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Alimentary Tract

Geranylgeranylacetone protects against small-intestinal injuries induced by diclofenac in patients with rheumatic diseases: A prospective randomized study

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ABSTRACT

Background: We aimed to explore the effect of geranylgeranylacetone on small-intestinal mucosal injuries induced by diclofenac sodium in patients with rheumatic diseases.
Methods: The patients were randomly divided into two groups in our prospective study. The patients in the geranylgeranylacetone group received diclofenac sodium plus geranylgeranylacetone, and those in the control group received only diclofenac sodium for 12 weeks. We examined small-intestinal mucosal injuries using capsule endoscopy before and after treatment.
Results: There were no significant differences between geranylgeranylacetone ($n = 21$, male: 42.9%; age: 31.0 ± 9.0 year) and control ($n = 19$, male: 68.4%; age: 31.0 ± 11.0 year) groups in terms of the numbers of patients with petechiae/red spots, denuded areas and mucosal breaks at baseline capsule endoscopy. After treatment, the numbers of patients with denuded areas ($\chi^2 = 0.000$, $P = 1.000$) and mucosal breaks ($\chi^2 = 1.750$, $P = 0.186$) did not increase in the geranylgeranylacetone group. However, the numbers of patients with petechiae/red spots ($\chi^2 = 5.216$, $P = 0.022$), denuded areas ($\chi^2 = 8.686$, $P = 0.003$) and mucosal breaks ($\chi^2 = 7.795$, $P = 0.005$) increased after treatment in the control groups. Geranylgeranylacetone improved both the Lewis score ($Z = -2.459$, $P = 0.017$) and degree ($\chi^2 = 5.414$, $P = 0.020$) on capsule endoscopy 12 weeks later.
Conclusions: In patients with rheumatic diseases, geranylgeranylacetone is effective for protecting against small-intestinal mucosal injuries induced by diclofenac sodium.

1. Introduction

Gastroduodenal mucosal injuries, such as upper gastrointestinal erosion, ulcers and bleeding, are well-known adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) [1]. Relatively small-intestinal mucosal injuries have not attracted enough attention because NSAID-induced small-intestinal mucosal injuries are usually asymptomatic and are not easily detected using the common diagnostic modalities. The development of capsule endoscopy (CE) and double balloon endoscopy has made the investigations of NSAIDs-induced small-intestinal mucosal injuries possible. It has been reported that 55–68% of patients taking NSAIDs develop mucosal damage in the small intestine [2–4]. Small-intestinal mucosal injuries may manifest as petechiae/red spots, denuded areas, mucosal breaks, bleeding, diarrhoea, occasional strictures due to diaphragmatic disease, and perforations.

However, there are still no new promising drugs or breakthrough interventions for NSAID-induced small-intestinal mucosal injuries [5,6]. Proton pump inhibitors (PPIs) effectively prevent NSAIDs-induced gastroduodenal mucosal injuries but are not effective at preventing NSAID-induced small-intestinal mucosal injuries [7].

The pathogenesis of NSAID-induced small-intestinal mucosal injuries includes intestinal hypermotility, microcirculation disorders, decreased mucus secretion, increased mucosal permeability, mucosal invasion of enterobacteria or bile acid and mitochondrial damage-induced disruption of intercellular junctions [6]. Increased

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intestinal permeability permits mucosal exposure to luminal bacteria with a predictable inflammatory reaction. This inflammation leads to mild or severe erosions and ulcers [8].

Geranylgeranylacetone (GGA) is a mucosal protective agent that protects the gastric mucosa by activating heat shock protein 70 (HSP70), a cellular protective protein induced by stress. GGA was shown to prevent indomethacin-induced small intestinal lesions in rats as a result of induction of HSP70 and increased mucus in the mucosa [9,10]. Niwa et al. [11] studied the protective effect of GGA on the intestinal mucosa in 10 healthy volunteers using CE, and found that GGA prevented the formation of lesions following treatment with diclofenac for 7 days. Shiotani et al. [12] studied the protective effect of GGA in 20 healthy volunteers using CE and reported that low-dose enteric-coated aspirin for 7 days produced damage in the small intestine in 90% (erosions or ulcers in 60%) of healthy volunteers. However, GGA was found to have no significant effect on the formation of aspirin-induced intestinal lesions [12].

To clarify the discrepancies of GGA effects on NSAID-induced small-intestinal mucosal injuries, we aimed to assess the effect of GGA on small-intestinal mucosal injuries induced by diclofenac sodium in patients with rheumatic diseases who did not take NSAIDs in the preceding six months.

2. Materials and methods

2.1. Study population

Patients with rheumatic diseases who did not take NSAIDs in the preceding 6 months were enrolled in this study from May 2011 through May 2013 at the First Affiliated Hospital of Sun Yat-Sen University. The symptoms of the underlying rheumatic diseases lasted for at least one month before diagnosis, which were confirmed by two rheumatologists after thorough clinical assessment and laboratory tests. The enrolled patients met the following inclusion criteria: 18–65 years of age; rheumatic diseases such as ankylosing spondylitis (a chronic inflammatory disease of the axial skeleton, with variable involvement of the peripheral joints and nonarticular structures), rheumatoid arthritis (an autoimmune disease that results in a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks flexible joints) and undifferentiated arthritis; planning to take diclofenac sodium for at least 12 weeks; and informed consent based on their full understanding. Patients were excluded based on the following: a history of peptic ulcer or gastrointestinal bleeding; serious liver, kidney, heart, or lung disease; suspected small-bowel obstruction; a history of gastrointestinal surgery except for appendectomy; history of or current drug addiction or alcoholism; pregnancy or a planned pregnancy during the study period; the administration anti-secretory drugs such as PPIs or H_2 receptor antagonists (H_2RA), or other gastric mucosal protective drugs; a lack of consent to the surgery required if the capsule endoscope was retained in the body; or inappropriateness of this study as determined by the investigator. All subjects received an explanation of the study and provided written informed consent prior to participation. The study was conducted in accordance with the Declaration of Helsinki (1995), and the protocol was approved by the Ethics Review Committee of the First Affiliated Hospital of Sun Yat-Sen University.

2.2. Study design

This was a prospective randomized study and was registered in the ClinicalTrials.gov Protocol Registration System on November 13, 2008 (ID: NCT01547559).

First, two of the investigators (XH and LL) recorded the demographic characteristics, underlying diseases and medication history of the patients; then they performed physical examinations and laboratory studies including a complete blood count and blood chemistry analysis on all of the recruited patients. All eligible patients who consented to participate underwent a baseline CE and were then randomly assigned to the GGA (Selbex; Eisai, Tokyo, Japan) or control group using computer-generated random numbers. The patients in the GGA group received diclofenac sodium 75 mg once a day plus GGA 50 mg three times daily and those in the control group received diclofenac sodium 75 mg once a day with no additional medication. Twelve weeks later, the patients underwent the second CE.

2.3. CE procedure and evaluation

The CE of the small intestine was performed with a PillCam^{TM}SB video capsule (Given Imaging, Yoqneam, Israel). The patients fasted for 12 h before swallowing the capsule. Data were collected for up to 8 h after capsule ingestion, and then the images were downloaded onto a computer workstation for analysis. Investigators (LX and MC) who evaluated the results of the CE of the small intestine were required to attend a standardized training session on the use of the Given Diagnostic System and had no knowledge of the demographic details, diagnosis, or drug treatment of the trial patients.

The slightly modified damage scale in the small intestine was classified as follows [6,13]: category 1, petechiae/red spots (demarcated, usually circular, area of red mucosa with preservation of villi); category 2, reddened folds ($\geq$1 valvulae conniventes showing discrete patchy or continuous erythema); category 3, denuded areas (loss of villous architecture without a clear breach of the epithelium that may or may not be associated with surrounding erythema); category 4, mucosal breaks (mucosal erosions and/or ulcers, both represent discrete lesions with central pallor and surrounding hyperemia and loss of villi; these are included together because by definition, an ulcer requires a degree of penetration (through the muscularis mucosa) and the angle of the image taken by the capsule is often such that it is impossible to evaluate the depth of the lesions); category 5, strictures; and category 6, presence of blood without a visualized lesion.

We also adopted the CE Lewis score developed by Gralnek et al. [14] in the present study. The Lewis score was created based on three capsule endoscopic variables: villous appearance, ulcers and stenosis [14]. Villous appearance was defined as oedema where the villous width is equal to or greater than villous height. Ulcers were defined as mucosal breaks with white or yellow bases surrounded by red or pink collars. Estimation of ulcer size was based on the largest ulcer observed in each tertile. The number of lesions was defined as single, few (two to seven lesions) or multiple (eight or more lesions). Stenosis scores were based on whether they appeared ulcerated and whether the capsule was able to traverse the stenosis. The small bowel transit time was divided into three equal parts, creating tertiles. Small bowel segment length involvement was defined by the percentage of a particular tertile that was involved in the mucosal change. A short segment was defined as $\leq$10% of a tertile. A long segment was defined as equal to 11–50% of a tertile and a whole segment was defined as >50% of a tertile [14]. A score <135 was designated as normal or clinically insignificant mucosal inflammatory change, a score between 135 and 790 was considered mild, and a score $\geq$790 was moderate to severe [14].

2.4. Sample size

The sample size was based on our estimation of the proportion of subjects that would be expected to exhibit mucosal breaks at post-treatment based on CE. We estimated that the incidence of mucosal injuries would be approximately 20% in the GGA group based on a preliminary study by Niwa et al. [11]. The required sample size was