Does the rapid healing of duodenal ulcers mean longer remissions?

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هل الالتئام السريع لقرحات الاثني عشري يعني هدآت أطول؟

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خلاصة: أجريت دراسة لاختبار مدى استجابة قرحات الاثني عشري المؤكد تشخيصها بالمنظار، للمعالجة، وتحديد معدلات انتكاسها. فأجري التنظير الداخلي للتحقق من الالتئام بعد أربعة أسابيع ثم ثمانية أسابيع للحالات التي تتلقى مـحصرات H2 وميزوبرستول. كما أجري التنظير بعد 14 يوماً ثم 28 يوماً للحالات التي تتلقى مثبطاً لمضخة البروتون. ثم أعيد التنظير الداخلي بعد شهر وثلاثة أشهر وستة أشهر ثم 12 شهراً لتحري حـدوث أي انتكاس. وتبين أن مـعدلات الالتـئام كـانت 61% - 77% بعد أربعة أسابيع، وبلغت 75% - 85% بعد ثمانية أسابيع في المجموعة التي تتلقى محصرات H2 وميزوبرستول. كـما بلغت معدلات الالتئام 68% و100% في اليوم الرابع عشر واليوم الثامن والعشرين على التوالي في المجموعة التي تتلقى مثبط مضخة البروتون. وكانت معدلات الانتكاس خلال ثلاثة أشهر 72% - 86% و100% على التوالي. ويتضح من هذه الدراسة أنه كلما تسارع التئام القرحة، تسارع كذلك حدوث الانتكاس.

ABSTRACT A study was conducted to test the response to therapy and the relapse rates of endoscopically-confirmed duodenal ulcers. Endoscopy to check for healing was performed at 4 and 8 weeks in cases receiving H2-blockers and misoprostol and at 14 and 28 days in cases receiving a proton pump inhibitor. Endoscopy was repeated at 1, 3, 6 and 12 months to check for relapses. Healing rates were 61%–77% and 75%–85% at 4 and 8 weeks in the group receiving H2-blockers and misoprostol. Healing rates were 68% and 100% at days 14 and 28 with the proton pump inhibitor. The relapse rates within 3 months were 72%–86% and 100% respectively. This study indicates that the faster the ulcer healed, the earlier the relapse occurred.

La cicatrisation rapide d'un ulcère duodénal annonce-t-elle des rémissions plus longues?
RESUME Une étude a été réalisée pour contrôler la réponse au traitement et les taux de rechute des ulcères duodénaux confirmés à l'endoscopie. Un examen endoscopique pour contrôler la cicatrisation a été effectué à 4 et 8 semaines pour les cas auxquels on a administré des anti-H₂ et du misoprostol et à 14 et 28 jours pour les cas auxquels on a administré des inhibiteurs de la pompe à protons. L'endoscopie a été répétée à 1, 3, 6 et 12 mois pour contrôler les rechutes. Les taux de cicatrisation étaient de 61%–77% et 75%–85% à 4 et 8 semaines dans le groupe auquel on a administré les anti-H₂ et le misoprostol. Ils étaient de 68% et 100% aux 14ᵉ et 28ᵉ jours avec les inhibiteurs de la pompe à protons. Les taux de rechute dans les 3 mois étaient de 72%–86% et 100% respectivement. Cette étude indique que plus la cicatrisation de l'ulcère a été rapide, plus la rechute est intervenue tôt.

Introduction

Duodenal ulcer is a chronic relapsing disease which needs intermittent and occasionally continuous treatment. Many international data are available on the healing and relapse rates of ulcers with various drugs, but local data are scarce. The efficacy of various anti-ulcer drugs in ulcer healing and relapse prevention without maintenance is not well established [1]. The introduction of newer and more potent drugs has made the choice of treatment more difficult, especially in terms of preventing relapses. The present study was performed to determine the efficacy of various anti-ulcer drugs in ulcer healing and to determine the most effective and suitable drug with the lowest relapse rate.

Patients and methods

Patients of either sex, aged between 17 and 77 years, with endoscopically proven duodenal ulcers were included in the study. Patients with gastric ulcers, Zollinger-Ellison syndrome, oesophageal strictures, concurrent bowel disease, severe pulmonary, cardiac, renal or liver diseases, malignancies or unstable diabetes mellitus were excluded. Pregnant and lactating mothers, patients who had had upper gastrointestinal surgery, and patients on H2 blockers, nonsteroidal anti-inflammatory drugs, steroids and anticholinergic therapy were also excluded from the study.

Gastroscopy under topical anaesthesia was performed at entry into the study within 3 days prior to treatment. Each patient was physically examined and details of age, general medical history, duration of disease and addictions were recorded.

Cases were randomly allocated to receive 4 weeks of treatment with either cimetidine 800 mg HS, ranitidine 300 mg HS, famotidine 40 mg HS (all H2-blockers), misoprostol 200 mg q.i.d or omeprazole (a proton pump inhibitor) 20 mg after breakfast for two weeks. Endoscopy was repeated on completion of therapy to check for ulcer healing. Ulcer healing was defined as the complete epithelialization of the ulcer crater. Those who failed to heal were given another course of 4 weeks therapy of H2 blockers or misoprostol or 2 weeks treatment of omeprazole. Clinical evaluation and endoscopy were repeated on completion of therapy to verify final healing.

All cases with healed ulcers were followed without maintenance therapy for a year to determine the relapse rate. Endoscopy was repeated early in cases in which symptoms recurred; otherwise, it was performed at 1, 3, 6, 9 and 12 months (the end point of the study) to determine ulcer recurrence.

Statistical analysis was done using the Student t-test and χ^2-test.

Results

A total of 149 cases of endoscopically confirmed duodenal ulcers were included in the study, of which 16 cases were lost to follow-up. Of 133 cases analysed, 28 patients each received cimetidine, 29 received ranitidine, 26 received famotidine, 25 received misoprostol and 25 received omeprazole. Demographic characteristics of each group are shown in Table 1. There were more males than females in each group with an overall 4:1 male to female ratio. Although ages ranged from 17 to 77 years, most of the cases were aged 30 to 50 years. Differences regarding age, sex, duration of symptoms and addiction patterns were statistically not significant.

Table 1 **Characteristics of treatment groups**

Item	Cimetidine		Ranitidine		Famotidine		Misoprostol		Omeprazole	
Total cases	28		29		26		25		25	
Sex										
Male	22	(79%)	23	(79%)	22	(85%)	21	(84%)	20	(80%)
Female	6	(21%)	6	(21%)	4	(15%)	4	(16%)	5	(20%)
Age										
Range (years)	17–75		19–73		18–55		17–77		18–70	
Mean ± *s*	42 ± 16		44 ± 15		38 ± 11		39 ± 13		39 ± 13	
Duration of symptoms (months)										
Mean ± *s*	59 ± 93		42 ± 56		40 ± 26		47 ± 37		50 ± 81	
Addictions										
Smoking	11		11		11		11		9	
Pan with tobacco	7		2		4		5		2	
No addiction	10		16		11		9		14	

Omeprazole = Proton pump inhibitor
Cimetidine, ranitidine and famotidine = H2 blockers
s = standard deviation

Table 2 **Comparison of cumulative healing rates of anti-ulcer drugs**

| Anti-ulcer drug | No. of cases | | Healed at: | | | | | | No response | |
			2 weeks		4 weeks		8 weeks			
Omeprazole	25		17	(68%)	25	(100%)	–		–	
Cimetidine	28		–		17	(61%)	21	(75%)	7	(25%)
Ranitidine	29		–		21	(72%)	24	(83%)	5	(17%)
Famotidine	26		–		20	(77%)	22	(85%)	4	(15%)
Misoprostol	25		–		17	(68%)	21	(84%)	4	(16%)

Omeprazole = Proton pump inhibitor
Cimetidine, ranitidine and famotidine = H2 blockers

Cumulative healing rates with the various anti-ulcer drugs over 8 weeks are shown in Table 2. Healing rates ranged from 61% to 100%. The best results were achieved with omeprazole. About 15%–25% of cases failed to respond to medication and were thus classified as non-responders (Table 2). After initial healing, an additional 41 cases were lost to follow-up. This left only 92 cases available for evaluation of relapse. Relapse rates of the various drugs ranged from 72% to 100% and were highest with the PPI (Table 3).

Discussion

The introduction of H2 blockers revolutionized the treatment of duodenal ulcers [2]. Since then, several H2 blockers

Table 3 **Comparison of relapse rates**

Anti-ulcer drug	No. followed-up	Relapse rate (%) at:				
		1	3	6	9	12 months
Omeprazole	22	59	100	–	–	–
Cimetidine	18	6	17	28	39	72
Ranitidine	15	0	53	57	80	86
Famotidine	22	32	50	64	73	82
Misoprostol	15	7	27	53	73	80

Omeprazole = Proton pump inhibitor
Cimetidine, ranitidine and famotidine = H2 blockers

with improved healing rates have been introduced [3–4]. In the search for newer and better drugs, prostaglandin was introduced [5], but the drug did not fulfil expectations. The introduction of proton pump inhibitors has reduced the duration of treatment of duodenal ulcers by almost 50% [6,7].

Although duodenal ulcer healing has markedly improved with the newer drugs, very little is known about the relapse rates of ulcers after cessation of treatment [8]. It is reported that 40% to 100% of patients relapse with or without symptoms within 12 months of cessation of therapy [9]. In most studies endoscopy was repeated at 6 to 12 months or at the recurrence of symptoms. Other studies show a poor correlation between ulcer relapse and recurrence of pain and report that the more frequently endoscopy is repeated, the higher the chances are of detecting a relapse [10].

Advanced age, male sex, long duration of disease, smoking, high acid output and larger ulcers may adversely affect ulcer healing [11,12]. All parameters except for acid output and ulcer size were evaluated in this study. Only medium to large-sized ulcers were included in this study and small or bleeding ulcers were excluded. Male to female ratio in all groups was generally 4:1. Although ages ranged from 17 to 77 years, the median age of all groups was near 40 years. Duration of symptoms and addiction patterns in all groups were comparable and were statistically not significant.

This study found that initially the healing rates were similar with H2 blockers, misoprostol and omeprazole, but at 8 weeks other H2 blockers showed better results than cimetidine. The difference was statistically non-significant. Omeprazole showed 100% healing at 4 weeks ($P < 0.05$). This and other reported studies confirm that ranitidine is better than cimetidine, famotidine is better than ranitidine and misoprostol, and omeprazole is the best for healing duodenal ulcers [13–15].

The results of our follow-up study are different from other studies [8,16,17]. Relapse rates at 1 month were highest with famotidine and omeprazole ($P < 0.05$), but at 3 months, the highest relapse rate was with the omeprazole group ($P < 0.05$). The relapse rates increased at 6 and 9 months in the misoprostol and H2 blocker groups (Table 3). At the end of one year, relapse rates were statistically non-significant in these groups.

The present study indicates that the higher the healing rate of a drug, the higher its relapse rate. In the case of omeprazole, the relapse rate is not only higher but also more rapid. Its more rapid and higher relapse rate could be due to rebound acid hypersecretion and increased meal-stimulated gastrin response as reported in H2 blocker therapy [18.19]. This phenomenon may be exaggerated with the use of more potent acid inhibitory agents like omeprazole which has been shown to produce hyper-

gastrinaemia without trophic effects on the parietal cells [20].

In spite of rapid advancements in the field of anti-ulcer therapy, the high relapse rates noted after the discontinuation of treatment with H2 receptor antagonists and omeprazole remain a great concern. It will be worthwhile in future studies to measure the serum gastrin level in these cases of ulcer so that it can be correlated with relapse rates.
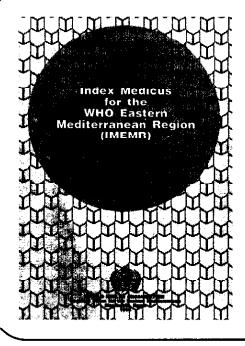
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