Randomised crossover trial of tripotassium dicitrato bismuthate versus high dose cimetidine for duodenal ulcers resistant to standard dose of cimetidine

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SUMMARY Of 212 patients with duodenal ulcer treated with four weeks of one gram daily cimetidine, 25 had ulcers which underwent no reduction in size despite treatment. The effects of tripotassium dicitrato bismuthate (TDB) tablet four times a day or cimetidine 1.6 g daily on the healing of these cimetidine resistant ulcers were compared in a randomised crossover trial. Ten of 12 patients on tripotassium dicitrato bismuthate and five of 13 patients on high dose cimetidine had complete healing ($p < 0.02$). On crossing over, seven of the eight ulcers not healed by high dose cimetidine completely healed with TDB in another four weeks, and one of the two ulcers not healed by TDB healed with high dose cimetidine. Overall, TDB healed 85% of cimetidine resistant ulcers, whereas high dose cimetidine healed 40% ($p < 0.006$). Tripotassium dicitrato bismuthate is recommended for cimetidine resistant duodenal ulcers.

Approximately 70% of duodenal ulcers would heal after four to six weeks of one gram daily cimetidine.^{1,2} There are no clear guidelines for the management of the cimetidine non-responders. Further cimetidine treatment for four to eight weeks may heal another 5-20% of patients.³ Switching over to ranitidine, a newer and more potent H_2 -receptor antagonist, has been reported with some success,⁴ but the evidence is not clear as the studies were not controlled. Surgery thus appears to be a reasonable treatment and is frequently advised.

Controlled trials have shown that the colloidal bismuth, tripotassium dicitrato bismuthate (TDB), also heals approximately 70% of patients with duodenal ulcer.⁵ Although the exact mechanism of healing is unknown, TDB has been shown to adhere preferentially to the ulcer base,⁶ and thereby exists a local action.

The aim of this study is to compare, using a randomised, controlled, crossover method, the efficacy of an increased dose of cimetidine vs TDB tablets, which are more palatable than the TDB liquid, in the healing of duodenal ulcers resistant to the standard dose of cimetidine.

Methods

PATIENTS

A duodenal ulcer is considered to be resistant to cimetidine (200 mg three times a day and 400 mg at bedtime), if at the end of four weeks of treatment its longest diameter as observed endoscopically has decreased by less than 25%, remained unchanged, or become bigger. The 25% limit was accepted because of the known variability of endoscopic estimation of ulcer size. Twenty five patients whose duodenal ulcers fit into these criteria were recruited from among 212 cimetidine treated patients. There were 17 men with a mean age of 48.0 years (range 21-65 years) and eight women with a mean age of 41.9 years (range 18-55 years). They did not have previous gastric surgery nor did they have any concomitant major medical problem such as cardiac, pulmonary, hepatic, or renal insufficiencies. None had a fasting serum gastrin concentration in the range of the Zollinger-Ellison syndrome.

TRIAL DESIGN

A series of new patients with endoscopically proven duodenal ulcer attending the ulcer clinic of the combined gastrointestinal unit underwent a programme which included a detailed recording of their clinical features, personal habits, and endo-

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scopic characteristics,⁷ as well as a two morning physiological measurement of their basal acid output, pentagastrin stimulated maximal acid output, pentagastrin D_{50} – that is, dose responsible for half maximal acid output derived from a dose response curve,⁸ fasting serum gastrin, and integrated gastrin response to a standard meal,⁹ in addition to routine haematology, biochemistry, and blood group. Caution was taken to stop such drugs as anticholinergics or H_2 -receptor antagonists for at least 72 hours before the physiological tests. They were treated with cimetidine 200 mg three times a day with meals and 400 mg at bedtime, and were reendoscoped at the end of four weeks. Drug compliance was checked by counting the returned drugs.

Thus the 25 patients underwent an initial endoscopy and the above tests, were then given the standard dose of cimetidine at the ulcer clinic for four weeks, and were found afterwards at reendoscopy to have a resistant duodenal ulcer. Their drug compliance for cimetidine was $94.6 \pm 0.5\%$. They were then randomised to either (1) tripotassium dicitrato bismuthate (Gist Brocades), one tablet to be chewed and swallowed half an hour before breakfast, lunch, and supper, and at bedtime, or (2) cimetidine (Smith, Kline & French Laboratories) orally 400 mg three times a day with meals and 400 mg at bedtime. Endoscopy was again performed after four weeks of outpatient treatment. If the ulcer was healed – that is, its base completely disappeared with or without residual inflammation (usually hyperaemia or granularity) – the study was ended. If the ulcer was not healed, the patient was crossed over to the other form of treatment for another four weeks, and reassessed subsequently by endoscopy. No other medications were given during the study period. Compliance was ascertained by recording the number of any remaining tablets in the returned bottle at the end of each treatment period. Each patient was given a diary card, on which the number of day time and night time pain episodes and their severity (mild, moderate, or severe) were recorded.

The endoscopist was not aware of the clinical data and any previous endoscopy results. The longest diameter was estimated using the tips of the biopsy forceps. Each patient was examined by the same endoscopist throughout the study.

Analysis of variance and χ^2 test with Yate's correction¹⁰ were used, and *p* values of less than 0.05 were considered significant.

Results

There were no significant differences between the

TDB treated and cimetidine treated patients with respect to the clinical, personal, physiological, and endoscopic characteristics listed in Table 1. No patient defaulted, and drug compliance was $91.8 \pm 0.5\%$ and $93.2 \pm 0.4\%$ respectively for the TDB groups and the cimetidine group. Compared with cimetidine, TDB resulted in significantly more healing but not symptomatic improvement in the initial four weeks of treatment and in the overall assessment after eight weeks of treatment (Table 2).

Discussion

Previous reports on cimetidine non-responders did not specify whether the ulcer size remained stationary despite treatment.³ It is possible that some of these ulcers became smaller at the end of the short term treatment, and should be more appropriately called slow responders. This study reports a series of duodenal ulcers the size of which remained unchanged after four weeks of one gram daily cimetidine; the mean ulcer diameter was in fact slightly larger afterwards. This series, therefore, are more likely to represent the truly cimetidine resistant ulcers. Such ulcers are uncommon and occurred in 11.8% of our duodenal ulcer population.

Increasing the dose of cimetidine to 1.6 g daily healed only about 40% of such cimetidine resistant ulcers, whereas the use of TDB tablets healed over 80%. The results of the subsequent crossover study further supports the efficacy of TDB, which again healed over 80% of the patients who did not respond to high dose of cimetidine. Overall, TDB achieved over 85% of success in cimetidine resistant patients, whereas increasing the dose of cimetidine achieved only about 40%, and the difference was statistically significant. It is to be noted that 1.6 g daily cimetidine is a particularly high dose for Chinese patients, since 0.5 g daily dose was shown to have identical acid inhibition and efficacy as the 1 g daily dose in these patients.¹¹

Short term TDB is known to heal approximately 70% of duodenal ulcers.⁵ The effectiveness of TDB in cimetidine resistant ulcers as shown in this study has important implications. Firstly, this suggests that acid inhibition is not important in the healing of such ulcers, as they represent cimetidine failures and TDB is not an antacid. Tripotassium dicitrato bismuthate forms a microscopic layer of bismuth which adheres to the base of an ulcer for at least six hours, and attracts a large influx of macrophages to the ulcer edge.⁶ The bismuth layer may insulate the ulcer from the aggressive peptic force in the bowel lumen. The role of the macrophages, which are

Table 1 Characteristics of patients treated with tripotassium dicitrato bismuthate (TDB) and cimetidine tablets

	TDB	Cimetidine 1.6 g/day	p<
Patient no	12	13	
Male, %	75.0	61.5	0.6
Age, yr	50.2±3.0	41.9±4.7	0.2
Age of onset of symptoms, yr	39.4±2.3	34.5±4.8	0.6
Early onset age (<30 yr), ¹⁴ %	33.3	38.5	0.6
Duration of symptoms, yr	10.6±2.6	7.0±1.6	0.2
Gastrointestinal bleeding, %	41.7	46.1	0.6
Family history of dyspepsia, %	33.3	46.1	0.5
Blood group O, %	33.3	46.1	0.5
Cigarette smokers, %	66.7	53.8	0.5
>20 cigarettes/day, %	58.3	38.5	0.3
Alcohol users, %	25.0	15.4	0.5
>50 g alcohol/day, %	16.7	15.4	0.6
Analgesic users, %	8.3	7.7	0.5
Basal acid output, mmol/h	2.3±0.7	3.1±0.8	0.5
Maximal acid output, mmol/h	25.7±3.1	27.4±2.7	0.7
mmol/h/kg	0.45±0.05	0.54±0.06	0.2
Hypersecretors (>0.45 mmol/h/kg), ¹⁵ %	50.0	61.5	0.5
D ₅₀ (corrected for basal acid), ng/kg/h	145±44	119±32	0.7
Fasting serum gastrin, nmol/l	40.2±5.5	50.1±7.5	0.6
Postprandial serum gastrin, nmol/min/l	10.8±1.4	10.0±1.4	0.7
Pain free before treatment, %	23.1	30.8	0.5
Longest ulcer diameter, mm			
Before standard dose of cimetidine	7.8±1.4	7.5±0.9	0.8
Before randomisation	8.3±0.9	8.7±1.1	0.8

known to be important in wound healing,¹² is as yet unknown. The exact mechanism of TDB in ulcer healing deserves further investigation.

Secondly, this study also suggests that cimetidine resistant duodenal ulcers may be regarded as a subgroup of duodenal ulcers with separate pathophysiology. It is now generally recognised that the physiologic abnormality of duodenal ulcer is heterogeneous.¹³ We have reported in a separate paper that patients whose ulcers do not heal by standard doses of cimetidine are more often cigarette

smokers who smoke more heavily, have more pentagastrin sensitive parietal cells, and have more apical ulcers and bigger ulcers than those whose ulcers heal after four weeks of treatment.⁷

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Table 2 Comparison of the efficacy of tripotassium dicitrato bismuthate (TDB) and high dose cimetidine in the treatment of duodenal ulcers resistant to standard dose of cimetidine

	TDB tablets	Cimetidine 1.6 g/day	p<
Initial treatment, no	12	13	
Healed, no (%)	10 (83.3)	5 (38.5)	0.02
Pain free week 1 (%)	50.0	46.1	0.66
week 4 (%)	83.3	76.9	0.52
Crossover, no	8	2	
Healed, no (%)	7 (87.5)	1 (50.0)	0.21
Pain free week 4 (%)	87.5	50.0	0.21
Overall, no	20	15	
Healed, no (%)	17 (85.0)	40.0	0.006

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