EFFICACY OF SUCRALFATE IN PREVENTING GASTROINTESTINAL SIDE EFFECTS OF NSAIDs

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ABSTRACT

To find out the efficacy of sucralfate in preventing gastrointestinal side effects of non-steroidal anti-inflammatory drugs (NSAIDs) a prospective, randomised single blind study was conducted from 1989 to 1992. Patients with osteoarthritis, rheumatoid arthritis and other long standing painful conditions, who were expected to receive NSAIDs for over three months, were recruited into the study. All medicines were discontinued for a period of 10-15 days prior to initial endoscopic assessment. NSAID therapy was started and the patients were randomised to receive either placebo (group A) or sucralfate (group B) in addition. Patient were reassessed clinically every week and an endoscopic examination was repeated after 6-8 weeks of follow-up. A total of 176 patients were studied in group A (n=91) and group B (n=85). At the end of 8 weeks gastrointestinal symptoms were present in 30.6% and 26.4% patients of group A and B respectively. Endoscopic assessment showed superficial lesions in 36.5% and 18.7% while endoscopic ulcer in 2.4% and 1.1% patients of groups A and B respectively. Thus in patients receiving chronic NSAID therapy, simultaneous administration of sucralfate reduces the incidence of superficial gastric lesions but has no significant effect on symptoms or ulcer formation.

MJAFI 1994; 50 : 93-96

KEY WORDS : Gastropathy; Sucralfate; Nonsteroidal anti-inflammatory drugs

Introduction

Non-steroidal-anti-inflammatory drugs (NSAIDs) which form the corner stone of therapy in cases of various rheumatic disorders, can cause significant damage to gastrointestinal (GI) tract [1,2]. The mucosal injury to GI tract is attributed to the inhibitory effect of NSAIDs on the endogenous biosynthesis of prostaglandins [3]. Some prostaglandin analogues have been shown to prevent NSAIDs induced gastric injury [4], but they are not routinely available in this country as yet. Sucralfate, on the other hand, has been shown to increase the synthesis and release of endogenous prostaglandins by the gastric mucosa [5]. Although sucralfate is widely used for treating peptic ulcers, its efficacy to prevent NSAID induced GI mucosal damage has not yet been adequately studied. Therefore the present work was undertaken to evaluate a routinely available

drug for preventing the GI side effects of NSAID.

Material and Methods

All patients attending the rheumatology clinics of two major service hospitals from 1989 to 1992 were studied. Those with rheumatoid arthritis, osteoarthritis and other painful conditions who were expected to require NSAIDs for over three months were recruited into this study after an informed consent. Patients known to be suffering from upper gastrointestinal disease or those suffering from acute hepatitis, pancreatitis, renal insufficiency, bleeding diathesis or any other disease requiring antineoplastic drugs, anticoagulants or anti ulcer drugs were excluded from the study. Patient with history of surgery on upper GI tract were also excluded.

The study was a prospective, randomised, single blind comparison of sucralfate (2 gm

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12 hourly, taken on empty stomach and a placebo capsule taken in a similar manner. These drugs were given in addition to NSAID therapy prescribed to them by the rheumatologist for patient's primary disability. After recruitment all medicines were withdrawn for a period of 10 to 15 days, following which initial endoscopic examination was performed. Within 48 hours of the endoscopic examination, NSAID therapy was started and patients were serially randomised into two groups as per random tables supplied by the statistician. Group A patients received placebo while group B patients received sucralfate in addition to the NSAIDs. Patients were clinically evaluated every two weeks for any GI symptoms and their stools were tested for occult blood. An endoscopic examination was repeated 12 to 16 weeks after the randomisation. Presence of superficial erosions and petechiae were classified as superficial lesions while ulcers more than 0.5 cm in size were separately considered [8]. Chi square test was used to compare the abnormalities noted in two groups.

Results

A total of 176 patients were studied. Of these 85 patients were randomised to group A and 91 to group B. There were no statistically significant differences between these two groups with respect to their clinical and demographic characteristics (Table 1). The mean age of the patients was 51.2 (range 28 to 78) years and majority were males (129/176, 73.3%). Aspirin, ibuprofen and naproxen were the commonest NSAIDs being used. About one third of the patients in both the groups were smokers while alcohol intake was reported by almost half the patients. Past history of dyspepsia was given by 38 patients and the mean duration of NSAID use prior to randomisation was 2.1 years.

Fifty one patients developed dyspeptic symptoms during the period of follow-up. The symptoms were described as upper abdominal discomfort (43), pain in epigastric region (37), burning in upper abdomen (25) and retrosternal area (28) and bloating sensa-

TABLE 1

Demographic and clinical characteristics of the two groups of patients studied

Patients characteristics	Group A	Group B
Patients (number)	85	91
Mean age (range) in years	49.3 (28-71)	52.2(36-78)
Sex : Male (%)	59 (69.4)	70 (76.9)
NSAIDs used		
(a) Aspirin	21 (24.7)	25 (24.2)
(b) Ibuprofen	27 (31.7)	28 (29.4)
(c) Naproxen	15 (17.6)	17 (17.8)
(d) Diclofenac	13 (15.3)	14 (15.4)
(e) Indomethacin	9 (10.6)	7 (7.7)
Smokers (%)	27 (31.7)	29 (31.8)
Alcohol intake (%)	41 (48.2)	43 (45.3)
History of dyspepsia (%)	19 (22.3)	25 (24.2)
History of NSAID use in past (%)	68 (80)	83 (92.2)
Mean duration of intake in patients who received NSAID in past	2.2 years	1.9 years

tion after meals (19). The frequency of these symptoms was not significantly different in the two groups studied (Fig. 1). Occult blood was found to be positive in 11 patients at the time of initial evaluation, prior to institution of NSAID therapy. The number of patients with positive test were found to be 38, 43, 29, 23, 19 and 14 on subsequent evaluation carried out at two weekly intervals. Here again no significant difference was noted in two groups (Fig. 2). Endoscopic examination at the end of the study however showed that, while superficial lesions were noticeable in 31 patients in group A, only 17 had such endoscopic findings in group B. The difference between the two groups is statistically significant ($\chi^2 = 6.14$, $p = 0.013$). Peptic ulcers larger than 3 mm in size were seen in 2 and 1 patients respectively in groups A & B ($p = 0.474$). All three patients who developed peptic ulcers, gave previous history of dyspepsia and the site of ulcers was antrum of stomach in two and near cardia, on lesser curve in 1 patient.

Discussion

Our study indicates that sucralfate significantly reduces the incidence of superficial

**Significance: *p=0.534, **p=0.542;
#p=0.013; +p=0.474**

Fig. 1 Frequency of gastrointestinal symptoms, GI microbleeding, endoscopic superficial gastric mucosal lesions and peptic ulcer in patients treated with and without sucralfate.

Fig. 2 Peak frequency of GI microbleeding in patients treated with and without sucralfate with respect to type of antiinflammatory agent.

mucosal lesions in patients receiving long term NSAID treatment for various rheumatological diseases. However, sucralfate does not significantly alter the incidence of GI symptoms or GI microbleeding. Even the reduction in incidence of peptic ulcer was not statistically significant though, a larger sample size may show more definite results.

In short term studies done in animals, sucralfate was shown to increase mucosal prostaglandins production [7,8], which is thought to be related to minor epithelial damage caused by aluminium radicle in this drug. Thus it was thought that pretreatment with sucralfate may protect the gastric mucosa against subsequent noxious stimuli. Significant reduction in superficial gastric lesions seen in our study may be related to this effect of sucralfate. An earlier short term study had, however, shown that sucralfate does not provide protection against gastric mucosal damage produced by aspirin in healthy volunteers [9].

Failure to prevent GI symptoms, GI microbleeding and peptic ulcers appears contrary to above hypothesis and may suggest that prostaglandin production is blocked effectively by the concomitant NSAID therapy [5,10]. A few studies have shown that history of peptic ulcer disease is a significant risk factor for the development of NSAID-induced mucosal injury [2,11]. A significant proportion of our patients gave past history of dyspepsia (Table 1). The relative contribution of this risk factor in two groups can not be evaluated as no previous radiological/endoscopic examinations had been carried out.

Should sucralfate be recommended for routine use in patients taking regular NSAID therapy? In spite of the fact that sucralfate significantly reduced the incidence of superficial gastric lesions the answer to this question appears to be negative at present. superficial gastric lesions do not progress into chronic peptic ulcers [12]. Moreover, with continued use of NSAIDs, gastric mucosa adapts to its noxious effects and the extent of superficial injuries declines with time [13].

Our study and another recent study [14] showed that sucralfate use did not reduce the frequency of dyspeptic symptoms, GI bleeding or peptic ulcer, hence it's use with chronic NSAID therapy is not recommended.

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