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Review article: the role of rebamipide in the management of inflammatory disease of the gastrointestinal tract

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SUMMARY

Rebamipide stimulates the generation of endogenous prostaglandins in the gastric mucosa and is reported to accelerate ulcer healing. This review discusses whether rebamipide can prevent *Helicobacter pylori* infection, reduce inflammation, accelerate healing after eradication, promote ulcer healing, and prevent progression of preneoplastic lesions. Furthermore, we evaluate its usefulness in other inflammatory conditions of the gastrointestinal tract.

We conclude that rebamipide is an important candidate for long-term suppression of gastro-intestinal inflammation, praticularly if reducing the complications of *H. pylori* infection without eradicating the organism becomes accepted. If its ability to accelerate mucosal normalization is confirmed, rebamipide could be added to eradication regimens. Little information exists on whether such therapy could help limit the development of pre-neoplastic lesions. In light of the dearth of effective drugs to control inflammation in idiopathic inflammatory bowel disease, the potential of any promising new and safe compound deserves to be fully explored. The next step is to devise a targeted plan of translational research, so that results from the bench may be used to design rigorously controlled international clinical trials.

INTRODUCTION

Helicobacter pylori induces gastritis in all infected subjects. The relative intensity and topographic distribution of the mucosal inflammation, which varies in different individuals and populations, determine the outcome of gastritis.[1] This may include an asymptomatic condition that will never cause significant disease, or the development of peptic ulcer disease, atrophic metaplastic gastritis, adenocarcinoma of the stomach, or primary gastric lymphoma. The concept of eradicating *H. pylori* in all those infected has been the object of considerable debate:[2] some researchers consider the dangers of emerging antibiotic resistance and the perceived risk of developing post-eradication gastro-oesophageal reflux disease unacceptably high.[3]

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In response to such concerns, a possible strategy would be to develop ways of decreasing or suppressing gastric inflammation while allowing *H. pylori* to colonize the stomach. An agent which was able to decrease or suppress gastric inflammation could also be used as adjunct therapy after the eradication of *H. pylori*: lymphocytic and plasmacellular infiltrates and lymphoid follicles usually take months or even years to regress after eradication.[4] The negative consequences of the long persistence of this chronic mucosal inflammation are unknown, but it would seem intuitively desirable to accelerate a return to normal as much as possible.

Rebamipide (2-(4-chlorobenzoylamino)-3[2(1H)-quinolonin-4-yl] proprionic acid, Mucosta™ is a drug that stimulates the generation of endogenous prostaglandins in the gastric mucosa and has been reported to facilitate and accelerate ulcer healing.[3, 5] This drug appears particularly interesting because of its local action at the target organ (the stomach), with virtually no systemic activity.[6] To determine whether rebamipide

may be broadly employed to improve the outcome of *H. pylori* infection and reduce its complications, it will be necessary to acquire a thorough understanding of its mechanism of action and its effects, both in experimental systems and in controlled clinical studies. The fundamental questions that need to be examined may be summarized as follows: Can rebamipide: (i) prevent *H. pylori* infection; (ii) reduce inflammation in infected subjects; (iii) accelerate healing after eradication therapy; (iv) promote ulcer healing; (v) prevent progression of pre-neoplastic lesions?

This review will attempt to answer these questions by critically examining the present status of our knowledge of the activities of rebamipide. First it will consider its documented efficacy in certain human conditions related to gastritis, and then review the most relevant functions *in vitro* and in experimental animal models. This overview will be followed by speculations about the possible future clinical uses of rebamipide.

REBAMIPIDE IN CLINICAL TRIALS

Rebamipide has been tested in various clinical situations with diverse goals: in acute and chronic *H. pylori* gastritis to evaluate the improvement of the inflammatory responses, and as an adjunct to antimicrobial therapy; for the prevention and treatment of peptic ulcer disease; for the prevention of gastric mucosal damage induced by nonsteroidal anti-inflammatory drugs (NSAID); and for the amelioration of nonulcer dyspepsia. In this latter situation rebamipide has joined a vast array of other drugs that have failed to perform better than placebo: in a large multicentre study no significant improvement of individual symptom scores was observed in either rebamipide group compared with placebo, although the belching score was significantly reduced in the rebamipide 100 mg and 200 mg groups at week 2 ($P = 0.017$ and $P = 0.012$, respectively) in the *Helicobacter pylori*-positive patients.[7] Importantly, no significant side-effects were experienced by any subjects.

In several studies that have evaluated the addition of rebamipide to standard anti-*Helicobacter* therapies, the rebamipide groups had significantly higher eradication rates than subjects treated with dual[8] or triple therapies alone.[9–11] In Hahm *et al.*'s study,[11] not only were eradication rates between the two groups significantly better (58% vs. 75%; $P < 0.05$), but mucosal MDA levels and myeloperoxidase activities were significantly lower in the rebamipide-treated group than in the untreated group. Mucosal levels of cytokines IL-1, IL-6, and TNF-α and of chemokines IL-8, GRO-α and RANTES were all significantly decreased after treatment for *H. pylori*, especially in the rebamipide-treated group. Thus, the addition of rebamipide to *H. pylori* eradication regimens seems to have both quantitative and qualitative advantages: it increases the eradication rates while decreasing the oxidative stress and cytokine levels generated by *H. pylori* infection.

Rebamipide has also been proven effective in improving inflammatory scores in patients with *H. pylori*-gastritis who did not undergo eradication therapy. Haruma *et al.*[12] studied 86 *H. pylori*-infected patients: 53 were treated with rebamipide and 33 served as controls. Significant decreases in mononuclear cell infiltration into the antrum (from 1.42 ± 0.15 to 1.02 ± 0.15; $P < 0.01$) and corpus (from 1.60 ± 0.15 to 1.21 ± 0.14; $P < 0.05$) were noted in the rebamipide treatment group. Levels of infiltrating neutrophils also decreased in the antrum (from 0.98 ± 0.14 to 0.70 ± 0.13; $P < 0.05$) and were associated with a decrease in iNOS production. Sera from patients treated with rebamipide showed a significant decrease in gastrin (from 276.3 ± 58.3 pg/mL to 173.0 ± 34.2 pg/mL; $P < 0.05$), whereas no change was observed in the control group. These results suggest that long-term rebamipide treatment can reduce gastric inflammation and decrease serum gastrin levels in *H. pylori*-infected subjects.

In one study rebamipide was found to be as effective as omeprazole and amoxicillin in preventing the recurrence of gastric ulcers in patients with *H. pylori* infection.[13] Finally, in a double-blind placebo-controlled study in healthy volunteers, rebamipide prevented both indomethacin-induced upper gastrointestinal symptoms and the development of gastric mucosal injury.[14]

IN VITRO STUDIES

The wide variety of actions of rebamipide in isolated cell and tissue culture systems can be conveniently divided into effects on the adhesion of *H. pylori* to epithelial cells, antioxidant effectiveness, inhibition of neutrophil activation and permeability.

A drug that prevented the adhesion of *H. pylori* to gastric epithelial cells could potentially be used to prevent and perhaps cure *H. pylori* infection. In a system that used MKN-28 and MKN-45 cells derived from human gastric carcinomas as target cells, pretreatment with rebamipide alone was effective in

preventing bacterial adhesion.[15] This effectiveness was enhanced by the simultaneous addition of ecabet sodium, another gastro-protective agent. Rebamipide and ecabet sodium each partially inhibited *H. pylori* adhesion. In contrast, adhesion was almost completely inhibited by pre-treating target cells and *H. pylori* with a combination of rebamipide and ecabet sodium. The results of these studies suggest that the synergistic anti-adhesive activity of rebamipide and ecabet sodium is greater than that of each anti-ulcer agent alone.[16] In spite of these interesting findings, several as-yet unpublished studies recently presented at a topic-specific symposium suggested that oral rebamipide does not prevent experimental infection with *H. pylori* in laboratory rodents. However, one must consider that while natural infections are likely to be acquired by the ingestion of few bacteria at a time, experimental intragastric inoculations consist of cultures of millions of *H. pylori.* Anti-adhesion may be ineffective against such large inocula.

In an experiment which used a luminol-dependent chemiluminescence assay to compare the effectiveness of rebamipide in scavenging the oxygen-derived free radicals produced by *H. pylori* with other known antioxidants (N-acetylcysteine, ascorbic acid and glutathione), the antioxidant activity of rebamipide was shown to be more potent than any of the other three antioxidants.[17] In this respect, it should also be noted that Suzuki *et al.*[18] reported that rebamipide attenuated the increase in luminal-dependent chemiluminescence evoked from isolated neutrophils incubated with *H. pylori* bacterial suspensions. Rebamipide was also shown to prevent oxidation of the cytoskeletal protein actin and monolayer barrier dysfunction in a human intestinal monolayer system challenged with reactive oxygen metabolites.[19]

Ceramide is a lipid second messenger that has become recognized as an important mediator of the action of several cytokines. *H. pylori*-dependent ceramide production may activate nuclear factor κB and mediate interleukin-8 expression in human gastric cancer cell lines. Masamune *et al.*[20] evaluated the effect of rebamipide on *H. pylori*-dependent ceramide production and subsequent interleukin-8 expression in Kato III cells. Rebamipide inhibited ceramide-induced interleukin-8 expression in a dose-dependent manner, and decreased the ceramide-induced increase of the interleukin-8 mRNA levels. Rebamipide suppressed interleukin-8 gene transcription and nuclear factor κB-dependent transcriptional activity as assessed by a luciferase assay. It also inhibited the ceramide-dependent activation of mitogen-activated protein kinases and significantly attenuated the *H. pylori*-dependent increase in intracellular ceramide level. These results provide useful insights into a novel mechanism by which rebamipide may protect against the mucosal inflammation associated with *H. pylori* infection.

In a series of experiments designed to determine the effect of rebamipide on the activation of isolated human neutrophils and to identify the signal transduction pathway involved in its regulation, it was established that rebamipide exerts a broad spectrum of suppressive actions toward the biological functions of human neutrophils. When neutrophils were stimulated with the chemotactic peptide formyl-methionyl-leucyl-phenylalanine, the granules fused to form elongated tubular structures and spherical vacuoles. Rebamipide inhibited the reorganization of alkaline phosphatase-containing granules along with up-regulation of alkaline phosphatase activity and CD16, a marker of the granules. It also suppressed chemotaxis, an increase in intracellular calcium ion concentration, and NADPH oxidase activation in cells stimulated with formyl-methionyl-leucyl-phenylalanine. In contrast, it showed no inhibitory action towards the up-regulation of alkaline phosphatase activity and CD16, and activation of NADPH oxidase in cells stimulated with phorbol myristate acetate, an activator of protein kinase C. These results suggest that the upstream point of protein kinase C is the signal transduction pathway involved in the regulation of rebamipide-associated neutrophil activation.[21] Rebamipide also suppresses neutrophil adherence to *H. pylori*-infected Kato III cells, probably through the inhibition of IL-8.[22, 23] Moreover, the *H. pylori*-induced production of other cytokines, including IL-10, TNF-α and IL-1α, is inhibited in a dose-dependent manner by rebamipide.[24] Similarly, rebamipide inhibits the neutrophil oxidative burst resulting from their nonopsonic activation by *H. pylori.*[25]

The ulcer-healing activity of rebamipide may be explained, at least in part, by its ability, demonstrated by Tarnawski's group,[26] to produce a significant increase in EGF and EGF-R expression in the normal gastric mucosa of rats and to increase the expression of EGF and EGF-R in the regenerating glands of the ulcer scar. Since EGF and its receptor are crucial for epithelial cell proliferation, re-epithelialization, and gland reconstruction, these actions may partially explain its ulcer healing action.

Other *in vitro* work focusing on the effects of rebamipide on COX-2 expression has shown that it increases PGE^2 levels and enhances gastric mucosal defence in a COX-2-dependent manner. These findings elucidate yet another mechanism by which rebamipide enhances gastric mucosal protection.[27]

Animal models

Several experimental rodent models have been used to assess the functions of rebamipide. In restrained rats, an infusion of indomethacin causes severe gastric haemorrhage. While pre-treatment with omeprazole did not have any significant effects, rebamipide was more effective than cimetidine in suppressing the gastric haemorrhage.[28] Since anti-rat PMN (polymorphonuclear leucocytes)—which caused the depletion of circulating neutrophils—also suppressed the indomethacin-induced haemorrhage in this model, the authors speculate that rebamipide acts by limiting the release of reactive oxygen species from neutrophils, although others have proposed alternate explanations.[29, 30] Similarly, ammonia-induced gastric mucosal haemorrhagic lesions in rats were improved by the intraperitoneal administration of rebamipide. This reduced the xanthine oxidase activity, lipid peroxide content in ammonia induced haemorrhagic lesion, suggesting that the therapeutic effect of rebamipide on gastric mucosal lesions may in part be due to the inhibitory activity of xanthine oxidase and the conversion rate of the enzyme.[31] Another possible mechanism by which rebamipide may exert its protective effect on the gastric mucosa is through the stimulation of glycosaminoglycan (GAG) synthesis, which may also contribute to the healing process of gastric ulcers.[32] Suzuki *et al.*[33] studied the effects of oral rebamipide in a model of ethanol-induced injury in Mongolian gerbils experimentally infected with *H. pylori*. After 4 weeks, treated animals had a much greater rate of 'natural disappearance' of the bacteria, and a significantly mitigated mucosal damage. However, other studies in Mongolian gerbils which were recently presented at a topic-specific symposia, have been less encouraging. In our laboratory, we performed both short- and long-term studies to address the following questions: (i) can the chronic active inflammation caused by *H. pylori* and the gastric ulcers that develop in experimentally infected Mongolian gerbils be reduced or prevented by treatment with rebamipide? and (ii) does rebamipide accelerate the healing of inflammation after cure of *H. pylori* infection? Our results showed that when administered in daily oral doses of ~100 mg/kg to Mongolian gerbils infected with *H. pylori*, rebamipide seems to exert a mildly protective effect with regard to the development of pyloric channel ulcers. In contrast, the overall inflammatory scores of the gastric mucosa are not affected. The administration of rebamipide shortly before and for long periods after eradication of *H. pylori* infection does not seem to alter the course of the post-treatment normalization of the mucosa. These data suggest that, while rebamipide may somewhat decrease the ulcer risk in infected animals, in the gerbil model it does not exert any inflammation-decreasing activity. The experience of Japanese and Korean investigators, also presented at these symposia, has been similar to ours.

An interesting finding published by Matysiak-Budnik *et al.*,[34, 35] and further expanded by these authors in recent presentations, is related to the ability of rebamipide to prevent the increased mucosal permeability caused by *H. felis* infection in mice as well as *in vitro*. In the *in vivo* model, even after *H. felis* is eradicated, gastric permeability to macromolecules remains increased, and rebamipide can facilitate the normalization of gastric permeability after bacterial eradication. The implications of these studies are important, because they provide a sound foundation for the concept of using rebamipide as an adjunct therapy after *H. pylori* eradication. Furthermore, since many alimentary allergies are believed to be associated with an abnormal mucosal permeability to certain macromolecules, these studies lend a theoretical basis for the design of clinical trials aimed at evaluating the effects of rebamipide in patients with gastrointestinal hypersensitivities.

EXTRA-GASTRIC ACTIVITY

Another potentially fertile area of investigation is the effect of rebamipide on other segments of the digestive tract. The *in vitro* and *in vivo* permeability studies discussed above[34, 35] suggest potential uses in allergic conditions of the gastrointestinal tract and in intestinal inflammatory diseases. The attenuation of colitis indices induced by rebamipide in a rat model studied by Kishimoto *et al.*[36] indicated that these effects are attributable to its inhibition of inflammatory cytokine-mediated granulocyte (neutrophil) infiltration into the colon. Other groups demonstrated that rebamipide can decrease or suppress chemically induced colitis in rodents, and that attenuation of the inflammatory

responses appeared to be largely related to the inhibition of the production of reactive oxygen species.[37] The results of this body of work indicate that this drug might have beneficial effects in the treatment of human ulcerative colitis. Such a study, limited to patients with proctitis, has recently been proposed in a letter to the editor.[38]

REBAMIPIDE IN CLINICAL PRACTICE

At the time of writing, more than 100 studies on various aspects of the multifaceted functions of rebamipide have been published and many more have been presented as abstracts. *In vitro* studies have revealed numerous and previously unsuspected mechanisms of action, and have suggested potential new uses. Clinical studies have been encouraging, but more controlled data are needed. Animal work, particularly with the *H. pylori* Mongolian gerbil model, has been useful in illustrating the basic mechanisms of action, but it has generally yielded modest clinical results. This reflects the limitations of animal models, particularly in an area such as *H. pylori* gastritis, in which only rarely are the features of human disease reproduced.

The collective message that one can gather from this work is that rebamipide may be an important candidate for the long-term suppression of gastro-intestinal inflammation. If the concept of attempting to reduce the complications of *H. pylori* infection without eradicating the organism becomes widely accepted, the use of a safe local anti-inflammatory medication with essentially no systemic effects could be a pivotal component of such maintenance therapy. Rebamipide could find an important indication as an adjunct to existing eradication regimens, particularly if a significant acceleration of the gastric mucosal normalization could be demonstrated in controlled studies. As of today, no information exists on whether such therapy could help to limit the development of pre-neoplastic lesions, and this could represent a fertile, if indeed laborious, area for clinical investigation. As an anti-ulcer agent and as a promoter of ulcer healing, rebamipide is already being used in Japan and Korea, and studies validating these effects in other populations could help to expand its geographical scope to other areas of the world. Finally, in light of the dearth of effective drugs for controlling inflammation in idiopathic inflammatory bowel disease, the potential of any promising new and safe compound deserves to be fully explored.

The next step to reach for these objectives is to devise a targeted plan of translational research, so that results from the bench may be used to design clinical trials. Such trials, rigorously controlled and conducted in diverse geographical locations, are indispensable for better defining the effects of such treatment and the patient populations that would best benefit from this promising drug.

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