

Clinical markers of slow healing and relapsing gastric ulcer

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SUMMARY The aim of the study was to identify the clinical markers useful in characterising slow healing and relapsing gastric ulcer patients. Ninety nine subjects entered the short term and 79 the long term study (12 months). The following parameters were taken into account: therapy, sex, age, smoking habit, alcohol consumption, analgesic intake, peptic ulcer family history and onset of the disease. Results of the studies were analysed by means of χ^2 test and logistic regression, both in stepwise and in specifying models. Cigarette smoking was found to be the most important risk factor of non-healing ($p=0.04$). In women with late onset of the disease, cigarette smoking identified the gastric ulcer subjects at higher risk of non-healing with a predictive probability of 0.4679. Age under 50 years was found to be the most important risk factor of relapsing throughout the entire 12 month follow up period ($p=0.025$). In those under 50 years, cigarette smoking and negative peptic ulcer family history in combination, identified the gastric ulcer subjects at higher risk of relapsing, the predicted probability being 0.6027. It is concluded that cigarette smoking is the most important risk factor for non-healing and those who relapse under the age of 50. The possibility of singling out categories of patients more prone not to heal and to relapse suggests new strategies in the management of gastric ulcer disease.

Despite the introduction in routine therapy of active antisecretory drugs (cimetidine, ranitidine, pirenzepine), nine to 25% of gastric ulcer patients do not heal after six to eight weeks full dose treatment.¹⁻¹¹ Conflicting (but substantially negative) results have been reported on the importance of various factors in influencing gastric ulcer healing: age, sex, analgesic intake, cigarette smoking, ulcer size and site, alcohol consumption, duration of the disease, were all found not to be really important in singling out gastric ulcer subjects more prone not to heal.^{4,6,7,10,13-19} More recently, in 75 hospitalised patients, Okada *et al*²⁰ found that age (>50 years), ethanol intake (>60 g/daily), pain lasting more than three days, single ulcer and ulcer of the lesser curvature represent useful factors in characterising

subjects more prone not to heal, the risk being higher in patients presenting two or more of these markers.

Fewer data are available as yet on the long term follow up of gastric ulcer. H₂-blockers are effective in maintaining gastric ulcer remission, although eight to 21% of patients have an endoscopically documentable recurrence of the disease within the first 12 months of follow up.^{6,11,21-25} Cigarette smoking has been reported as not influencing gastric ulcer outcome.^{4,11,17,25-28} Old age, size of ulcer and analgesic intake have been found by Piper *et al* in a four year study to be the major factors involved in ulcer relapse;²⁷ these data have not been confirmed by others.^{4,14,17,21,25} Duration of ulcer disease and a past history of gastric ulcer were found recently to predispose patients to ulcer recurrence.²⁵

Predictors of duodenal ulcer slow healing and relapse have recently been under study;²⁹ we singled out some biochemical and clinical 'risk factors' of duodenal ulcer relapse.^{30,31} In an attempt to ascertain

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Received for publication 13 June 1986.

whether simple clinical parameters are useful in identifying slow healing and relapsing subjects, we analysed the results of a short and long term (one year) study in a large gastric ulcer sample.

Methods

PATIENTS

Ninety nine consecutive patients (63 men, 36 women, mean age 53 years, range 27–82) with an endoscopically and histologically proven benign active gastric ulcer were retrospectively studied.

The Figure illustrates the protocol of the study. The patients had openly received either 1000 mg cimetidine (69 patients), 300 mg ranitidine (16 patients), 100 mg pirenzepine (five patients) or other drugs such as sulglicotide (150 mg), trithiozine (1.2 g), oxmethylene (800 mg) (nine patients) daily.

Eighty patients (54 men, 26 women, mean age 50 years, range 23–78) underwent an upper gastrointestinal endoscopy at 42 ± 2.3 days (mean \pm SD), to assess healing. Nineteen subjects dropped out. The seventy nine patients who entered the 12 month follow up had endoscopic evidence of ulcer healing. Fifteen patients were left untreated apart from low dose antacids (Mg-Al hydroxide) as required. The remaining 64 subjects were treated with the same drug used in the active phase, but in maintenance low dosages: either 400 mg cimetidine (56 patients) or 150 mg ranitidine (eight patients) at night. An upper gastrointestinal endoscopy was done at the third, sixth, and 12th month of follow up in all asymptomatic patients, and at every symptomatic relapse lasting more than three days. Three to 10 biopsies, either around the active lesion or on its scar, were taken at every endoscopy with the aim of excluding a gastric carcinoma. Patients had a clinical check up before each endoscopy.

Nine patients withdrew at the third, six at the sixth and two at the 12th month of follow up because they failed to attend the endoscopic examination. Therefore, 62 patients (41 men, 21 women, mean age 51 years, range 27–70) completed the long term study (Table 1).

The following parameters were considered in order to assess the most important in influencing either the healing of the lesion or its recurrence throughout the 12 month follow up: therapy, sex, age (under or over 50), smoking habit (less or more than 10 cigarettes daily – that is, mild or non-smokers vs heavy smokers, alcohol consumption (less or more than 60 g of ethanol intake daily – that is, mild or non-drinkers vs heavy drinkers), analgesic intake, family history of peptic ulcer, early onset of the disease (before the third decade of life). The cimetidine treated patients were also considered separately as a further control group to exclude any bias caused by the treatment carried out.

STATISTICAL ANALYSIS

Chi-squared test was first used to compare the various treatment groups, then statistical analysis was done through logistic regression, both in stepwise and by specifying models using the program of the BMDP statistical package.³²

Through stepwise logistic regression, the proportion of failures (unhealing, relapse) can be predicted by the logistic model: $\exp(U)/(1+\exp(U))$, where U is a linear combination of independent variables (predictors) chosen in a stepwise fashion – that is, selected as the most useful variables. To verify important interactions among predictors, tentative models must be specified: a set of variables which are assumed to interact. In the present work all predictors were simplified as either categorical or binary. Once a good model is found to fit the proportion of failures, the probability of failure of a new patient can be predicted, using the coefficients of the linear combination U appended to the particular values of patient predictors. Coefficients indicate the relative importance of predictors in the model.

Results

No significant differences were detected among the treatment groups with the exception of 'early onset of the disease', which was significantly more frequent in the 'other drugs' group (Table 2).

Table 1 Gastric ulcer: assessment after long term follow up (12 months)

	Total	Endoscopic controls						Total relapses	Total drop outs
		3rd month		6th month		12th month			
		DO	R	DO	R	DO	R		
Therapy carried out									
Cimetidine 400 mg nocte	56	5	3	4	9	2	–	12	11
Ranitidine 150 mg nocte	8	3	–	1	–	–	1	1	4
None	15	1	1	1	–	–	5	6	2
Total	79	9	4	6	9	2	6	19	17

DO=drop outs; R=relapses.

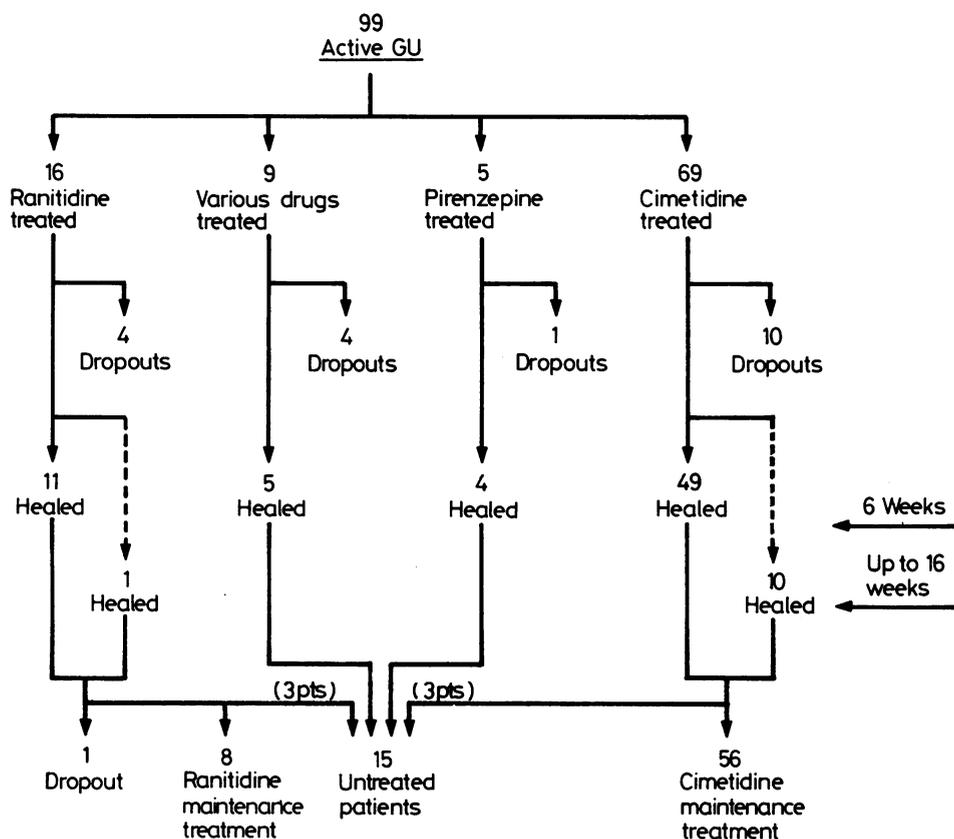


Figure. Protocol of the study.

Eleven out of the 80 gastric ulcer patients who completed the short term study (13.75%) were found to be not healed at endoscopic examination. Logistic regression analysis shows that smoking habit, sex, and onset of the disease are the most important factors in singling out unhealed gastric ulcer subjects ($p=0.04$, $p=0.10$, $p=0.16$, respectively). Only smoking habit had a p value less than 0.05. Table 3 shows the predicted probabilities of all possible combinations of values of variables in detecting unhealed gastric ulcer patients. In the cimetidine treated subgroup of patients the above reported results were largely confirmed, with the same parameters – that is, smoking habit, sex, and onset of the disease, being the most significant ($p=0.05$, $p=0.12$, $p=0.08$, respectively). The predicted non-healing probability of a cimetidine treated female heavy smoker with a late onset of the disease was found to be $p=0.5435$.

Nineteen out of the 62 gastric ulcer patients who completed the long term study (30.6%) relapsed at some time in the observation period (Table 1).

Logistic regression analysis showed that age, smoking habit, and peptic ulcer family history are the most important factors in singling out relapsing gastric ulcer subjects ($p=0.025$, $p=0.11$, $p=0.16$, respectively). Only age had a p value less than 0.05. Table 4 shows the predicted probabilities of all possible combinations of values of variables in singling out relapsing patients. In the H2-blocker – treated group of patients, the above reported results were partially confirmed with the same parameters – that is, age and peptic ulcer family history, being the most significant ($p=0.05$, $p=0.08$, respectively). Smoking habit did not reach statistical significance in this group. The predicted relapsing probability of an H2-blocker treated patient with a negative peptic ulcer family history and an age under 50 years was found to be $p=0.5165$.

Discussion

Cigarette smoking is reported to be the most important exogenous factor characterising duodenal

Clinical markers of slow healing and relapsing gastric ulcer

Table 2 Clinical details and treatment of gastric ulcer patients who completed the short term and long term study

Short term study	Cimetidine (n=59)	Ranitidine (n=12)	Other drugs (n=9)	P
Men	36	10	8	NS
Heavy smokers	31	9	3	NS
Heavy drinkers	13	2	3	NS
Positive PU family history	31	9	4	NS
Early onset of the disease	11	2	5	<0.05
Age under 50 years	35	8	8	NS
Analgesic (Occasional intake)	11	1	2	NS
Analgesic (Habitual intake)	4	1	—	NS
Long term study	H2-blockers (n=49)	Antacids (n=13)		P
Men	32	9		NS
Heavy smokers	25	6		NS
Heavy drinkers	14	1		NS
Positive PU family history	21	5		NS
Early onset of the disease	10	2		NS
Age under 50 years	30	10		NS
Analgesic (Occasional intake)	9	1		NS
Analgesic (Habitual intake)	3	1		NS

Table 3 All possible combinations of values of variables in the model and the predictive probability of unhealing

Sex	Smoking habit	Onset of the disease	Predicted probability*
F	<10	<III	0.1996
M	<10	<III	0.0367
M	<10	>III	0.0119
F	<10	>III	0.0731
M	>10	>III	0.1185
M	>10	<III	0.2983
F	>10	>III	0.4679

*Predicted probability ranges between 0 (absence of the event) and 1 (presence of the event); M=Male; F=Female; <10=less than 10 cigarettes daily; >10=more than 10 cigarettes daily; <III=before third decade of life; >III=after third decade of life.

ulcer patients with a poorer clinical outcome; both slow healing³³⁻³⁵ and relapse^{29,31,35-37} are closely connected with heavy smoking.

The results in literature of the effect of cigarette smoking on gastric ulcer outcome are conflicting: some authors report no influence^{4,6,10,16,17,20} and Leroux *et al* surprisingly found a positive effect.⁷ Our data are in agreement with that of Doll,¹³ who reports a significantly negative influence. Other clinical parameters – that is, female sex and late onset of the disease, were also found to be important, though less so statistically. These results are substantially in disagreement with the few that have appeared in the literature.^{4,6,7,10,20} In accordance with the more recent literature,^{9,11} full dose cimetidine and ranitidine seem to be equally effective in promoting gastric ulcer healing.

As regards long term follow up, absence of peptic

Table 4 All possible combinations of values of variables in the model and the predicted probability of relapsing

Smoking habit	PU family history	Age	Predicted probability*
<10	YES	>50	0.0483
>10	YES	>50	0.1108
>10	NO	>50	0.2301
<10	NO	>50	0.1085
<10	YES	<50	0.2048
<10	NO	<50	0.3820
>10	YES	<50	0.3874
>10	NO	<50	0.6027

*Predicted probability ranges between 0 (absence of the event) and 1 (presence of the event); <10=less than 10 cigarettes daily; >10=more than 10 cigarettes daily.

ulcer family history, cigarette smoking and, mainly, age under 50 years, characterised our gastric ulcer patients with a higher risk of relapse. These results are in disagreement with the observations of many authors, who have found that gastric ulcer relapse is influenced neither by cigarette smoking^{4,11,17,21,26-28} nor by age.^{4,17,21,26} Unlike Piper,²⁷ we found that gastric ulcer subjects under 50 years have a significantly higher risk of relapse. This might be accounted for by the inverse correlation between age and gastric acid secretion³⁸ or greater stress generally linked to work. Therapy did not significantly influence outcome: 50% of untreated as opposed to 26% of treated patients relapsed (0.05>p<0.10). This may be explained by the small sample of untreated subjects and unequal composition of the three groups. Our findings in the entire gastric ulcer population, however, were substantially confirmed by those in the more homogeneous group of H2-blocker treated subjects.

As far as we are aware, the present study constitutes the first attempt at specifically detecting predictive markers of both slow healing and relapsing gastric ulcer. Our results show that: (1) cigarette smoking is the most important risk factor of gastric ulcer non-healing; (2) relatively young age (under 50 years) significantly characterises relapsing subjects. The statistical method we used was able to predict the non healing- and relapsing risk for each of the possible combinations of values of the most useful variables: acquired (eliminable) factors – that is, cigarette smoking, on the one hand, and genetic factors – that is, female sex, late onset of the disease, negative peptic ulcer family history and young age, on the other, were together able to identify gastric ulcer patients with a risk of poorer outcome.

It remains to be established whether stopping smoking and a different therapeutic approach to 'high risk subjects' may increase the gastric ulcer healing and remission rate.

This study was conducted under the auspices of the Roberto Farini Foundation and for Gastroenterological Research, and partially supported by a grant for the Ministero Pubblica Istruzione, Project 83.02119.04.

We should like to thank Ms Margherita Ulrych for her linguistic help in preparing the manuscript.

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