

学位論文の要旨

氏名 角 昇平

学位論文名 Evaluations of Gastric Acid Pocket Using Novel Vertical 8-channel pH Monitoring System and Effects of Acid Secretion Inhibitors

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著者名 Shohei Sumi, Norihisa Ishimura, Hironobu Mikami,
Eiko Okimoto, Yuji Tamagawa, Tsuyoshi Mishiro,
Yoshikazu Kinoshita, Shunji Ishihara

論文内容の要旨

INTRODUCTION

Gastroesophageal reflux disease (GERD) is characterized by the presence of reflux symptoms, such as heartburn and regurgitation, and/or esophageal mucosal injury caused by reflux of gastric contents into the esophagus. Although the majority of gastroesophageal reflux episodes occur during the postprandial period, that finding is paradoxical, because intragastric acidity is reduced during that period by the buffering effects of food. In 2001, Fletcher et al. were the first to report the presence of an unbuffered acidic region in the proximal stomach during the postprandial period. This acid layer on top of an ingested meal, which escapes any buffering effects and is referred to as a gastric acid pocket, is now considered to be an important mechanism of GERD. However, details regarding acid pocket formation in GERD patients as well as healthy adults in Japan remain to be fully elucidated. In addition, no known report regarding the effects of vonoprazan, a new potassium-competitive acid blocker, on acid pockets have been presented. To address these issues, we developed a novel catheter equipped with 8 vertically arrayed pH sensors. The aim of this study was to evaluate gastric acid pockets formed in healthy Japanese subjects during the postprandial period using this pH sensor catheter. In addition, we sought to determine postprandial changes of the gastric acid pocket following administration of vonoprazan as compared to rabeprazole, a conventional proton pump inhibitor (PPI), with our system.

MATERIALS AND METHODS

Twelve healthy adult volunteers were recruited (7 males, 5 females; mean age 24.0 ± 2.6 years). Our novel pH sensor catheter is equipped with 8 vertically arrayed pH sensors and was developed in cooperation with Star Medical, Inc. (Tokyo, Japan). Eight-channel pH data can be simultaneously recorded by connecting the catheter to 4 portable digital recorders (Pocket Monitor GMMS-200pH; Star Medical). For the present study, a catheter was inserted transnasally and positioned under X-ray guidance, then postprandial acid pocket formation was monitored over time with the subject in a sitting position.

The enrolled subjects participated in 2 study sessions. In the first session, postprandial gastric acid pocket formation and the effects of vonoprazan at 20 mg on that were assessed. In the second session, the effects of rabeprazole at 20 mg on the acid pocket were assessed. PPIs are known to be slow to achieve steady-state inhibition of gastric acid secretion, typically requiring 2 to 3 days to reach a therapeutic range, thus rabeprazole was administered for 2 days prior to performing pH measurements. A washout period of at least 2 weeks between the study sessions was used.

Recorded data were analyzed using computer software (Eight Star; Star Medical). An acid pocket was defined as the distinct region just below the esophago-gastric junction in the proximal stomach, which is clearly more acidic ($\text{pH} < 4$) than other parts of the esophagus and stomach. To assess its characteristics, length, appearance time, lasting time, and mean pH of the most acidic channel were evaluated in each subject. In addition, the separate effects of vonoprazan and rabeprazole on acid pocket formation were assessed.

The study protocol was approved by the Ethics Committee of Shimane University Faculty of Medicine and written informed consent was obtained from each of the subjects.

RESULTS AND DISCUSSION

All subjects completed the first study session, though the acid pocket was not appropriately measured in 2 due to catheter position, thus they were excluded. The remaining 10 subjects proceeded to the second study session and all completed the testing.

In the first study session, length, appearance time, lasting time, and mean pH for post-prandial acid pockets were assessed. An acid pocket was observed in all 10 analyzed cases and were appropriately measured, with a mean length of 2.2 ± 0.4 channels. The mean appearance time of an acid pocket after completion of a meal was 19.4 ± 6.8 minutes, while mean lasting time was 145.5 ± 17.9 minutes and mean pH was 2.4 ± 0.4 .

Next, the effects of vonoprazan on postprandial gastric acid pocket development were evaluated. Following that administration, the acid pocket was completely eliminated in all cases. The mean onset time for apparent acid inhibition by vonoprazan was 133.9 ± 34.2 minutes. In

addition, the mean pH after administration was 7.6 ± 0.4 , which was neutralized within 3 hours in each case. The effects of rabeprazole on postprandial gastric acid pocket formation were also evaluated. Similar to treatment with vonoprazan, the acid pocket was eliminated in 7 of the 10 analyzed subjects. In the 3 with a remaining postprandial acid pocket, the length was reduced and mean pH was greater as compared to before administration. These results suggested that acid pockets examined in the present subjects had a higher incidence of elimination with vonoprazan as compared to rabeprazole, though there was no significant difference between those drugs ($p=0.11$).

In the present study, formation of a gastric acid pocket in healthy Japanese adults was revealed using our novel 8-channel pH sensor catheter. Results regarding appearance time, length, and mean pH of the pocket were consistent with another investigation conducted in Asia. Previous studies have also performed gastric acid pocket measurements using a pull-through method with a dual sensor catheter, though difficulties with observing changes over time were noted. As compared with a pull-through technique, visualization of acid pocket changes that occurred during the examination period was easily obtained with the present system by viewing color surface contour plots with a pH-metry.

This is the first known report to present findings regarding the effects of vonoprazan on gastric acid pockets. This drug has been consistently found to provide quicker and stronger acid inhibition than PPIs, while the present results indicate that the postprandial acid pocket was completely eliminated and gastric pH neutralized within 3 hours after a single administration of a standard dose (20 mg). In contrast, in 3 of the 10 subjects who received rabeprazole, the acid pocket remained observable for three days after that administration. Consistent with our results, another recent report demonstrated that on-demand therapy using vonoprazan (20 mg) was an effective alternative maintenance therapy for mild reflux esophagitis. An acid pocket is now recognized as an important source of postprandial acid in GERD cases and thus represents a unique therapeutic target. Accordingly, on-demand therapy with vonoprazan may provide effective treatment for GERD symptoms during the postprandial period.

CONCLUSION

We successfully examined postprandial gastric acid pocket formation in healthy adults in Japan using our novel vertically arrayed 8-channel pH sensor catheter. Acid pocket development was strikingly suppressed following administration of either vonoprazan or rabeprazole. Moreover, a single administration of vonoprazan completely eliminated the acid pocket in each examined subject within a short period of time, suggesting the effectiveness of that drug as treatment for GERD.