Effect of Rebamipide on Gastric Ulcer Healing Caused by *Helicobacter pylori* and/or NSAIDs or Non NSAIDs-Non *H. pylori*

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Background: *Rebamipide, a gastro-protective drug, acts on stimulation of prostaglandin and mucus glycoprotein synthesis, inhibition of reactive oxygen species, inflammatory cytokines, and neutrophils activation.*
Objective: *To investigate the effect of rebamipide (mucosta®) on healing of gastric ulcer caused by various etiologies.*
Material and Method: *Thirty patients with gastric ulcer underwent gastric antral and body biopsies for histopathology. Group classifications depended on H. pylori status using CLO test, histology or urea breath test and history of NSAIDs taking. All patients received rebamipide 100 mg, three times a day, for 8 weeks. The symptoms and adverse effects were assessed in 4 weeks and 8 weeks after prescription. At the end of the present study, an endoscopy was repeated to evaluate ulcer healing and biopsy for gastric inflammation grading.*
Results: *According to the ulcer cause, there were seven patients with H. pylori+ NSAIDs+, nine patients with H. pylori + NSAIDs-, three patients with H. pylori - NSAIDs +, and 11 patients with H. pylori - NSAIDs-. The ulcers were completely healed in most patients with a history of NSAIDs use. There was a significant improvement of symptom scores from baseline in all groups (5.9 vs. 0.6, $p < 0.001$). The improvement of gastric inflammation scores were favorable in NSAIDs users (2.38 vs. 1.75, $p = 0.011$). All patients were satisfied as there were few adverse effects.*
Conclusion: *Rebamipide is effective and well tolerated for treatment of gastric ulcers especially those caused by NSAIDs, as it promotes the improvement of gastric inflammation scores, clinical symptoms, and ulcer healing.*

Keywords: *Rebamipide, NSAIDs, Non-steroidal anti-inflammatory agents, Helicobacter pylori, Symptoms score, Gastric inflammation*

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Peptic ulcer is one of the major public health problems affecting morbidity and mortality of thousands of people each year. Pathogenesis of peptic ulcer is due to imbalance between aggressive factor (gastric acid secretion) and protective factor (gastric mucus, mucosal blood flow, reepithelialization after injuries) and major risk factors affecting cause of disease are *Helicobacter pylori* infection and NSAIDs use[2]. Many medications have been introduced aiming to reduce acid secretion (antisecretory agent namely H_2 receptor antagonist and proton pump inhibitor) or to improve protective factor (rebamipide, misoprostal, sucralfate) or eradication of *Helicobacter pylori* (antibiotics)[2].

Rebamipide, a 500 amino acids analog of 2(1H)-quinolinone[1], is a gastroprotective drug widely used in Japan nowadays. It acts through stimulation of

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prostaglandin and mucus glycoprotein synthesis, inhibition of reactive oxygen species, inflammatory cytokines, and neutrophil activation[1,7,8]. Multiple clinical trials have proposed the effect of rebamipide on healing of *H. pylori*[3,5,6,9,10] and/or NSAIDs induced peptic ulcers[4]. In the present study, the authors investigated the effect of rebamipide on healing of gastric ulcers caused by various etiologies.

Material and Method

The present study was a descriptive study conducted at Chulalongkorn Memorial Hospital for 12 months between January and December 2004. This trial was approved by the Ethical Committee of Faculty of Medicine, Chulalongkorn University. Written informed consents were obtained from all anticipating patients after acknowledgement of all information concerning trial methods, benefits, and risks.

Subjects

Thirty patients with proven gastric ulcer by endoscope with ulcer diameter between 0.5-2.5 cm, were enrolled in the present study. The exclusion criteria were (1) suspicious or confirmed malignancy, (2) lactating or pregnant women, (3) previous use of PPI or H_2 receptor antagonist, (4) uncontrolled GI bleeding, (5) previous gastrectomy or vagotomy, (6) severe co-morbid disease, (7) coagulopathy and (8) patients who cannot be followed.

All patients underwent esophagogastroduodenoscopy (EGD) with biopsy. Specimens were obtained from the different sites, 2 at antrum and 2 at body, for rapid urease test (CLO test®, Utah, USA) and histopathology each. The authors divided patients into 4 groups depending on *H. pylori* status and history of NSAIDs use composing of *H. pylori*+ NSAIDs+, *H. pylori*+ NSAIDs-, *H. pylori*- NSAIDs+, and *H. pylori*- NSAIDs-. *H. pylori* status was determined by CLO test, histopathology and urea breath test. If at least one of the three tests was positive, they would be classified as *H. pylori*+ but if all the tests were negative, they were *H. pylori*-. NSAIDs user was the patient who use NSAIDs within 7 days at any doses or on low dose ASA for cardiac or stroke prophylaxis within 2-3 months.

Study design

All groups of patients enrolled in the trial received 300 mg of rebamipide daily for 8 weeks. After completion of treatment, all patients were subjected to endoscopy and biopsy one at the antrum and one at the body for evaluation of gastric ulcer healing rate and gastric inflammation grading score. Histopathology of gastric inflammatory grading score before and after treatment was classified as mild, moderate, and marked inflammation using updated Sydney's system[11]. Morphological grading comprised multiple variables, such as *H. pylori* density, neutrophil activity, chronic inflammatory cells, glandular atrophy, and intestinal metaplasia. Gastric healing was classified as complete response (> 75% healed; comparing ulcer diameter before and after treatment), partial response (50-75% healed) and not response (< 50% healed). Furthermore, the authors also evaluated the improvement of clinical symptoms such as epigastric pain, heartburn, nausea/vomiting, and abdominal bloating at 4 and 8 weeks after treatment by using symptom grading scale ranging from 0-5 compared with symptom scale given before treatment and asked all patients about adverse effects experienced after the use of rebamipide including satisfaction of its use.

Statistic analysis

Results were reported as mean $\pm$ standard deviation (SD). Continuous variables were analyzed by Student's t-test (paired or unpaired), while non-continuous variables were analyzed by Chi-square test. All analysis was performed using SPSS program version 16.0 for Windows. Statistical significance was defined at the $p < 0.05$.

Results

Thirty patients were enrolled in the present study, including 14 male (46.7%) and 16 female (53.3%). Mean age of patients was 56.17 years. According to ulcer causes, there were seven patients (23.3%) with *H. pylori*+ NSAIDs+, nine patients (30%) with *H. pylori*+ NSAIDs-, three patients (10%) with *H. pylori*- NSAIDs+, and 11 patients (36.7%) with *H. pylori*- NSAIDs- (Table 1). There were neither statistically significant correlation between sex and

Table 1. Demographic data in each groups

	n (%)	Sex		Mean age (years)
		Male	Female	
HP+ NSAIDs+	7 (23.3%)	4	3	55.14
HP+ NSAIDs-	9 (30.0%)	5	4	52.78
HP- NSAIDs+	3 (10.0%)	0	3	61.33
HP- NSAIDs-	11 (36.7%)	5	6	58.18

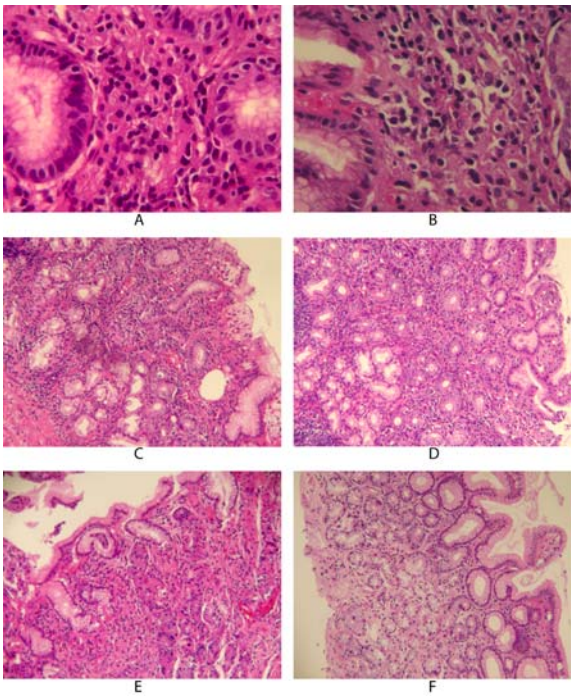
NSAIDs use (p = 0.45) nor sex and *H. pylori* infection (p = 0.225). After 8 weeks of treatment, six patients were lost from endoscopic follow-up (2 in *H. pylori*+ NSAIDs+, 2 in *H. pylori*+ NSAIDs- and 2 in *H. pylori*- NSAIDs-) and four patients did not answer the questionnaire about satisfaction on treatment.

Ulcer healing result is shown in Table 2. The ulcers were completely healed in all patients in *H. pylori*- NSAIDs+ group but there was no statistical significance among 4 groups. Comparing ulcer healing between NSAIDs+ group and NSAIDs- group, the authors found that 70% of patients with a history of NSAIDs use had significant completely healed ulcers, in contrast with 35% of completely healed ulcers in non-NSAIDs users ($p < 0.05$).

Overall histopathology of gastric inflammation grading score before and after treatment using updated Sydney's system[11] was statistically significantly improved (p = 0.009) (Table 3). Moreover, the improvement of gastric inflammation grading score after treatment was found statistically significant in NSAIDs users (p = 0.011) but not in non-NSAIDs users (p = 0.164). In contrast with a comparison of pre- and post-treatment pathological score in *H. pylori* positive group and *H. pylori* negative group, neither groups showed significant improvement (Fig. 1).

Symptom score was significantly improved at 4 and 8 weeks after treatment compared with before treatment (at 4 weeks $p < 0.001$, 95% CI = 3.60-6.17, and at 8 weeks $p < 0.001$, 95% CI = 3.89-6.67, respectively) (Table 4). The result mentioned above was in accordance with the results analyzed separately in each group (symptom score was also improved significantly after treatment in every group).

Satisfaction of treatment was divided into none, some, good, and most satisfied. There were 18 patients (60%) reported as good satisfied and five patients (5%) as most satisfied (Table 5). There were no adverse reactions found by the patients after the use of rebamipide in the present study.



A) *H. pylori*+ NSAIDs+ patient, before treatment
B) *H. pylori*+ NSAIDs+ same patient, after treatment
C) *H. pylori*+ NSAIDs- patient, before treatment
D) *H. pylori*+ NSAIDs- same patient, after treatment
E) *H. pylori*- NSAIDs- patient, before treatment
F) *H. pylori*- NSAIDs- same patient, after treatment

Fig. 1 Histopathology of gastric inflammation before and after treatment in various groups

Table 2. Ulcer results in different groups

Ulcer result	Group (n)				Total
	HP+ NSAIDs+	HP+ NSAIDs-	HP- NSAIDs+	HP- NSAIDs-	
Completely healed	4	3	3	4	14
Partially healed	0	4	0	4	8
Not response	1	0	0	1	2
Loss F/U	2	2	0	2	6
Total	7	9	3	11	30

Completely healed = > 75% ulcer healed
Partially healed = 75-50% ulcer healed
Not response = < 50% ulcer healed

Table 3. Pre- and post-treatment gastric inflammation grading score (complete; n = 24)

	No	Mild	Moderate	Severe
before treatment (n)	0	9	10	11
after treatment (n)	0	14	5	5

	Mean	SD
Pathological score before treatment	2.0	0.83
Pathological score after treatment	1.63	0.82
Pathological score difference before treatment - after treatment	0.375 (95% CI = 0.10-0.69)	0.65

Inflammation grading score using updated Sydney's system
No inflammation = 0
Mild inflammation = 1
Moderate inflammation = 2
Severe inflammation = 3

Table 4. Symptom score before treatment and 4 and 8 weeks after treatment

	n	Mean	SD	95% CI
Symptom score before treatment - 4-wk after treatment	26	4.88	3.18	3.60-6.16
Symptom score before treatment - 8-wk after treatment	25	5.28	3.36	3.89-6.67

Table 5. Satisfaction of the treatment

Satisfaction	Group (n)				Total
	HP+ NSAIDs+	HP+ NSAIDs-	HP- NSAIDs+	HP- NSAIDs-	
None	0	0	0	0	0
Some	1	2	0	0	3
Good	4	4	2	8	18
Most	1	2	1	1	5
No report	1	1	0	2	4
Total	7	9	3	11	30

None = < 25% satisfied (free of symptom)
Some = 25-50% satisfied
Good = 51-75% satisfied
Most = > 75% satisfied

Discussion

Rebamipide, a gastroprotective agent, has been used clinically for treatment of acute gastritis, peptic ulcer disease, prevention of NSAIDs induced ulcer and possibly an alternative anti-ulcer therapy for *H. pylori* associated peptic ulcer[1,8]. Many studies have investigated the effect of rebamipide on *H. pylori* and NSAIDs associated peptic ulcer and gastritis.

In the present study, the authors demonstrated effect of rebamipide in the treatment of gastric ulcers associated with *H. pylori* infection and/or NSAIDs use or neither both in the aspect of improvement of symptoms, ulcer inflammation grading, ulcer healing rate, and satisfaction on treatment. As seen from the results, rebamipide was very effective in improving symptoms of peptic ulcers in all groups of various

H. pylori status and NSAIDs use. The result presented in the present study was in accordance with a study data from Terano et al[10], which showed that the symptom-free rate significantly increased after rebamipide therapy and could be maintained throughout the treatment course. Furthermore, most of the patients were satisfied with the treatment since there was no bothersome adverse effect. However, some studies[9,10] have demonstrated adverse effects of rebamipide including diarrhea, vomiting, and abdominal pain, but they were judged as non-serious side effects and did not affect the patient's safety. Rebamipide was also found to have an efficacy in reducing inflammation of gastric ulcers, as seen from the improvement of ulcer inflammation grading score. Even though this positive effect could not be seen when analyzing four different groups separately, the authors discovered that rebamipide was obviously effective in ameliorating ulcer inflammation score in NSAIDs users but not in non-NSAIDs users or *H. pylori* associated gastric ulcers. The present study result supported the effectiveness of rebamipide on chronic inflammation reported by Fujioka et al[9] who demonstrated that rebamipide significantly improved inflammation score in post *H. pylori* eradication patients after 16-week treatment with rebamipide. Rebamipide seemed to promote better outcome of ulcer healing in NSAIDs users rather than non-NSAIDs users. Anyway, ulcer-healing rate did not significantly differ between the four groups of different *H. pylori* status and NSAIDs use.

In conclusion, rebamipide was an effective alternative for treatment of NSAIDs induced peptic ulcers, since it was shown to improve clinical symptoms, ulcer inflammation grading score and promote ulcer healing. On the contrary, rebamipide could not be proven to be helpful in *H. pylori* associated gastric ulcers. Therefore, further studies with more patients enrolled are needed to assess the effectiveness of rebamipide on *H. pylori* associated peptic ulcer.

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ผลของยารีบามิไพด์ ในการรักษาแผลกระเพาะอาหาร ทั้งชนิดที่มีสาเหตุจากการติดเชื้อเฮลิโคแบคเตอร์ไพลอไร และหรือจากยาต้านการอักเสบเอ็นเสทหรือไม่ใช่ทั้งสองสาเหตุ

ดวงพร ทองงาม, มณีรัตน์ ชยานุภัทร์กุล, นฤมล คล้ายแก้ว, รังสรรค์ ฤกษ์นิมิตร, วโรชา มหาชัย

ภูมิหลัง: *ยารีบามิไพด์ เป็นยารักษาแผลกระเพาะอาหารโดยมีฤทธิ์ในการกระตุ้น การสร้างโพสตาแกลนดิน และเยื่อเมือกในกระเพาะอาหารยับยั้งการอักเสบ การสะสมของเม็ดเลือดขาว การศึกษานี้มีขึ้นเพื่อต้องการศึกษาผลของยารีบามิไพด์ ในการรักษาหายของแผลกระเพาะอาหารจากสาเหตุต่าง ๆ โดยทำการศึกษาในผู้ป่วยแผลกระเพาะอาหาร 30 ราย ตัดชิ้นเนื้อบริเวณแอนทรัมและบอดี้ เพื่อตรวจทางพยาธิวิทยา แบ่งสาเหตุการติดเชื้อเฮลิโคแบคเตอร์ไพลอไร โดยใช้ผลบวกของยูรีเอส การวัดลมหายใจยูเรีย หรือ จากชิ้นเนื้อพยาธิวิทยา รวมทั้งประวัติการกินยาต้านการอักเสบเอ็นเสท ผู้ป่วยทุกรายจะได้รับยารีบามิไพด์ ขนาด 100 มิลลิกรัม วันละ 3 ครั้ง เป็นเวลา 8 สัปดาห์ ประเมินผลอาการและผลข้างเคียงที่เวลา 4 และ 8 สัปดาห์ หลังรับยา เมื่อครบกำหนดทำการส่องกล้องเพื่อดูการหายของแผล เปรียบเทียบการอักเสบของเนื้อเยื่อกระเพาะอาหาร*

ผลการศึกษา: *แบ่งผู้ป่วยเป็น 4 กลุ่ม ตามสาเหตุได้ดังนี้ กลุ่ม 1 H. pylori+, NSAIDs+ จำนวน 7 ราย กลุ่มที่ 2 H. pylori+, NSAIDs- จำนวน 9 ราย กลุ่มที่ 3 H. pylori-, NSAIDs+ จำนวน 3 ราย และกลุ่มที่ 4 H. pylori-, NSAIDs- จำนวน 11 ราย พบว่ามีการหายสนิทของแผลกระเพาะอาหารในผู้ป่วยเกือบทั้งหมดที่มีสาเหตุจากยาเอ็นเสท มีการดีขึ้นของคะแนนอาการอย่างมีนัยสำคัญทางสถิติ (5.9 เทียบกับ 0.6, p = 0.0001) การดีขึ้นของคะแนนการอักเสบของกระเพาะอาหาร ในกลุ่มสาเหตุจากยาเอ็นเสทอย่างมีนัยสำคัญทางสถิติ (6.25 เทียบกับ 4.37, p = 0.018) ผู้ป่วยที่ได้รับยาทุกรายพอใจโดยไม่พบผลข้างเคียงจากการใช้ยา*

สรุป: *ยารีบามิไพด์ มีประสิทธิภาพดีในการรักษาแผลกระเพาะอาหาร โดยเฉพาะเมื่อแผลนั้นมีสาเหตุจากยาเอ็นเสท โดยพบการดีขึ้นของคะแนนการอักเสบกระเพาะอาหาร, การดีขึ้นของคะแนนอาการ และการมีการหายสนิทของแผล*