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PHARMACOLOGICAL AND CLINICAL PROFILE OF REBAMIPIDE: NEW THERAPEUTIC TARGETS

Giyosova Khabibakhon Isakjonovna

Faculty of Pharmacy

Department of Pharmaceutical Sciences

Abstract: Rebamipide is a cytoprotector developed in Japan, where it has been successfully used to treat stomach diseases for 30 years. The initially discovered mechanisms of action of the drug included the induction of prostaglandins and the removal of free oxygen radicals. Over the past 10 years, studies have been conducted that have discovered new therapeutic targets for the drug, its new dosage forms have been developed, which has made it possible to use rebamipide to treat diseases such as NSAID enteropathy, ulcerative colitis, radiation colitis, reservoirs, enteropathy with impaired membrane digestion. It is used in endoscopy, ophthalmology, chemotherapy, rheumatology.

Keywords: rebamipide, cytoprotector, enteropathy, disaccharidases, peptic ulcer, ulcerative colitis, radiation colitis.

INTRODUCTION

Rebamipide is an optically active derivative of the α-amino acid 2(1H)-quinolinone, synthesized and approved in Japan for the treatment of gastric ulcer [1, 2]. The antiulcer effect has been proven in a model of gastric ulcer induced by acetic acid in rats [3]. Rebamipide is a white crystalline powder, odorless, bitter to the taste. To avoid bitterness, the drug is film-coated. Japanese pharmacists are developing orally soluble tablets with cocoa powder, convenient for patients with dysphagia [4]. Rebamipide has low oral bioavailability (10%). In order to increase it, lipid nanoemulsions based on olive oil and egg lecithin have been created.

MATERIALS AND METHODS

After a single oral administration of 100 mg rebamipide to 27 healthy men, the drug was rapidly absorbed: Cmax 216±79 ng/ml and Tmax 2.4±1.2 h, the half-life in plasma was 1.9±0.7 h [1]. In animal studies, rebamipide was absorbed primarily from the upper small intestine by passive transport. The absorption of rebamipide is influenced by dose, gastric acidity, and diet. After a single oral administration of 100 mg rebamipide, 10% of the administered dose is excreted in the urine, the remainder is found in the feces as inactive metabolites [2].

RESULTS AND DISCUSSION

The initially discovered main mechanisms of action of rebamipide included prostaglandin induction and elimination of oxygen free radicals. Over the past few years, fundamental and clinical studies have been conducted that have identified several molecules considered as therapeutic targets of rebamipide and explaining its diverse pharmacological action. A large

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number of studies have been published devoted to the study of the gastroprotective effect of the drug, which is associated with the induction of cyclooxygenase-2 (COX-2) expression, a decrease in the amount of reactive oxygen species, inhibition of neutrophil activity and cytokine production [3]. However, the action of the drug is not limited to the above mechanisms. One of the main points of application of the drug is a change in the permeability of the gastrointestinal mucosa by increasing the expression of zonula occludins-1 (ZO-1) and claudin proteins [4]. K. Hashimoto et al. reported that hydrogen peroxide increases the permeability of the gastric epithelium due to the degradation of claudin-3 in epithelial cells and that these changes are eliminated by rebamipide [2]. In a study by T. Gweon et al. on a model of gastroesophageal reflux disease in rats, it was established that rebamipide works synergistically with proton pump inhibitors (PPIs), increasing the expression of claudin-3 and claudin-4 - structural components of tight junctions of epithelial cells, thereby regulating the barrier function of the gastrointestinal mucosa, reducing its permeability. These results are confirmed in many works by Japanese authors [3].

The study by T. Masanobu et al. provides the first evidence for the existence of molecular pathways of rebamipide action responsible for its cytoprotective effect. The authors studied the effect of rebamipide on the restoration of normal human keratinocyte cultures treated with rebamipide in combination with 5-fluorouracil or cisplatin [1]. The cytotoxic effects of 5-fluorouracil and cisplatin were significantly suppressed by rebamipide by inducing the following signaling pathways: ERK1/2, Akt, JNK, p38MAPK and mTOR. To confirm this information, normal human keratinocyte cells were treated with specific inhibitors of these signaling pathways, which reduced the cytoprotective effect of rebamipide. The results obtained showed that the cytoprotection of rebamipide is, at least in part, mediated by signaling pathways. Rebamipide was also found to induce the activation of the p38 MAPK signaling pathway, an important component of the intestinal injury healing response, and COX-2 production [2], which leads to the synthesis of prostaglandin E2 (PGE2) and protection of the gastric mucosa [3]. These data suggest that the signaling pathways activated by rebamipide (ERK1/2 and p38 MAPK) may play a role in mucin production and COX-2 production in normal human oral keratinocyte cells. The study demonstrated that the cytoprotective effect through activation of the Akt/mTOR pathway leads to an increase in the production of anti-apoptotic proteins Bcl-2 and Bcl-xL and suppression of the expression of pro-apoptotic proteins Bax and Bim. Thus, the results obtained by T. Masanobu et al. [4] not only expand the data on the mechanism of action of rebamipide, but also indicate the advisability of its use for the prevention and treatment of oral mucositis induced by chemotherapy. It is known that oral mucositis is the most common side effect of standard antitumor drugs and develops in 20–40% of patients, thereby limiting the possibilities of chemotherapy.

Functional dyspepsia is one of the most common clinical problems encountered by gastroenterologists. A double-blind, placebo-controlled, multicenter study of rebamipide was conducted in the USA to evaluate the efficacy and safety of the drug in reducing the symptoms of functional dyspepsia depending on the presence of H. pylori. No significant differences in the frequency of individual symptoms were found at the end of treatment, but many patients receiving rebamipide 100–200 mg three times a day noted a decrease in belching starting from the 2nd week [2]. Another double-blind, placebo-controlled study was conducted to evaluate the quality of life in patients receiving rebamipide for dyspeptic

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symptoms. Although rebamipide was not superior to placebo in reducing all symptoms of dyspepsia after 4 weeks of treatment, a significant reduction in flatulence, belching, pain and abdominal discomfort after meals was nevertheless noted [3]. T. Chitapanarux et al. noted the positive effect of rebamipide not only on clinical symptoms, but also on endoscopic and histological characteristics of chronic gastritis in patients with dyspepsia symptoms refractory to PPIs [4].

CONCLUSION

Further studies should be aimed at dynamic observation of patients in order to determine the duration of the stimulating effect of rebamipide and the need for maintenance therapy. Nevertheless, the cytoprotective mechanisms of rebamipide already provide the basis for the formation of a new direction in the strategy for the treatment of diseases of the stomach and intestines.

REFERENCES

1. Takano H, Uchida S, Kashiwagura Y, et al. Preparation of Cocoa Powder-Containing Orally Disintegrating Tablets of Rebamipide (Rebamipide Chocolet) and Evaluation of Their Clinical Palatability. Chem Pharm Bull. 2019;67(2):112-9. doi: 10.1248/cpb.c18-00629

2. Kim KT, Lee JY, Park JH, et al. Capmul MCM/Solutol HS15-Based Microemulsion for Enhanced Oral Bioavailability of Rebamipide. J Nanosci Nanotechnol. 2017 Apr;17(4):2340-344. doi:10.1166/jnn.2017.13314

3. Hasegawa S, Sekino H, Matsuoka O, et al. Bioequivalence of rebamipide granules and tablets in healthy adult male volunteers. Clin Drug Investig. 2003;23:771-9. doi: 10.2165/00044011-200323120-00002

4. Naito Y, Yoshikawa T. Rebamipide: A gastrointestinal protective drug with pleiotropic activities. Expert Rev Gastroenterol Hepatol. 2010;4(3):261-70. doi: 10.1586/egh.10.25