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Controlled therapeutic trial to determine the optimum dose of antacids in duodenal ulcer

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SUMMARY Antacids are widely used in the management of duodenal ulcer but the optimum dose of antacid required for ulcer healing has not been determined. We therefore studied 107 patients with endoscopically diagnosed duodenal ulcer who were allotted at random to one of the following treatment groups; placebo (group P) and antacid (groups A, B and C). A liquid antacid (Aludrox MH, Wyeth) with neutralising capacity of 2·3 mmol HCl/ml was administered in graded doses of 7·5 ml (Group A), 15 ml (Group B), and 30 ml (Group C), one hour and three hours after each meal, six times a day for four weeks. Patients in group P received 15 ml liquid placebo in a similar fashion. Complete symptomatic relief was obtained in 33% of patients in the placebo group, 54% in antacid group A, 89% in group B, and 92% in group C. Endoscopic assessment at the end of four weeks of treatment gave an ulcer healing rate of 29% in the placebo group, 46% in group A (103·5 mmol antacid/day), 85% in group B (207 mmol/day), and 88% in group C (414 mmol/day). There was no significant difference in the healing rates and pain relief between placebo and antacid group A, while both groups B and C had significantly higher ulcer healing rates and pain relief compared with placebo ($p<0·001$) and antacid group A ($p<0·01$). Drug related unwanted effects were recorded only in group C – 28% of patients suffered from diarrhoea. It is concluded that the optimum antacid requirements for the treatment of duodenal ulcer is 90 ml (acid neutralising capacity, 207 mmol HCl) per day.

It is well established that antacids used in large doses (210 ml/day; neutralising capacity 800–1000 mmol HCl/day) and at fixed intervals (one hour and three hours after meals, and at bed time) promote healing of duodenal ulcer at a rate which is comparable with that reported with cimetidine.[1–5] Recent studies show that even smaller doses of antacids are equally effective.[6–8] For example, Berstad *et al*[8] using antacid tablets with a total neutralising capacity of 280 mmol HCl/day recorded a healing rate of 81%, compared with 24% in patients treated with placebo. Lam *et al*[6] also used antacid tablets with a total neutralising capacity of 175 mmol HCl/day and obtained a ulcer healing with or without residual duodenitis in 77%, compared with 33% in the placebo treated group. In a recent study using a liquid antacid in a dose of 90 ml (neutralising capacity 210 mmol HCl/day) a healing rate of 76%[9] was obtained. Thus antacids used in daily neutralising capacity ranging from 175 to over 1000 mmol have resulted in almost identical healing rates for duodenal ulcer. The optimum antacid requirements have not been determined, however, and we therefore carried out a controlled therapeutic trial using graded doses of antacid in order to study this further.

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Method

PATIENTS

One hundred and seven patients with endoscopically confirmed duodenal ulcer were included in the study. None of the patients was receiving specific anti-ulcer treatment before the trial. Patients with ulcer-related complication such as haemorrhage and perforation, previous gastric surgery, or with any systemic illness were excluded from the study.

A liquid antacid (Aludrox MH, Wyeth; neutralising capacity 2·3 mmol HCl/ml) was used. The composition of antacid was aluminium hydroxide 61 mg/ml and magnesium hydroxide 20 mg/ml. A liquid placebo (provided by Wyeth),

identical in appearance to the antacid but with no neutralising capacity was used in the control group. The placebo and antacid were administered in six daily doses one hour and three hours after each meal. Treatment was continued for four weeks. Patients were randomly allocated to one of the following groups.

Antacid groups: group A, 7·5 ml/dose 6 (45 ml/day); group B, 15·0 ml/dose 6 (90 ml/day); group C, 30·0 ml/dose 6 (180 ml/day).

Placebo group: group P, 15·0 ml/dose 6 (90 ml/day).

Total daily neutralising capacity of the antacid used was 103·5 mmol, 207 mmol, and 414 mmol HCl in groups A, B, and C respectively.

Patients were assessed clinically every week and symptoms were recorded on a form designed for this purpose. Endoscopy was repeated at the end of four weeks and the findings were categorised as: (a) healing of ulcer with, or without residual duodenitis, or (b) non-healing of ulcer irrespective of size. Endoscopic examination was carried out in a "blind" fashion so that the endoscopist was unaware of the treatment received by the patient. Patients were considered to be symptomatic if they complained of any discomfort, or pain during the previous week. Drug related unwanted effects were specifically asked for and recorded.

STATISTICAL ANALYSIS

χ^2 test was used to compare the ulcer healing rates with different doses of antacid and placebo.

Results

Six of the 107 patients entering the trial dropped out of the study; three in the placebo group because of intractable pain, and three in the antacid group C because of severe diarrhoea.

Mean age and sex ratios of the patients in different treatment groups were comparable. The duration of symptoms before starting the trial and the proportion of cigarette smokers did not differ significantly (Table 1).

SYMPTOMATIC RESPONSE

The results are shown in Table 2. At the end of first week symptomatic response to treatment was poor in placebo and antacid group A; only 8% and 12% being relieved of pain in the two groups respectively. In contrast, 52% and 63% of patients in groups B and C respectively were completely asymptomatic. The same trend continued during the whole period of study. At the end of four weeks there was no significant difference in relief of pain between the placebo-treated patients and antacid group A. Antacid groups B and C, however, had significantly better pain relief than groups P and A; this difference was observed at the end of the first week and was maintained throughout the study.

Table 1 *Clinical details of patients in the different treatment groups*

	Total number of patients 107			
	Placebo	*Antacid groups*		
	P	*A*	*B*	*C*
Total no	24+(3)*	26	27	24+(3)*
Male/female	22/2	24/2	23/4	20/4
Age (yr) mean ± SD	37±9	39±12	37±11	40±11
Duration of symptoms (yr)				
Median	4·0	4·5	5·0	4·0
(Range)	(1–10)	(1–12)	(1–12)	(1–13)
Smokers	58%	61%	67%	62%

* Dropped out of study

ULCER HEALING

After four weeks of treatment endoscopy showed ulcer healing in seven of 24 (29%; 95% confidence limits 11–47) patients given placebo, compared with 12 of 26 (46%; confidence limits 27–65) in group A, 23 of 27 (85%; confidence limits 72–98) in group B, and 21 of 24 (87%; confidence limits 74–100) in group C (Figure). There was no significant difference in the healing rates between placebo and group A, while healing rates in groups B and C were significantly superior compared with placebo ($p<0·001$) and group A ($p<0·01$). There was no significant difference in the healing rates between groups B and C.

Table 2 *Weekly clinical assessment*

	Asymptomatic			
	Placebo	*Antacid groups*		
	P n=24	*A* n=26	*B* n=27	*C* n=24
First	2 (8%)	3 (12%)	14 (52%)	15 (63%)
Second	4 (17%)	6 (23%)	18 (67%)	18 (75%)
Third	7 (29%)	10 (39%)	20 (75%)	18 (75%)
Fourth	8 (33%)	14 (54%)	24 (89%)	22 (92%)
Weeks	*P* vs *B*	*P* vs *C*	*A* vs *B*	*A* vs *C*
First	p<0·01	p<0·001	p<0·01	p<0·001
Second	p<0·001	p<0·001	p<0·01	p<0·001
Third	p<0·01	p<0·01	p<0·01	p<0·01
Fourth	p<0·001	p<0·001	p<0·01	p<0·01

P *vs* A NS in all four weeks
B *vs* C NS in all four weeks

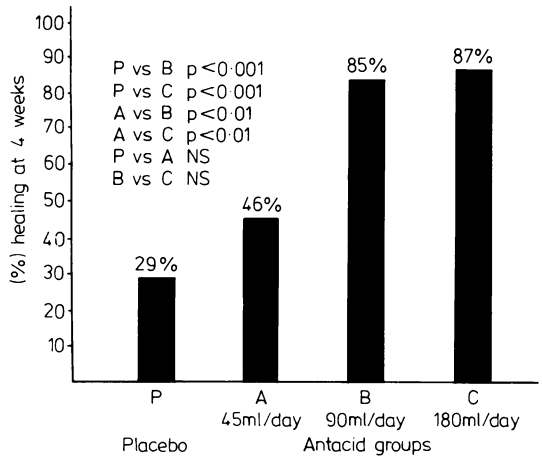

Figure *Comparison of endoscopic healing rates in different treatment groups.*

DRUG RELATED UNWANTED EFFECTS

Three of 27 patients (11%) on the placebo dropped out of the study because of severe uncontrolled pain. In group C, three of 27 (11%) developed severe diarrhoea and discontinued the treatment; of the remaining 24 patients, four (17%) had a mild bowel upset (mainly diarrhoea), but continued taking the drug. Thus, the overall incidence of unwanted effect in group C was 28%. In contrast, no patients in the other groups had any unwanted effects attributable to the treatment.

Discussion

Although there is evidence that antacids heal duodenal ulcer, the dose response and optimum requirements of antacids for pain relief and ulcer healing have not been properly determined. In the present study, we have shown that the optimal results were obtained with 90 ml/day (neutralising capacity 207 mmol HCl/day). A further increase in the dose of antacid to 180 ml/day (neutralising capacity 414 mmol HCl), did not significantly alter the healing rates, but resulted in appreciable unwanted effects; 28% suffered from diarrhoea and in 11% it was severe enough to discontinue the treatment. In contrast, drug related unwanted effects were not recorded in the other treatment groups. The ideal dose of antacid appears to be one which is sufficient to neutralise about 200 mmol HCl a day.

It is interesting to note that antacids even in small quantities of 45 ml/day (neutralising capacity 103·5 mmol) resulted in a better healing rate compared with placebo (46% *vs* 29%), although the differences were not statistically significant. This point is worth emphasising as patients taking part in trials of new drugs for duodenal ulcer are invariably given a liberal supply of antacids and this could affect the final results.

Although most physicians share the belief that antacids relieve ulcer pain, this matter has not been satisfactorily resolved. For example, Sturdevant *et al*[10] in a comparative study showed that antacids were not superior to placebo for pain relief, although we found them definitively superior to placebo, in providing pain relief. Three (11%) patients in the placebo group dropped out of the study because of severe pain, while none did so in the antacid groups. Pain relief was to some extent related to the dose of antacid used. At the end of four weeks group A had better relief of pain than placebo (54% *vs* 33%) although the difference was statistically not significant, while groups B and C were significantly better than placebo and group A. No significant difference was observed between groups B and C (Table 2). For pain relief, as well as for healing of duodenal ulcer the best dose in this study was 90 ml/day.

The question arises as to which antacid preparation should be used as they vary considerably in their neutralising capacity, (1·3–8·4mmol HCl/ml), and cost.[11 12] Assuming that antacids produce their therapeutic effect by neturalising gastric acid, the present study, as well as others,[6 8] suggests that the dose of a particular antacid should be adjusted so as to neturalise about 200 mmol of acid a day. These observations indicate that the quantity of antacids used in the past resulting in neturalisation of 800–1000 mmol HCl/day were excessive.[1 2] A low dose of antacid therapy would not only improve compliance, but also decrease the cost and the incidence of unwanted effects of the treatment.

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