucosal integrity. These findings clearly showed that omeprazole is a more effective drug than famotidine for preventing acute gastric mucosal erosions. Thus, intravenous omeprazole will expand the clinical applications of antisecretory therapy.

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