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SHORT COMMUNICATION

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Efficacy and Safety of Rebamipide in Prevention of NSAID-Gastropathy

Serhiy Tkach, PhD, ScD[1]; Liudmila Onischuk[2]*; Anna Balabantseva[3]

[1]*Ukrainian Scientifically Practical Center of Endocrine Surgery, Kyiv, Ukraine*
[2]*Bogomolets National Medical University, Kyiv, Ukraine*
[3]*Medical Academy named after S.I. Georgievsky, Simferopol, Republic of Crimea*

Abstract

Background: Nonsteroidal anti-inflammatory drugs (NSAID) are one of the most widely used drugs in medical practice. However, all medical benefits of NSAID are paid for by increased risk of developing numerous side effects. One of the most clinically significant side effects is a NSAID-induced gastrointestinal lesion that develops in, on average, 30% of NSAID users, even with the absence of ulceration; NSAID-induced ulcers and bleeding cause 61% of deaths related to side effects of these medicines. The main aim of this study was to compare the incidence of erosive and ulcerative lesions of the gastroduodenal zone as a result of patients receiving diclofenac on the background of concomitant prophylactic use of proton pump inhibitor (PPI) omeprazole or rebamipide.

Materials and Methods: To achieve this goal we have conducted a randomized comparative study, which included 118 patients aged from 25 to 65 years (mean age, 45±18 years) with osteoarthritis (94 patients) and rheumatoid arthritis (24 patients), who had taken a once-daily dose of 100 mg diclofenac (Dikloberl) over 1 month. Depending on the treatment, all patients were randomized into 3 groups by using the computer method of random numbers. Within 1 month, patients of Group 1 (n=42) received additionally a once-daily dose of 20 mg omeprazole (Omez), and patients of Group 2 (n=46) - rebamipide at a dose of 100 mg three times a day. Patients of Group 3 (n=30) received only diclofenac. The primary endpoint was the cumulative incidence of development of erosions and ulcers in the gastroduodenal zone, which was determined after the treatment according to data from the endoscopy. The secondary endpoint was the incidence of development of dyspeptic symptoms and side effects.

Results: During 1 month of continuous reception of diclofenac, peptic ulcers of stomach and duodenum were found in 2/4.8% and 2/4.8% patients of Group 1 and in 3/6.5% and 2/4.3% patients of Group 2, respectively. In Group 3, peptic ulcers of stomach and duodenum were found in 5/16.6% and 3/10% patients, respectively, and in 2 cases, these ulcers (1 gastric ulcer and 1 duodenal ulcer) have manifested into gastrointestinal bleeding. Thus, all peptic ulcers of the gastroduodenal area were detected in 4/9.5% patients of Group 1, 5/10.9% patients of Group 2, and 8/26.6% patients of Group 3. **(Int J Biomed. 2017; 7(1):57-59.)**

Key Words: NSAID • side effects • gastropathy • rebamipide

Introduction

Nonsteroidal anti-inflammatory drugs (NSAID) are one of the most widely used drugs in medical practice that tens millions of patients all over the world use every day. Their popularity and widespread use are due to their significant anti-inflammatory effect that relieves pain in various states, including arthritis, and other musculoskeletal pathology. However, all medical benefits of NSAID are paid for by increased risk of developing numerous side effects, including some that are life-threatening. For example, a prospective analysis has shown that in the United Kingdom, NSAID were the main class of drugs that cause side effects (on average in 30% over 18000 hospitalized patients); in the USA, side effects of NSAID were the 15th leading cause of death.[1] One of the most clinically significant side effects is a NSAID-induced gastrointestinal lesion that develops in, on average, 30% of NSAID users, even with the absence of ulceration; NSAID-induced ulcers and bleeding cause 61% of deaths related to side effects of these medicines.

***Corresponding author:** Lyudmila Onyshchuk, MD. Bogomolets National Medical University, Kyiv, Ukraine. Email: lyudmila.onishhuk@mail.ru*

Rebamipide (Otsuka Pharmaceutical Co., Japan) is a cytoprotective anti-ulcer drug that increases the protective mechanisms of gastric mucosa by increasing the production of gastric mucus and stimulation of endogenous production of prostaglandins. The efficiency of rebamipide in the prevention of NSAID-induced gastric damage was confirmed in healthy volunteers during their treatment with indomethacin.[2-4] Rebamipide was also found to be efficacious in reducing gastric injury in healthy subjects taking aspirin 1500 mg once a day.[5] However, there are not enough data concerning the efficiency of rebamipide in the prevention of NSAID-induced gastrointestinal lesion.

The main aim of this study was to compare the incidence of erosive and ulcerative lesions of the gastroduodenal zone as a result of patients receiving diclofenac on the background of concomitant prophylactic use of proton pump inhibitor (PPI) omeprazole or rebamipide.

Materials and Methods

To achieve this goal we have conducted a randomized comparative study, which included 118 patients aged from 25 to 65 years (mean age, 45±18 years) with osteoarthritis (94 patients) and rheumatoid arthritis (24 patients), who had taken a once-daily dose of 100 mg diclofenac (Dikloberl) over 1 month. The study excluded patients with concomitant severe liver or kidney disease, those with clinically significant upper gastrointestinal pathology confirmed during endoscopy (GERD, esophageal varices, peptic ulcers or tumors), patients after operations on the stomach, and patients who have taken over the last 4-weeks antisecretory drugs, cytoprotectors, prokinetics, NSAID, corticosteroids and anticoagulants.

Depending on the treatment, all patients were randomized into 3 groups by using the computer method of random numbers. Within 1 month, patients of Group 1 (n=42) received additionally a once-daily dose of 20 mg omeprazole (Omez), and patients of Group 2 (n=46) - rebamipide at a dose of 100 mg three times a day. Patients of Group 3 (n=30) received only diclofenac. Informed consent was signed by each participant.

All patients before the study underwent esophagogastroduodenoscopy, which was repeated at the end of the treatment after 4 weeks, or in the case of severe pain syndrome and/or dyspeptic symptoms that additional antacids did not stop, signs of overt or latent gastric bleeding, anemia. Ulcers are defined as breaks in the mucosal surface 3 mm or more in diameter measured by using biopsy forceps during endoscopy. Erosions were defined as superficial mucosal defects of less than 3 mm in diameter, and intramucosal hemorrhage – hemorrhagic lesions without superficial mucosal defects. Endoscopic mucosal damage was assessed using the modified Lanza scale (MLS) ranging from 0 to 5, during the screening and at the end of the study. In all cases during screening endoscopy, the rapid urease test was performed to find the presence of Helicobacter pylori infection, and photo and video documentation of this procedure were made.

The primary endpoint was the cumulative incidence of development of erosions and ulcers in the gastroduodenal zone, which was determined after the treatment according to data from the endoscopy. The secondary endpoint was the incidence of development of dyspeptic symptoms and side effects.

The obtained results were statistically processed. Group comparisons with respect to categorical variables are performed using chi-square tests with Yates correction or, alternatively, Fisher's exact test. A probability value of $P<0.05$ was considered statistically significant.

Results and Discussion

During 1 month of continuous reception of diclofenac, peptic ulcers of stomach and duodenum were found in 2/4.8% and 2/4.8% patients of Group 1 and in 3/6.5% and 2/4.3% patients of Group 2, respectively. In Group 3, peptic ulcers of stomach and duodenum were found in 5/16.6% and 3/10% patients, respectively, and in 2 cases, these ulcers (1 gastric ulcer and 1 duodenal ulcer) have manifested into gastrointestinal bleeding. Thus, all peptic ulcers of the gastroduodenal area were detected in 4/9.5% patients of Group 1, 5/10.9% patients of Group 2, and 8/26.6% patients of Group 3. Thus, the cumulative incidence of peptic ulcers in Groups 1 and 2 was not significantly different among themselves ($P=1.000$), but was significantly lower than in Group 3 ($P=0.037$). It should be noted that all patients with peptic ulcers had concomitant gastroduodenal erosive changes (from 1 to 5 according to the Lanza scale). The cumulative frequency of occurrence of gastroduodenal erosions, evaluated according to the Lanza scale, in Groups 1, 2 and 3 was 19%, 23.9% and 46.6%, respectively ($P=0.027$). Thus, the frequency of endoscopic visible damage of gastroduodenal area in groups with rebamipide and omeprazole (19% and 23.9%, respectively) was not significantly different among themselves ($P=0.614$), but was significantly lower than in the control group ($P=0.017$).

The vast majority of patients with NSAID-induced gastroduodenopathy in Groups 1, 2, and 3 (87.5%, 90.9% and 85.7%, respectively) were infected with *Helicobacter pylori* (*H. pylori*). These data support the preconceived notion that *H. pylori* infection and NSAID have a synergistic damaging effect on gastric mucosa, and the fact that eradication of *H. pylori* can act as one of the most effective strategies for the prevention of NSAID-gastropathy.

As can be seen, the frequency of development of NSAID-induced dyspeptic symptoms and complications in Groups 1 and 2, except diarrhea syndrome, did not differ significantly, but was significantly lower than in Group 3 patients receiving no omeprazole or rebamipide. In addition, 2 patients in Group 3 had gastrointestinal bleeding stopped by conservative treatment, which was not observed in Groups 1 and 2. Thus, the use of rebamipide in patients who require long-term use of NSAID should be considered as a safe method of preventing NSAID-gastropathy and its complications, and their effectiveness is not inferior to the preventive effect of PPI.

Our findings are consistent with 4 earlier foreign randomized placebo-controlled trials. S. Ono et al.[6] also showed that rebamipide significantly prevented low-dose aspirin-induced erythema in the antrum compared with

placebo (*P=0.0393*). In the study by Kawai et al.,[7] the number of gastric lesions were counted to evaluate low-dose ASA-induced gastrointestinal injuries compared among the placebo, omeprazole, and rebamipide group. The number of erythema, erosions, petechia were evaluated as changing their numbers compared with before starting study and after (after had three points, 24 h, 3 days, and 7 days). Thus, the number of erythema was increased in the placebo group at 3 days compared with the omeprazole and the rebamipide groups, 9.6±10.5 vs 1.4±6.8 (*P=0.0611*) vs 0.3±4.2 (*P=0.0327*). The number of petechiae was increased in the placebo group at 7 days compared with the omeprazole and the rebamipide groups: 8.3±8.8 vs 5.6±23.6 (*P=0.0213*) vs 1.6±5.2 (*P=0.0335*), respectively.

The efficacy of rebamipide in reducing NSAID-induced gastric injury has been reported in healthy volunteers on indomethacin treatment.[8] In the study by Kim et al.,[9] twenty healthy volunteers were randomized two groups. The placebo group took ibuprofen, 600 mg t.i.d., and placebo for 7 days. The rebamipide group took ibuprofen, 600 mg t.i.d., and rebamipide, 100 mg t.i.d., for 7 days. After 7 days of the administration of ibuprofen and either placebo or rebamipide, severe gastric mucosal lesions, MLS ≥3, were found in six (60%) of the placebo group and none (0%) of the rebamipide group (*P=0.011*).

In 2008, Naito et al.[10] investigated the efficacy of rebamipide and famotidine in *H.pylori*-negative healthy volunteers taking NSAID. This study was a randomized, two way crossover study comparing the preventive effect rebamipide 100 mg, t.i.d. and famotidine 10 mg, b.i.d against indomethacin (25 mg, t.i.d.)-induced gastric mucosal injury in *H. pylori*-negative healthy volunteers. The incidence of gastric lesions (MLS ≥2) was 17% (2/12) in the rebamipide group and 25% (3/12) in the famotidine group. Peptic ulcers did not occur in both groups.

Our study, which confirmed the efficacy and safety of rebamipide in the prevention of NSAID-gastropathy, has some drawbacks and limitations. They are a relatively small sample size, lack of comparisons with the placebo, short-term use of NSAID and rebamipide (1 month). Nevertheless, these results allow us to recommend using rebamipide more widely as an effective and safe method of prevention of NSAID gastropathy. To clarify the protective effects of rebamipide on the lower gastrointestinal tract, further research is needed.

Competing interests

The authors declare that they have no competing interests.

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