Gastroenterology 2017;152:980–982

BRIEF REPORTS

Rifaximin Reduces the Number and Severity of Intestinal Lesions Associated With Use of Nonsteroidal Anti-Inflammatory Drugs in Humans

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The intestinal microbiota might contribute to enteropathy associated with use of nonsteroidal anti-inflammatory drugs (NSAIDs), but there have been few human studies of this association. We performed a placebo-controlled study to determine whether a delayed-release antibiotic formulation (rifaximin-extended intestinal release [EIR]) prevents the development of intestinal lesions in subjects taking daily NSAIDs. Sixty healthy volunteers (median age, 26 y; 42% female) were given the NSAID diclofenac (75 mg twice daily) plus omeprazole (20 mg once daily), and either rifaximin-EIR (400 mg) or placebo, twice daily for 14 days. Subjects were assessed by videocapsule endoscopy at baseline and after 2 weeks of treatment. The primary end point was the proportion of subjects developing at least 1 small-bowel mucosal break at week 2. Secondary end points were the change in the mean number of mucosal lesions and the number of subjects with large erosions and/or ulcers after 14 days of exposure. We detected mucosal breaks in 20% of subjects given rifaximin and in 43% of subjects given placebo ($P = .05$ in the post hoc sensitivity analysis). None of the subjects in the rifaximin group developed large lesions, compared with 9 subjects in the placebo group ($P < .001$). Our findings indicate that intestinal bacteria contribute to the development of NSAID-associated enteropathy in human beings. Clinical trial no: EudraCT 2013-000730-36.

Keywords: Controlled Trial; Microbiome; Gastrointestinal Adverse Event; Prevention.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are very effective medications, but their use is associated with a broad spectrum of adverse reactions involving the liver, kidney, cardiovascular system, skin, and gut. Gastrointestinal (GI) adverse effects are the most common and cover a wide clinical spectrum, ranging from dyspepsia, heartburn, and abdominal discomfort to more serious events, such as peptic ulcer with life-threatening ulcer complications of bleeding and perforation.[1]

Over the past decade, there has been a progressive change in the overall pattern of GI events leading to hospitalization, with a clear decreasing trend in upper GI events and a slight, but significant, increase in lower GI events.[2] Indeed, available studies[3,4] have shown that approximately 75% of NSAID users display intestinal mucosal injury, ranging from denuded areas (seen mainly in the proximal small bowel) to the so-called mucosal breaks (erosions and ulcers), observed in its distal part. Although the incidence of upper GI injury can be reduced by proton pump inhibitors, this is not the case for NSAID-associated intestinal lesions, which actually may be aggravated by acid suppression.[5]

The pathogenesis of small intestinal damage is complex and still not completely understood. Several lines of experimental evidence have implicated commensal enterobacteria in the pathogenesis of NSAID enteropathy and suggest that luminal bacteria may represent a potential target for prevention and/or treatment.[6] In this context, the efficacy of a delayed-release formulation of rifaximin, a poorly absorbed antibiotic,[7] in the prevention of NSAID-associated lesions was evaluated in human beings by means of videocapsule endoscopy (VCE).

Sixty healthy volunteers (median age, 26 y; 42% female) were randomized to receive diclofenac slow release 75 mg twice daily plus omeprazole 20 mg once daily and either rifaximin-EIR 400 mg or rifaximin-EIR matching placebo twice daily for 14 days (Supplementary Figure 1). The primary end point was the proportion of subjects developing at least 1 small-bowel mucosal break at final VCE. Secondary end points were the change at VCE in the mean number of

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Abbreviations used in this paper: CI, confidence interval; EIR, extended intestinal release; GI, gastrointestinal; mFA, modified full analysis; NSAID, nonsteroidal anti-inflammatory disease; VCE, videocapsule endoscopy.

Most current article

0016-5085
http://dx.doi.org/10.1053/j.gastro.2016.12.007

Table 1. Primary and Secondary End Points of the Study

Primary end point	Rifaximin	Placebo	*P value*
Subjects developing at least 1 mucosal lesion, n	6/30 (20%)	13/30 (43%)	.0566[a]
Sensitivity analysis (treatment and sex as fixed effect and age as covariate)			.0490
Secondary end points			
Change in the mean number of mucosal lesions, ±SEM	0.3 ± 0.7	1.2 ± 2.3	.0103[b]
Subjects with large erosions and/or ulcers at the end of treatment, n	0	9	.001[c]

[a]Logistic regression analysis.
[b]Negative binomial regression analysis.
[c]Chi-square test.

mucosal lesions and the number of subjects with large erosions and/or ulcers at the end of treatment (see the Supplementary Materials and Methods section and Supplementary Table 1).

Six patients in the rifaximin group and 13 patients in the placebo group (12 of the per-protocol set) developed at least 1 mucosal lesion in the small bowel (primary end point). This provided an odds ratio of 0.33 (95% confidence interval [CI], 0.10–1.03) and 0.35 (95% CI, 0.11–1.12) in the modified full analysis (mFA) and per-protocol sets, respectively, for subjects in the rifaximin group to develop at least 1 mucosal lesion in the small bowel at logistic regression analysis.

The efficacy on primary end point was not significant. However, when post hoc sensitivity analysis, using age as covariate, was performed, the difference between the rifaximin and placebo groups became significant (Table 1). The average mucosal score (mFA set) at the end of treatment was 0.87 ± 0.13 vs 1.83 ± 0.28 for rifaximin and placebo, respectively ($P = .021$).

Both secondary end points were reached successfully in the study (Table 1). Subjects in the placebo group developed a higher number of mucosal lesions compared with those in the rifaximin group (1.2 ± 2.3 vs 0.3 ± 0.7 in the mFA set). Negative binomial regression analysis proved a protective effect of rifaximin on mean changes from baseline in total number of lesions (treatment effect point estimate, -1.41; 95% CI, -2.49 to -0.34; $P = .010$). A similar result was detected for the change from baseline in the number of lesions without hemorrhage (treatment effect point estimate, -1.44; 95% CI, -2.53 to -0.35; $P = .009$).

Both treatments were well tolerated and no serious adverse events were recorded.

This was a randomized controlled trial investigating the effect of an antibiotic on NSAID-induced intestinal mucosal injury in human beings. This study showed that fewer rifaximin-treated volunteers developed small-bowel lesions compared with placebo-treated subjects. The antibiotic also reduced the mean number of lesions and appeared to abolish the larger lesions, with a tolerability profile overlapping that of placebo. Although short-term studies, such as this one, and mucosal breaks may not have straightforward clinical implications,[8] the results of this proof-of-concept study strongly suggest the role of enteric bacteria in the pathogenesis of NSAID enteropathy and call for a prospective trial in patients on long-term NSAID therapy.

The entero-protective effect of rifaximin most likely depends on its broad spectrum of antibacterial activity.[7] Experimental studies[9–11] show not only that this antibiotic reduces the total bacterial load, but also modulates bacterial community composition, an effect associated with a reduction of intestinal inflammation[10,11] and improvement of gut barrier function.[10]

Recent evidence points out that—besides non-antimicrobial activities (for instance, the anti-inflammatory property)—rifaximin also may show "eubiotic" properties. Indeed, in patients with inflammatory conditions (such as inflammatory bowel disease, colonic diverticular disease, or hepatic encephalopathy), the drug, although not altering the overall structure of human colonic microbiota, increased the relative abundance of *Bifidobacteria* and *Lactobacilli*.[12,13]

NSAID enteropathy is associated with significant GI complications,[14,15] but there are no proven strategies for the prevention or treatment of this subtle clinical condition. However, there is now good evidence that intestinal bacteria play a pathogenic role in NSAID enteropathy in human beings. Treatments aimed at correcting the shift of intestinal microbiota toward proinflammatory gram-negative bacteria[6] are therefore potential avenues to explore in the prevention and treatment of NSAID enteropathy. After almost 40 years, with the advancement of knowledge on the pathogenic role of gut microbiota in NSAID enteropathy,[6] the time now seems ripe to study in well-designed, large, randomized, clinical trials, microbiota-directed interventions to protect the small bowel from NSAID injury and to allow safer anti-inflammatory therapy.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.12.007.

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