Factors influencing the healing rate of gastric ulcer in hospitalised subjects

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SUMMARY A multiple linear regression analysis was carried out on 75 inpatients with gastric ulcer. In order to elucidate the effects of various factors – endoscopic and roentgenological findings, age, sex, medical history, and drugs such as antacids, anticholinergics or both – on the healing rate, these factors were compared between those with ulcer which healed within eight weeks after treatment and those which did not. In patients over 50 years of age, alcohol consumption of over 60 g per day until admission, duration of present ulcer pain for over three months, single ulcer, ulcer located in the lesser curvature and uneven elevation around the ulcer, there was significant delaying effect on ulcer healing. Drug ingestion, sex, smoking habits until admission, size, depth, and shape of ulcer, coexisting gastritis, and past and family history of ulcer disease had no significant effect on healing after eight weeks. The patients with less than two unfavourable factors ($n=46$) had the best healing rate (100%) compared with those with three ($n=20$) or four or more ($n=9$) unfavourable factors. The healing rate of the latter two groups was 60% and 22%, respectively ($p<0.001$). A prognostic score based on these six factors represents the severity of gastric ulcer disease with regard to the healing rate in patients prescribed antacids, and/or anticholinergic drugs.

The healing of gastric ulcer is influenced by drug therapy as well as by other factors. There are a number of controlled studies¹⁻⁵ on the effect of various drugs on the healing rate of gastric ulcer, however, there is little documentation of the effects of factors other than drug treatment on the healing of gastric ulcer. The aim of the present study was to evaluate the effect of various factors such as medical history, endoscopic, and roentgenological findings, in addition to drug treatment on the healing of gastric ulcer under conditions of hospital admission.

Methods

PATIENTS

Eighty four Japanese patients with gastric ulcer admitted to our clinic from April 1976 to May 1978 were entered into the trial. The diagnosis was confirmed by both endoscopy and radiograph examination within 48 hours before the initiation of

treatment. Excluded from the study were pregnant women, patients with chronic liver or renal disease, or any other severe disease, patients regularly on acetylsalicylic acid or other ulcerogenic drugs, patients with a past history of ulcer surgery, and patients with pyloric or prepyloric ulcers. Informed consent was obtained from all patients.

The patients were randomly allocated to double blind treatment in three different groups. The order of the medications was randomised by a random number table into blocks of six patients.

Treatment started within 48 hours after endoscopy. All patients were treated as inpatients. As a rule, the patients got up at 7 am and went to bed at 9 pm. The patients were permitted to walk within the hospital during the day, but were not allowed to go out of the hospital. One group (anticholinergic group) were given dicyclomine hydrochloride (Bentyl®), 10 mg three times a day, and 10 mg at bedtime; a second group (antacid group) received dried aluminium hydroxide, 0.8 g three times a day, and 0.8 g at bedtime together with magnesia oxydum ponderosum, 0.4 g three times a day, and 0.4 g at bedtime (that is a buffering

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capacity of 200 mmol/day); and a third group (antacid/anticholinergic group) received both an antacid and an anticholinergic, in the same dose as above. Thus, all patients had to swallow four tablets and four powders per day.

Endoscopy was repeated every two weeks until ulcer healing was confirmed. The ulcer was regarded as healed when complete epithelialisation of the ulcer was achieved, as determined by endoscopy. The patient was discharged from hospital when ulcer healing was confirmed. During the period of admission, each of these patients took the above medication. If the ulcer had not healed at eight weeks after treatment, however, other drugs such as cimetidine etc were given. Gastric biopsy was done in all patients at the beginning of the study and gastric cancer was ruled out in all. Ulcer size was assessed by the method of Doll and Pygott.⁶ In cases of multiple ulcers, the diameter of the largest ulcer was measured. Those ulcers whose base appeared to be almost on a level with the surrounding mucosa were called flat, and those with a clearly depressed base of more than 3 or 4 mm from the margin were called deep. The coexisting gastritis was classified as only a superficial or erosive gastritis.

The duration of the present ulcer pain was dated from the inception of the present ulcer like symptoms. The patients stopped drinking alcohol after admission and were ordered to stop smoking.

The following items were compared between those with ulcer which healed within eight weeks after treatment and those which did not: age, sex, duration of present ulcer symptoms, smoking and drinking habits before admission, family and past history of gastric ulcer, drug treatment, ulcer size, and endoscopic findings such as shape, depth, number and site of ulcer, gastritis, uneven elevation around the ulcer and folds' convergence.

The relationship of ulcer healing to the foregoing variables was first examined by using χ^2 test with Yates' correction and unpaired Student's *t* test, and subsequently by using multiple stepwise linear regression analysis^{7,8} in which healing within eight weeks was the dependent variable. All factors which were statistically unfavourable for gastric ulcer healing were weighed equally, and were used to calculate a prognostic score.

Results

Of the 84 patients, nine dropped out: six patients had been treated with dicyclomine hydrochloride, two with antacid, and one with antacid/anticholinergic. The reason for drop out was discharge at two weeks with the ulcer unhealed because of personal reasons. Thus, 75 patients (50 men and 25 women)

were available for analysis of the healing within eight weeks after admission. Twenty seven had received antacids, 24 anticholinergics, and 24 antacid/anticholinergic. The ulcer healed in 60 of 75 (80%) patients within eight weeks.

Table 1 shows various characteristics of patients with healed or unhealed gastric ulcers. Among these characteristics, age was of significant importance for the healing rate – that is, patients over 50 years old had a significantly poorer healing rate. The present period of ulcer pain and alcohol ingestion had some effect on the healing rate, but the values did not reach the threshold of significance. Within eight weeks, the ulcer healed in 23 of the antacid group (85.2%), 17 of the anticholinergic group (70.8%), and 20 of the antacid/anticholinergic group (83.3%). These differences were not significant. The sex, smoking habits, and family and past history of gastric ulcer did not correlate with the healing rate.

Among the endoscopic and roentgenological findings, an ulcer size of over 20 mm and uneven elevation around the ulcer had a significant delaying

Table 1 Characteristics of patients with healed (*n*=60) and non-healed (*n*=15) gastric ulcer

	Gastric ulcer		Significance
	Healed*	Non-healed†	
Age (yr)			
Mean	48.3±15.8	57.9±10.8	p<0.05
<50	32	3	p<0.05
≥50	28	12	
Sex			
Male	42	8	NS
Female	18	7	
Duration of present ulcer symptoms (months)			
<3	50	9	p=0.11
≥3	10	6	
Cigarette smokers (≥10/day)			
Yes	35	8	NS
No	25	7	
Alcohol consumption over 60 g/day			
Yes	7	5	p=0.10
No	53	10	
Family history of gastric ulcer			
Yes	2	1	NS
No	58	14	
Past history of gastric ulcer			
Yes	6	3	NS
No	54	12	
Treatment			
Antacid	23	4	NS
Anticholinergic	17	7	
Antacid/anticholinergic	20	4	

* Ulcer which healed within eight weeks after treatment.

† Ulcer which did not heal within eight weeks.

effect on healing (Table 2). Single ulcer or ulcer located in the lesser curvature healed less rapidly, but the differences were not significant. Shape, depth, site such as body or angle, gastritis, or folds' convergence had no effect on the healing rate.

Table 3 shows the results of a multiple stepwise linear regression analysis. The following six factors had a significant delaying effect on healing: age over 50 years ($p<0.01$), alcohol consumption of over 60 g per day ($p<0.01$), ulcer located in the lesser curvature ($p<0.01$), single ulcer ($p<0.05$), duration of present ulcer pain for over three months ($p<0.05$), and uneven elevation around the ulcer ($p<0.05$). When these factors were taken into account, other factors such as drug, the sex, and ulcer size etc were not significant.

The scoring system was one in which each unfavourable factor was given equal weight. The patients with varying numbers of a total of six unfavourable factors were classified into five groups (Table 4). With the increment of the prognostic score, the healing rate decreased from 100% (score

of 1 to 2) to 60% (score of 3) and 22.2% (score of 4 to 5) ($p<0.001$).

Discussion

All but one⁹ of previously reported studies on factors influencing the healing of gastric ulcer involved an univariate analysis. As various factors influencing the healing of gastric ulcer are often interrelated, such an analysis may be inadequate. To clarify factors influencing the healing, the association between the healing and a single factor should be examined taking into account the various factors. A multivariate analysis is suitable for the purpose, as the relative importance of various factors in association with healing can be evaluated.

Slower healing in older patients has been observed by other workers,¹⁰⁻¹² though there were exceptions.¹³⁻¹⁵ Nakajima⁹ noted in a multivariate analysis that age was a significant factor influencing gastric ulcer healing, which agrees with our observations. Sonnenberg *et al*¹⁶ also recently reported a slower healing in such patients with duodenal ulcer. This is also the case with other reparative processes such as wound healing and healing of bone fractures.¹⁷⁻¹⁹

It is worth noting that alcohol consumption of over 60 g per day up to admission had a significant delaying effect on ulcer healing. This finding has not been reported, though there are data that alcohol is not a risk factor of gastric ulcer.²⁰ Sonnenberg and coworkers¹⁶ found that moderate drinking promotes ulcer healing in outpatients with duodenal ulcer. This finding may be explained by recent studies that prostaglandins are formed endogenously by administration of mild irritants such as low concentrations of alcohol and necrosis of the gastric mucosa is prevented.²¹ In our study, alcohol consumption of over 60 g per day – not a mild irritant – may bring about direct damage to gastric mucosa and the rate of healing would be slow. It is generally accepted that smoking delays the healing of duodenal ulcer.^{10 13 22 23} Concerning the effect of smoking on the healing of gastric ulcer, however, the results obtained have been conflicting.^{10 13 22} We found that smoking up to admission had no direct effect on gastric ulcer healing. As a rule, our patients stopped smoking after admission. Thus, the association between the amount of tobacco smoked after admission and ulcer healing was not a factor to be considered in this study.

In cases of duodenal ulcer, duration of present ulcer pain for more than three weeks had a significant delaying effect on ulcer healing.²³ Similarly, in the present study, a long duration of present ulcer pain had a significant delaying effect

Table 2 Characteristics of endoscopic findings in healed ($n=60$) and non-healed ($n=15$) gastric ulcer patients

	Gastric ulcer		Significance
	Healed*	Non-healed†	
Ulcer shape			
Round or oval	45	12	NS
Irregular	15	3	
Ulcer size (mm)	16.5±7.1	23.1±11.9	$p<0.05$
<20	43	6	$p<0.05$
≥20	17	9	
Ulcer depth			
Flat	12	1	NS
Deep	48	14	
Numbers of ulcers			
Single	38	13	NS ($p=0.15$)
Multiple	22	2	
Site (A)			
Body	33	6	NS
Angle	27	9	
Site (B)			
Lesser curvature	32	12	NS ($p=0.11$)
Others	28	3	
Gastritis			
Yes	6	3	NS
No	54	12	
Uneven elevation around the ulcer			
Yes	5	5	$p<0.05$
No	55	10	
Folds' convergence			
Yes	29	7	NS
No	31	8	

* Ulcer which healed within eight weeks after treatment.

† Ulcer which did not heal within eight weeks.

Table 3 Multiple stepwise regression analysis of factors related to ulcer healing within eight weeks after treatment

Step no	Factor	Unfavourable	F value	R ²
1	Elevation around the ulcer	Uneven	4.687*	0.0865
2	Age	Over 50	16.913†	0.1622
3	Alcohol consumption	Over 60 g/day	7.743†	0.2384
4	Dicyclomine HCL	Intake	3.500	0.2990
5	Site (B)	Lesser curvature	8.546†	0.3548
6	Duration of present ulcer symptoms	More than three months	6.315*	0.4340
7	No of ulcers	Single	6.349*	0.4863
8	Ulcer size	More than 20 mm	2.697	0.5310

* $p < 0.05$ † $p < 0.01$.Percentage of variation accounted for = $R^2 \times 100$. R = multiple correlation.

on gastric ulcer healing. In patients with a short period of pain, the ulcer would be diagnosed early and be treated early after the onset in order and rapid healing would follow. On the contrary, in patients with a long period of pain, the ulcer would be diagnosed later and be treated later after the onset and the healing would be slow.

Among the endoscopic data, single ulcer, ulcer located in the lesser curvature, and uneven elevation around the ulcer had a significant delaying effect on ulcer healing, while shape and depth of ulcer and gastritis had no significant effect on the healing after eight weeks. Uneven elevation around the ulcer appears to indicate submucosal fibrosis as a result of a repetition of recurrence. The reason why single ulcer and ulcer located in the lesser curvature tend to heal slowly is difficult to explain. Previous studies^{9 11 14} showed that large gastric ulcers healed more slowly than small ulcers. In our study, size had a significant effect on ulcer healing in the univariate analysis, but an insignificant effect in the multivariate analysis. This may be explained by the relationship between the ulcer size and other factors such as age ($r=0.232$, $p<0.05$), site B ($r=-0.300$, $p<0.05$), and duration of present ulcer symptoms ($r=0.236$, $p<0.05$).

In conclusion, the six factors such as age over 50 years, alcohol consumption of over 60 g per day up

to admission, duration of present ulcer pain for over three months, ulcer located in the lesser curvature, single ulcer, and uneven elevation around the ulcer had a significant delaying effect on healing of gastric ulcer. The greater the number of these six unfavourable factors in a patient, the less likely the ulcer is to heal. Further prospective studies should confirm reliability of these factors in affecting the healing process under conventional medical treatment in patients with gastric ulcer.

Addendum

The reliability of the effect of these six unfavourable factors on the healing rate of gastric ulcer has been confirmed in a prospective study of 60 consecutive cases admitted to our clinic from April 1980 to December 1982. These patients were given antacids, anticholinergics, or both. The criteria to enter the study were the same as conditions used in the first series. The ulcer was completely healed in 43 patients (healing rate 71.1%). Depending upon the number of unfavourable factors present, the healing rate within eight weeks after treatment is shown in the addendum Table. The greater the number of these unfavourable factors in a patient, the less expectation there was for healing. These results indicate the importance of these factors in the

Table 4 Gastric ulcer healing within eight weeks after treatment by number of unfavourable factors (n=75)

Patients with	Score						
	0	1	2	3	4	5	6
Healed ulcer	/	15	31	12	2	0	/
Non-healed ulcer	/	0	0	8	6	1	/

 $p < 0.001$.

Addendum Table Gastric ulcer healing within eight weeks after treatment by number of unfavourable factors (n=60)

Patients with	Score*						
	0	1	2	3	4	5	6
Healed ulcer	2	7	22	9	3	0	0
Unhealed ulcer	0	0	0	5	7	4	1

 $p < 0.001$.

* This relates to the prospective study using unfavourable factors from the initial study.

healing process of gastric ulcer, under conventional medical treatment such as antacids, anticholinergics, or both.

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