The Nonsteroidal Anti-inflammatory Drug Diclofenac Reduces Acid-Induced Heartburn Symptoms in Healthy Volunteers

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BACKGROUND & AIMS: **We investigated the effects of diclofenac, a nonsteroidal anti-inflammatory drug that inhibits prostaglandin production, on induction of esophageal sensation by acid perfusion in healthy men.**

METHODS: **We performed a prospective, double-blind, placebo-controlled, 2-period, cross-over study over 3 visits in 12 healthy men. Diclofenac was given 6 hours and 2 hours before an acid perfusion test. During the test, hydrochloric acid (0.15 mol/L) was perfused into the lower esophagus for 30 minutes; we evaluated upper gastrointestinal symptoms using a validated categoric rating scale. Then, we calculated and assessed the acid perfusion sensitivity score (APSS). Biopsy specimens were collected by endoscopy of the distal esophagus before and after acid perfusion; levels of prostaglandin E_2 (PGE_2) (pg/mg) were measured in the samples using an enzyme-linked immunosorbent assay.**

RESULTS: **Compared with placebo, diclofenac significantly reduced the APSS for heartburn (82.2 ± 12.2 for placebo and 47.5 ± 8.9 for diclofenac; $P < .01$). Of the upper gastrointestinal symptoms, only the APSS for heartburn was reduced significantly by diclofenac. Compared with placebo, diclofenac reduced the overproduction of PGE_2 by esophageal tissues after acid perfusion (23.3 ± 5.2 for placebo and 11.4 ± 3.5 for diclofenac; $P < .05$). APSS correlated with the development of heartburn and esophageal levels of PGE_2 ($r = 0.53$; $P < .05$ for diclofenac vs placebo).**

CONCLUSIONS: **Diclofenac attenuated acid-induced heartburn by inhibiting PGE_2 overproduction in the esophagus. Esophageal PGE_2 might be involved in producing heartburn symptoms. Clinical Trials Registry no: UMIN000014595.**

Keywords: NSAID; Reflux; Treatment; GERD; NERD.

The prevalence of gastroesophageal reflux disease (GERD) continues to increase in Western and Japanese populations[1–3] with heartburn likely to remain the most common symptom. Although proton pump inhibitors (PPIs) have improved outcomes significantly, a meta-analysis showed that up to 40% of patients with GERD are dissatisfied with standard PPI therapy because their symptoms are not fully resolved.[4–7] Furthermore, it is widely recognized that the persistent GERD symptoms resulting from PPI resistance worsen quality of life in patients with nonerosive reflux disease (NERD). Therefore, appropriate management of GERD symptom is very important. One reason why these unmet clinical needs persist is that the pathogenesis of the core symptom, heartburn, is not completely understood.[8,9] Therefore, it is important to investigate novel mechanisms of symptom generation for heartburn to provide additional therapeutic options for the treatment and control of heartburn in patients with GERD and NERD.

Prostanoids are produced during arachidonic acid metabolism in the cyclooxygenase (COX) pathway, and they are established as inflammatory mediators that contribute to inflammation and nociception.[10,11] Among the prostanoids, prostaglandin E_2 (PGE_2) is considered the principal proinflammatory and pro-nociceptive prostanoid,[12] and is known to induce sensitization and pain hypersensitivity through activation of prostanoid receptors on peripheral nerve terminals.[13–15] Recently,

Abbreviations used in this paper: APSS, acid perfusion sensitivity score; COX, cyclooxygenase; ED, elemental diet; ER, _____; GERD, gastroesophageal reflux disease; GI, gastrointestinal; NERD, nonerosive reflux disease; NSAID, nonsteroidal anti-inflammatory drug; PGE_2, prostaglandin E_2; PPI, proton pump inhibitor; RM-ANOVA, _____ analysis of variance.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2015.01.014

we reported that esophageal PGE_2 may be involved in generating heartburn in human beings. Specifically, we showed that acid perfusion in the esophagus induced PGE_2 generation in the esophageal mucosa and that the increased PGE_2 level was correlated significantly with changes in the esophageal symptom score for heartburn in healthy participants.[16]

On the basis of this theoretical background, we assumed that inhibiting PGE_2 production in the esophageal mucosa might prevent upper gastrointestinal (GI) symptoms, especially heartburn. To confirm this hypothesis, we used the nonsteroidal anti-inflammatory drug (NSAID) diclofenac as an inhibitor of prostaglandin production to premedicate healthy participants before an acid perfusion test, and we then investigated its effect on heartburn symptoms.

Therefore, we aimed to investigate whether diclofenac suppressed acid-induced heartburn in healthy participants by inhibiting PGE_2 overproduction in the esophagus, and whether esophageal PGE_2 levels correlated with the heartburn symptoms. In addition, we explored the effect of diclofenac on several upper GI symptoms.

Methods

Study Design

A prospective, double-blinded, placebo-controlled, 2-period, cross-over study was conducted over 3 visits. Eligibility for the study was determined at visit 1, and volunteers were randomized according to a cross-over sequence with diclofenac or placebo. A person who was not involved in the study generated the 2 comparison groups using simple randomization, with an equal allocation ratio, by referring to a table of random numbers. The randomization code was concealed until the end of the trial. At visits 2 and 3, we assessed upper GI symptoms during acid perfusion tests and obtained esophageal biopsy samples. To allow adequate time for complete washout of diclofenac, the interval between visits 2 and 3 was at least 2 weeks. We performed all experiments in accordance with human ethics regulations (Hyogo College of Medicine: no 1162) and obtained written informed consent. This trial is registered with the University Hospital Medical Information Network Clinical Trials Registry (Number UMIN000014595). The trial was conducted according to the principles governing human research in the Declaration of Helsinki. All authors had access to the study data and reviewed and approved the final manuscript.

Participants

We enrolled 12 healthy men. The status of daily upper abdominal symptoms was checked with a previously validated questionnaire, the frequency scale for the symptoms of GERD.[17] At visit 1, we excluded participants based on the following criteria: a frequency scale for the symptoms of GERD total score of greater than 8; any medical history of asthma or allergy to NSAIDs; any history of peptic ulcer or GERD or of upper GI tract surgery; any significant cardiovascular, kidney, liver, neurotic, or psychological disorders; and any subjects taking medications that may affect prostaglandin generation, including NSAIDs, COX-2 inhibitors, or prostaglandin-containing medications. At visit 2, we excluded significant upper GI pathology using endoscopy (eg, esophagitis, Barrett's esophagus, hiatus hernia, active peptic ulcer disease, and esophageal/gastric cancer).

Trial Protocol

We used sustained-release diclofenac sodium (37.5-mg Voltaren sustained release [SR] capsules; Novartis Pharma KK, Tokyo, Japan) in this trial. After a minimum 6-hour fast, Voltaren SR capsule or placebo was given at 6 hours and 2 hours before the acid perfusion test. For the test, participants were placed in the left lateral decubitus position and we performed a transnasal endoscopic examination (GIF-XP260N; Olympus Optical Company, Tokyo, Japan). At this point, we obtained baseline esophageal endoscopic biopsy samples from 3 cm above the esophagogastric junction using biopsy forceps (Radial Jaw 3; Boston Scientific Corporation, MA). After endoscopy, a 5F elemental diet (ED) tube (Nippon Sherwood Medical Industries Ltd, Tokyo, Japan) was inserted via the nasal passage with the distal tip placed 10 cm above the esophagogastric junction. Acid perfusions then were performed, followed by immediate removal of the ED tube and repeated endoscopic biopsies. The endoscopic esophageal mucosa samples were frozen immediately in a 1.5-mL sampling tube with liquid nitrogen and stored in a freezer at −80°C until used to measure PGE_2 levels.

Interventions

Acid perfusion test. The acid perfusion test was performed by modification of a previously reported method[18,19] with participants in an upright sitting position. After confirmation that no participant had heartburn during the initial saline perfusion (8 mL/min for 2 min), hydrochloric acid (0.15 mol/L) was infused for 30 minutes into the lower esophagus via the ED tube. Previous studies have indicated that this acid concentration induces esophageal hypersensitivity in the majority of healthy participants[20] and causes hyperalgesia in response to an electrical stimulus in human models.[21,22] Infusions were delivered at 8 mL/min for 30 minutes with an automatic infusion pump.

Assessment of reflux and upper gastrointestinal symptom severity. During acid perfusion, participants were