*Clinical trial***Tripotassium dicitrato bismuthate (TDB) versus two different dosages of cimetidine in the treatment of resistant duodenal ulcers**

G BIANCHI PORRO, F PARENTE, AND M LAZZARONI

From the Gastrointestinal Unit, L Sacco Hospital, Milan, Italy

SUMMARY The use of tripotassium dicitrato bismuthate (TDB) has been suggested recently for cimetidine resistant duodenal ulcers. This study compares the efficacy of TDB with two different cimetidine dosages in the treatment of duodenal ulcer patients who failed to respond to an eight week therapy with H₂-blockers. Fifty two patients (40 men, 12 women) were randomly allocated to one of the following three oral regimens: (1) TDB 120 mg qid, (2) cimetidine 400 mg tid, (3) cimetidine 400 mg with meals plus 800 mg at bedtime. Endoscopy was carried out after four weeks; if the ulcer had not healed patients continued with the same treatment for a further four week period when they were endoscopically reassessed. After four weeks similar percentages of ulcer healing were registered in the two cimetidine schedules (39% with 1.2 g and 44% with 2 g), whereas TDB resulted in a significantly higher healing rate (82%) compared with cimetidine 1.2 g ($p=0.01$) and with cimetidine 2 g ($p=0.025$). After eight weeks the cumulative percentages of healing were 65% on cimetidine 1.2 g, 75% on cimetidine 2 g, and 94% on TDB (TDB v cimetidine 1.2 $p=0.042$). These results confirm previous data that resistant duodenal ulcers are more responsive to an agent which strengthens the mucosal defences than to antisecretory compounds.

A four week treatment with cimetidine or ranitidine usually heals 70-80% of duodenal ulcers.^{1,2} Those remaining unhealed can be cured simply by continuing the therapy for another month;³ even after eight weeks, however, a small proportion of patients may be expected to remain unhealed, so appearing to be 'resistant' to these compounds.

The most appropriate method of medical management for such patients has not been well established as yet. Three different options may be considered: first, the current H₂-blocker regimen can be continued unchanged for several months;⁴ second, the dosage of H₂-blocker can be augmented in the attempt to improve the control of both day and night time gastric acid secretion;⁵ third, the antisecretory drug can be substituted for one exerting a mainly cytoprotective action.^{6,7}

The validity of these three different approaches has never been evaluated in a single controlled trial. We have therefore undertaken a randomised controlled study to compare the efficacy of two different doses of cimetidine (1.2 and 2 g daily respectively) with that of tripotassium dicitrato bismuthate (TDB) tablets in the healing of duodenal ulcers resistant to an eight week treatment with cimetidine 1.2 g or ranitidine 300 mg a day.

Methods**PATIENTS**

The initial recruitment was made from September 1984 to March 1986 among outpatients with endoscopically proven duodenal ulcer who underwent the endoscopic control in our Unit after an eight week course of H₂-blockers. Patients with unhealed ulcer and whose drug compliance was judged to be good by one examiner were considered eligible for the study. Fifty-two patients (40 men and 12 women) who failed

Address for correspondence: Prof G Bianchi Porro, Gastrointestinal Unit, L Sacco Hospital, 20157 Milano, Via G B Grassi, 74, Italy.

Received for publication 21 November 1986.

to respond to an eight week course of cimetidine 1.2 g or ranitidine 300 mg/day were enrolled; 41 were selected from the group of patients attending our department for ulcer disease, the remainder from duodenal ulcer patients referred to our Centre for the endoscopic follow up.

The largest ulcer diameter was not less than 5 mm and the patients did not have active bleeding, pyloric stenosis, concomitant gastric ulcer, previous gastric surgery, concurrent treatment with ulcerogenic drugs or any serious chronic disease which might influence the outcome of therapy. Pregnancy or lactation were also contraindications to enter the trial.

At the initial endoscopy the ulcer size was assessed by measuring its longest diameter with open standard biopsy forceps after pharmacological duodenal hypotension. Fasting serum pepsinogen I (Sorin Biomedica, Saluggia, Italy) and gastrin (Becton Dickinson, Orangeburg, New York) levels, basal acid output (BAO) and peak acid output (PAO), the latter after stimulation with pentagastrin 6 µg/kg, were determined in all patients before treatment. Detailed information on duration and age of onset of dyspeptic symptoms, family history of peptic ulcer, previous ulcer complications and social habits were collected on the same occasion from each patient.

After giving informed verbal consent, patients were allocated according to a randomisation list for 60 subjects, to one of the following three oral regimens: (1) TDB 480 mg/day (one chewable tablet half an hour before the three main meals and one at bedtime); (2) cimetidine 1.2 g/day (400 mg every eight hours); (3) cimetidine 2 g/day (400 mg with meals plus 800 mg at bedtime). Therapy began within five days of initial endoscopy and was continued for four weeks.

All patients were given commercially available antacid tablets (Maalox) to be taken when necessary for relief of pain. They were also instructed to daily record on a diary card both their pain episodes and the number of antacid tablets consumed. No dietary restrictions or modifications concerning smoking habits were prescribed.

Patients were seen by a physician after two and four weeks to evaluate symptoms, antacid consumption and compliance, the latter by counting the unused tablets returned at each visit by the patient. Within five days of completing the four week course of therapy, endoscopy was repeated by the same experienced operator who did the first examination; he was unaware of the patient treatment. If healing had occurred the study was ended; if not, the patient continued the same regimen for another four weeks and was then reassessed by endoscopy. If at the end of eight weeks the ulcer had not healed the patient was withdrawn from the trial.

Healing was defined as the complete disappearance of the ulcer crater; the presence of duodenitis with or without erosion did not affect the assessment of healing.

Statistical analysis of the results was carried out by means of χ^2 test, Fisher's exact test and Student's *t* test for paired and unpaired samples as appropriate. Differences with *p* value less than 0.05 were considered significant.

Results

Of 52 patients who entered the trial, 18 received cimetidine 1.2 g/day, 17 cimetidine 2.0 g/day and 17 TDB. The characteristics of these patients are reported in Tables 1 and 2.

Mean age, sex ratio, mean duration and age of onset of dyspeptic symptoms, family history of peptic ulcer, alcohol and daily cigarettes consumption and previous H₂-blocker therapy of the three groups were comparable (Table 1). They also did not differ significantly with respect to BAO and PAO values, fasting serum gastrin and pepsinogen I (PG I) concentrations and their longest ulcer diameter (Table 2).

One patient on cimetidine 2 g failed to attend the four week follow up endoscopy and one on cimetidine 1.2 g, unhealed after the first month, defaulted before completing the second month of treatment because lack of compliance.

Endoscopic evaluation after four weeks showed that ulcer healing occurred in 39% (7/18) of patients receiving cimetidine 1.2 g, in 44% (7/16) of those receiving cimetidine 2 g and in 82% (14/17) of those treated with TDB. The healing rate on TDB appeared to be significantly higher as compared with both that on cimetidine 1.2 g (*p*=0.01) and that on cimetidine 2 g (*p*=0.025) (Table 3). After eight

Table 1 Characteristics of patients at trial entry

	Cim 1.2 g	Cim 2 g	TDB
Patients (n)	18	17	17
Sex: male (n)	12	15	13
Mean age (years) ± SD	43 ± 13	38 ± 11	43 ± 12
Duration of dyspeptic symptoms (months), mean ± SD	119 ± 80	116 ± 63	129 ± 67
Age of onset of dyspeptic symptoms (years), mean ± SD	34 ± 13	29 ± 11	33 ± 12
Family history of peptic ulcer (%)	33.3	35.3	41.1
Smokers (%)	77.7	70.6	64.7
≥15 cigarettes/day (%)	66.7	52.9	47.0
Alcohol consumers (%) (≥50 g/day)	33.3	35.3	23.5
Previous H ₂ -blocker therapy:			
cimetidine 1.2 g/day (n)	13	12	14
ranitidine 300 mg/day (n)	5	5	3

Table 2 Characteristics of patients at trial entry

	Cim 1.2 g	Cim 2 g	TDB
BAO (mmol H ⁺ /h), mean±SD	8.4±5.8	11.6±9.2	8.6±6.3
PAO (mmol H ⁺ /h), mean±SD	47.8±12.5	48.2±16.0	47.1±18.1
Serum fasting gastrin (pg/ml), mean±SD	55.5±22.4	45.4±14.2	54.6±17.0
Serum fasting PG I (ng/ml), mean±SD	108.0±24.3	109.1±39.7	111.2±35.0
Longest ulcer diameter (mm), mean±SD	6.3±1.4	6.8±2.6	6.2±1.6

weeks treatment the cumulative percentages of healing were 65% on cimetidine 1.2 g, 75% on cimetidine 2 g and 94% on TDB. There was a statistically significant difference between TDB and cimetidine 1.2 g cure rate ($p=0.042$), while the difference between TDB and cimetidine 2 g, although numerically obvious, did not reach statistical significance. Computation of the 95% confidence intervals for the difference in the eight week healing rates between the latter two drugs ranged from 49% in favour of TDB to 11% in favour of cimetidine 2 g.

Tripotassium dicitrato bismuthate treated patient showed a significant decrease in antacids consumption during the first four weeks of therapy in parallel with the reduction in epigastric pain (Figure).

Conversely, the proportion of symptomatic patients as well as the antacid intake did not significantly modify during the course of the first month of therapy in both H2-blockers group (Figure). Compliance was good and similar in the three treatment groups (percentages of drugs consumed among patients who completed the trial were never less than 80%). No relevant side effects were observed with the three treatments although a reversible brown colouration of the tongue and stools occurred in most patients on TDB.

Discussion

An agreement has not been reached yet on which duodenal ulcer should be considered resistant to H2-blockers; the definitions by various authors include the following: (a) persistence of duodenal ulceration

after three months of treatment with cimetidine 1 g daily;⁴ (b) failure of duodenal ulcer to heal in six weeks on cimetidine 1 g a day;^{8,9} (c) decrease by less than 25% of the longest ulcer diameter within four weeks on cimetidine 1 g daily;⁶ (d) duodenal ulcer size unchanged after eight weeks' therapy with cimetidine 1 g or ranitidine 300 mg daily.^{7,10,11} In the present study we have defined 'resistant to H2-blockers' an ulcer still present after eight weeks treatment with cimetidine 1.2 g or ranitidine 300 mg daily and with its longest diameter not less than 5 mm. Such a definition takes into account both the usual maximal length of short term antiulcer trials and the lack of knowledge, in some patients, of the initial ulcer size due to the fact that the first diagnosis was not always established in our unit. For the same reason, the total ulcer population from which this series was recruited could not be determined; however, a measure of the magnitude of refractory duodenal ulcer as a clinical problem in the population under study can be drawn from the analysis of the short term antiulcer controlled studies involving H2-blockers done in our unit in the last few years.

Pooled results of the different trials,¹²⁻¹⁵ show that the mean frequency of refractoriness to an eight week treatment with cimetidine or ranitidine is 11% and 7% respectively. The optimal medical management of resistant duodenal ulcers has not yet been standardised although the efficacy of mucosal protecting agents has been recently suggested.¹⁶ This controlled trial shows that TDB significantly speeds up the healing process of resistant ulcers. Indeed, the healing rate at four weeks was significantly higher on TDB (82%) than on cimetidine 1.2 g (39%) and on cimetidine 2 g (44%). After eight weeks, TDB cure rate (94%) was again numerically superior to those of both cimetidine schedules (65% and 75% respectively), but only when compared with the lowest dose the difference reached statistical significance. These findings confirm, therefore, the view that resistant duodenal ulcers are more responsive to an agent which strengthens the mucosal defences than to an antisecretory compound⁶ and suggest the hypothesis that in the pathogenesis of this type of ulcer a weakening of the protective capacity of the mucosa

Table 3 Endoscopic evaluation of ulcer healing after 4 and 8 weeks. In parentheses are reported the 95% confidence intervals for the differences

Treatment	Healed at 4 weeks	Healed at 8 weeks
Cimetidine 1.2 g	$\left[\begin{array}{c} 7/18 (39\%) \\ 7/16 (44\%) \end{array} \right] \dagger (-0.44 + 0.34)$	$\left[\begin{array}{c} 11/17 (65\%) \\ 12/16 (75\%) \end{array} \right] \dagger (-0.27 + 0.47)$
Cimetidine 2 g	$(+0.08 + 0.77)^* \left[\begin{array}{c} 7/16 (44\%) \\ 14/17 (82\%) \end{array} \right] \dagger (-0.01 + 0.74)$	$(+0.02 + 0.6)^* \left[\begin{array}{c} 12/16 (75\%) \\ 16/17 (94\%) \end{array} \right] \dagger (-0.11 + 0.49)$
TDB		

* $p<0.05$; †p ns.

Figure Antacid consumption (mean $\pm$ SEM) and pain behaviour in the three treatment groups during the first month of therapy.

plays a more important role than aggressive peptic forces. Likewise H₂-blockers, TDB is known to heal approximately 90% of duodenal ulcers within eight weeks,¹⁷ thus it should be worth evaluating whether cimetidine heals those 10% of ulcers that do not respond to an initial course of TDB.

Regarding the possible usefulness of higher H₂-antagonist dosage, as suggested by uncontrolled studies,^{4,5} our work documents the lack of a clear advantage in increasing the dose of cimetidine in patients with resistant ulcers. In fact, among those continuing H₂-blocker treatment any further healing appeared due to the length of therapy itself rather than to the dosage used; this compares well with that observed in 'responder' duodenal ulcers, in which the 2 g dose of cimetidine was not found to be more effective than the standard 1 g dose.¹⁸

The failure of the higher cimetidine dosage to improve the healing rate of the lower dose could be explained by the observation that in cimetidine non-responders increasing the dosage from 1 to 2 g daily did not result in any further increment of acid inhibition.¹⁹

In conclusion, two sets of information can be drawn from this study: first, when H₂-blockers fail to heal a duodenal ulcer within eight weeks, TDB should be the treatment of choice because it expedites the further healing process; second, many of these so called 'resistant' ulcers may be expected to heal simply by prolonging H₂-antagonists administration provided that enough time – that is, eight weeks, is given. In the latter case the standard dosage appears to be the most suitable regimen.

This work was presented in part at the spring meeting of the British Society of Gastroenterology in Lancaster, and published in abstract form (*Gut* 1986; 27: 612–3).

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