Assessing the efficacy of famotidine and rebamipide in the treatment of gastric mucosal lesions in patients receiving long-term NSAID therapy (FORCE—famotidine or rebamipide in comparison by endoscopy)

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Background. Nonsteroidal anti-inflammatory drugs (NSAIDs) and Helicobacter pylori infection are major causes of gastric mucosal lesions. In Japan, histamine-2 receptor antagonists are frequently prescribed, but the literature regarding their efficacy is limited. In this study, we compare the effects of famotidine and rebamipide on NSAID-associated gastric mucosal lesions using upper gastrointestinal endoscopy. Methods. This study examined 112 patients taking NSAIDs for either gastric hemorrhage or erosion. Before treatment, the patients were assessed by endoscopy. Using blind randomization, patients were divided into two groups: group F (famotidine, 20 mg/day) and group R (rebamipide, 300 mg/day). Efficacy was examined 4 weeks later using endoscopy. Results. After treatment, the Lanza score decreased significantly in group F (P < 0.001) but not in group R (P = 0.478). The change in the Lanza score in group F was significantly greater (P = 0.002) than that in group R. Conclusions. Famotidine was superior to rebamipide in treating NSAID-associated mucosal lesions.

Key words: famotidine, rebamipide, randomized study, mucosal lesion, NSAID

Introduction

Aspirin, the first nonsteroidal anti-inflammatory drug (NSAID), was synthesized approximately 100 years ago; since then, various NSAIDs have been developed. Owing to their outstanding analgesic actions and relatively high safety levels, NSAIDs are widely used in the treatment of patients who suffer from various forms of chronic pain. Nevertheless, it is well known that NSAID administration, as well as Helicobacter pylori infection, are significant causes of gastric mucosal lesions.1,2

As the elderly population continues to grow, the number of patients with rheumatoid arthritis, osteoarthritis, osteoporosis, and spondylosis deformans is expected to escalate, with a consequent increase in the frequency of NSAID therapy. In addition, the spread of H. pylori eradication therapy is gradually reducing gastric mucosal lesions caused by H. pylori infection.3,4 Consequently, the significance of NSAID-associated gastric mucosal lesions is continuing to increase. The effect of various treatments for these gastric lesions, therefore, requires urgent investigation.

The inhibition of prostaglandin synthesis is believed to be the major mechanism of NSAID-associated gastric mucosal lesions.5 Other mechanisms, however, are also considered to play a role in NSAID-associated gastric mucosal lesions.6,7 NSAIDs may cause gastric mucosal lesions by reducing gastric mucosal blood flow.8 As with other peptic ulcers, the involvement of gastric acid in NSAID-associated gastric mucosal lesions is important.8 Therefore, acid suppressors are also consid-
ered effective for NSAID-associated gastric mucosal lesions, as are prostaglandin analogs and other so-called mucoprotective drugs. Indeed, the Guideline for Clinical Practice of Gastric Ulcer Based on EBM (evidence-based medicine) that was developed by a study team from the Ministry of Health, Labour and Welfare in Japan in April 2003 specified that NSAID-associated gastric ulcers should be initially treated by discontinuing NSAID therapy. However, for patients who cannot discontinue NSAIDs, the guideline recommends the administration of prostaglandin analogs or proton pump inhibitors, which are acid suppressors. Histamine-2 receptor antagonists (H2RAs) are also acid suppressors similar to proton pump inhibitors, although compared with proton pump inhibitors, evidence demonstrating the effect of H2RAs on NSAID-associated gastric mucosal lesions appears inadequate. Clinical studies have reported that famotidine, an H2RA, provides excellent prevention and therapeutic actions for NSAID-associated gastric ulcers at high dosages. In addition, basic studies have demonstrated that famotidine is significantly more effective than so-called mucoprotective drugs in the prevention of NSAID-associated gastric mucosal lesions. Despite the existence of such evidence, in addition to the fact that famotidine is the most generally used acid suppressor in Japan, no studies have investigated whether low-dose famotidine is effective for NSAID-associated gastric mucosal lesions among Japanese patients who continue NSAID therapy. This topic would therefore appear to be an important area to examine.

In current Japanese clinical settings, so-called mucoprotective drugs other than prostaglandin analogs are more frequently used for the prevention and treatment of gastric mucosal lesions in patients treated with NSAIDs. The major reasons for using this protocol are that the duration of proton pump inhibitor treatment is restricted in Japan and the use of proton pump inhibitors for treatment of NSAID-associated gastric ulcers is not covered under the Japanese health insurance system. Moreover, there are concerns that compliance with prostaglandin therapy may decrease owing to adverse drug reactions to prostaglandin analogs, such as diarrhea, and difficulties can arise with the use of prostaglandins in women who might be pregnant. The current study compared the effects of low-dose famotidine (20 mg/day) and the so-called mucoprotective rebamipide in the treatment of gastric mucosal lesions (hemorrhage or erosion) in patients receiving long-term NSAID therapy. To ensure objectivity in the determination of drug efficacy, an external endoscopist, who was not informed as to the type of drug administered or the timing of the endoscopy in relation to the therapy regimen, was asked to evaluate the endoscopy findings.

Because many patients with NSAID-associated gastric mucosal lesions do not have subjective symptoms, endoscopy was performed regardless of symptoms in order to examine the actual state of the gastric mucosa in patients receiving long-term NSAID therapy.

Materials and methods

Study institutions

The study was conducted jointly by gastroenterologists and orthopedic surgeons between May 2004 and July 2005 at the Nara Medical University and at four related medical facilities: Nara Prefectural Nara Hospital, Nara Prefectural Gojo Hospital, Kokuho Central Hospital, and Nishi-Nara Chuo Hospital.

Inclusion criteria

The subjects were outpatients, ranging in age from 20 to 75 years, who had been taking NSAIDs, excluding aspirin, for more than 4 weeks, and required continual NSAID therapy after the study.

Exclusion criteria

The following subjects were excluded from the study: those with a previous history of gastrectomy or vagotomy, those with a history of or complications from malignant tumors within 5 years of enrollment, and those with severe liver or kidney disease, severe heart disease, or blood disease. Subjects who were determined inappropriate for the study were also excluded, including pregnant and nursing patients; patients treated with an H2RA, proton pump inhibitors, muscarine-1 receptor antagonists (M1RAs), or prostaglandin analogs within 4 weeks of enrollment; patients who had altered their NSAID or disease-modifying antirheumatic drug (DMARD) treatments within 4 weeks of enrollment; and patients who had altered their glucocorticoid hormone treatments (except for external use) within 14 days of enrollment (including those who changed only administration or dosage).

Observance of ethical codes

All institutional review boards of the institutions conducting the study approved the protocol prior to the start of the study, which was conducted in accordance with good clinical practice protocols. Written informed consent was obtained from all enrolled patients.

Study methods

The following demographic factors were investigated in all subjects from whom informed consent was obtained: