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Improvement of intestinal metaplasia six month after misoprostol treatment

O. LERI, F. FIOCCA*, M. MASTROPASQUA, T. LOSI, S. TUBILI, P. PERINELLI, E. GRASSO*, G. SCOPELLITI, D. DE LUCA

Dipartimento di Malattie Infettive e Tropicali, *II Clinica Chirurgica, "La Sapienza" University, Rome (Italy)

Abstract. – ***Purpose:*** **To establish whether misoprostol (a synthetic prostanoid) is effective in improving intestinal metaplasia of dyspeptic patients.**

Patients: **Of the 206 dyspeptic patients without Helicobacter pylori, 18 (7.1%) had histological evidence of intestinal metaplasia (2 presented mild metaplasia, 9 moderate and 7 severe). They were treated with misoprostol 200 mg twice daily for six months and, after stopping the treatment, they all underwent endoscopic control.**

Results: **There was a statistical significant improvement of intestinal metaplasia ($p<0.001$) and of the activity of antral gastritis ($p= 0.03$). There were no significant changes in antral and body specimens during follow-up.**

Discussion: **Though the small number of the patients and the lack of control group, our results suggest that misoprostol allows regression and/or improvement of histological IM ($p< 0.001$). It has proved to be effective in prevention of both gastric and duodenal ulcers induced by NSAID therapy, probably related largely to replacement of endogenous prostaglandins inhibited by the use of NSAID and it may also exerts its protective effects through inhibition of gastric acid secretion. Moreover, misoprostol showed to increase the rate of gastric blood flow, inducing a mucosal protective effect against the factors damaging gastric mucosa. It has been also documented that misoprostol regulates inflammatory cytokines and prolonged the survival of transplants, reflecting both its immunosuppressive and anti-inflammatory effect. In conclusion, since intestinal metaplasia increases the risk of gastric cancer, the use of misoprostol, in this pathology, would be of some interest.**

Key Words:

Intestinal metaplasia, Misoprostol.

Introduction

The presence in the stomach of mucosa resembling that of intestine constitutes the condition known as intestinal metaplasia (IM). It is present in the duodenal bulb of up to two thirds of dyspeptic subjects even in the absence of ulceration, occurring with equal prevalence in *Helicobacter* positive and negative subjects, but having a greater extent in those who are positive[1]. Although it is documented that the extent of IM is due not only to *Helicobacter pylori*, but partly to other factors such as non steroidal anti-inflammatory drugs (NSAID) or duodenogastral bile reflux, it is well established that dual and/or triple therapy, independently of successful eradication of HP, could improve the extent of IM, probably due to its anti-inflammatory effect[2-7].

In this study, we focused our attention on the use of misoprostol, a prostaglandin E_1 analogue, that has proved to be effective in the prevention of haemorrhagic gastritis, erosions, or gastric ulceration associated with NSAID assumption[8,9]. Our objective was to determine if it is of some efficacy in improving IM of dyspeptic patients whithout *Helicobacter pylori*.

Patients and Methods

Four hundred fifty two output patients (230 F, 220M, mean age 51.66. SD 13.25 range 23-83) submitted to the Department of Infectious and Tropical Diseases with upper abdominal symptoms of at least one month's duration were considered as candidates for our study. Endoscopy was carried out in all patients and four biopsies were performed; two biopsies were taken in the anterior and posterior walls of the antrum within 2 cm from the pylorus and two in the body. Routine staining with Warthin-Starry silver tech-

nique was done for histopathologic diagnosis and detection of *Helicobacter pylori* (HP). The degree and activity of gastritis and HP colonisation were achieved according to the Sydney System; the extent of IM was cumulatively graded as follows: (0) none; (1) mild degree, consisting of a few tubules involving up to 30% of the total area biopsied, (2) moderate degree, consisting of 30 to 60% of the total area biopsied; (3) severe degree, consisting of more 60% of the total area biopsied[10,11]. Complete and incomplete IM were not further differentiated because mucin-histochemical studies were not performed. Subjects who were taking NSAID or who had taken antibiotics or received acid suppression treatment in the previous month and patients with gastric or duodenal ulcer were excluded. The 18 patients with histological evidence of IM, after verbal informed consent, were treated with misoprostol 200 mg twice daily for six months. After stopping the treatment, all the patients underwent endoscopic control.

The χ^2 was used for statistics of intestinal metaplasia, while gastritis variables were analysed by Fisher's exact test, that is the more appropriate for small n. The chosen level of the significance was 0.05.

Results

Among the 206 *Helicobacter pylori* negative dyspeptic patients, IM was found in 18 patients (7.1%) (9F, 9M mean age 58.89 SD 11.52 range 29-83) (two presented mild metaplasia, 9 moderate and 7 severe). With respect to age distribution in the group overall, IM was found more often with increasing age (p=0.02). No patient dropped out of the study due to adverse events; since the drug was not tolerated by 5 patients (because of mild diarrhea), they were instructed to reduce the dose back to half a tablet twice a day. Overall, the biopsy specimens from the antral mucosa of the patients with IM showed antral gastritis (100% of the cases), as compared with 37.7% of the specimens (n=5) obtained from the body mucosa. All the patients with IM had active antral gastritis, while only 5 had active body gastritis at the start of the therapy. At six months, there was a statistical significant improvement of both IM (p<0.001) and the activity of antral gastritis (p =0.03). There were no significant changes in antral and body specimens during follow-up (Table I).

Discussion

Although the cause of IM is not well understood and its significance regarding the risk, origin and behavior of gastric cancer is by no means clear, previous studies showed that epithelial change which particularly predisposes to malignancy is IM; therefore it can be assumed that any person with extensive metaplasia is at high risk for gastric cancer and should be subject to periodic screening[11-13]. That increased risk is proportional to the extent of metaplasia, that is probably more important than in the metaplastic subtype[3].

The risk could be generated by one or more mechanisms:

Table I. Histological changes of IM cured patients.

	Admission n = 18	After treatment n = 16
Antral gastritis		
Superficial	15	16
Deep	1	0
Atrophic	2	2
p NS		
Activity of gastritis		
No activity	0	0
Low acitivity	10	16
Severe activity	8	2
p= 0.03 Fisher test		
Body gastritis		
Superficial	5	5
Deep	0	0
Athrophic	0	0
p NS		
Activity of gastritis		
No activity	0	0
Low activity	0	1
Severe activity	5	4
p NS		
Intestinal metaplasia		
Absence	0	14
Mild	2	2
Moderate	9	1
Severe	7	1
p < 0.001		

1. the metaplastic tissue is an epigenetic change that raises the pH of gastric juice by replacing oxyntic mucosa, favouring the growth of bacteria capable of generating mutagens;

2. the metaplastic tissue is an early step of an induction process;

3. the metaplasia is a marker of chronic gastritis due to *Helicobacter pylori* infection or to pernicious anemia[13,14].

So, an appropriate therapy of this pathology would be of great importance. In the present study, 18 HP negative dyspeptic patients with IM were treated with misoprostol (a synthetic prostanoid) that has proved to be effective in prevention of both gastric and duodenal ulcers induced by NSAID therapy, probably related largely to replacement of endogenous prostaglandins inhibited by the use of NSAID. It may also exerts its protective effects through inhibition of gastric acid secretion[15,16]. The limiting factors, however, for its routine use as ulcer healing agent are its low efficacy with regard to ulcer pain and the high incidence of diarrhea[17]. Moreover, it has been also documented that misoprostol increases the rate of gastric blood flow, regulates inflammatory cytokines and continues the survival of transplants, reflecting both its immunosuppressive and anti-inflammatory effect[18]. Though the small number of the patients and the lack of control group, our results suggest that misoprostol allows regression and/or improvement of histological IM ($p< 0.001$), probably due to its mucosal protective effect against the factors damaging gastric mucosa. In fact, it is well documented that IM is a non-specific response to injury and inflammation (such as excess gastric acid output and *Helicobacter pylori* infection). Although the exact relationship between IM and gastric carcinoma has still not been elucidated, we didn't think it would be ethical to perform a placebo trial. In conclusion, whether misoprostol has to be effective in improving IM and its mechanism of action in this pathology, needs further research.

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Address for reprints:

Leri O., MD

Dipartimento di Malattie Infettive e Tropicali
Università "La Sapienza" Roma, Italia
Tel: International code +06/4957853
Fax international code +06/490623