

Clinical trial

Gastric ulcer healing with tripotassium dicitrato bismuthate and subsequent relapse

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SUMMARY Fifty patients with endoscopically proven gastric ulcers completed a one month double-blind randomised trial of tripotassium dicitrato bismuthate (TDB) (DeNol) compared with an identical placebo. Ulcer healing occurred in 18 (72%) of the 25 patients given TDB and in nine (36%) of the patients given placebo. The TDB group experienced significantly less pain than the placebo group. During a follow-up of 29 patients with healed ulcers for up to 44 months, relapse occurred in 13 (45%). It was highest in the first three months (27%) and had risen to 41% at two years.

Several studies have shown that tripotassium dicitrato bismuthate (TDB) (DeNol) is effective in promoting the healing of duodenal ulcers.^{1 2} Its value in gastric ulceration is less clear because early trials were not double-blind.³ The sole trial in the United Kingdom studied treatment groups of only 10 patients.⁴ Recent reports from Australia and South Africa suggest that it is effective in increasing ulcer healing,⁵⁻⁷ but did not significantly improve symptoms.^{5 6} Gastric ulcer recurrence after healing with TDB has not been reported. This study represents the results of a double-blind randomised trial of TDB in gastric ulceration, showing its effect on ulcer healing, patients' symptoms, and subsequent ulcer recurrence.

Methods

PATIENTS

Ambulant patients who had been shown to have a gastric ulcer by fiberoptic endoscopy within the previous four days were admitted to the trial. Prepyloric ulcers were not included as these may behave differently from other gastric ulcers. The nature of the trial was fully explained to the patients and their consent obtained. Patients with other gastrointestinal diseases or who had previous gastric surgery were excluded, as was any patient who was

pregnant, had renal disease, and was taking corticosteroids or anti-inflammatory drugs. Patients were not included if they had taken carbenoxolone, TDB, or cimetidine in the previous month.

All patients were allocated at random in an unrestricted double-blind manner to receive TDB or placebo for four weeks, according to a code held and administered solely by the pharmacy. The aim of the trial was to study 50 patients, 25 in each group. The placebo had an identical smell, taste, and colour to TDB. All patients were supplied with unlabelled gelucil antacid tablets to be taken when necessary for relief of ulcer pain. Other therapy was forbidden and patients were asked not to alter their consumption of alcohol or cigarettes.

Symptoms were assessed before entering the trial. Subsequently, all patients were asked to record in diary cards the number of days and nights that pain was experienced, its severity, and the number of antacids consumed.

Patients were seen after four weeks, or earlier if necessary, and endoscoped within two days of completing treatment. Ulcer healing was rigidly defined as complete disappearance of the ulcer. After endoscopy, the diary cards were inspected, symptoms were recorded, and the patients examined. Patients were not asked about the colour of their motions. Drug consumption was checked by inquiry and by returned bottles. All endoscopic examinations and assessments of diary cards were performed by the author, but the double-blind

nature of the trial was preserved until its completion.

After the trial, patients whose ulcers failed to heal were treated for a further four weeks and, in some, eight weeks with active TDB and assessed as at the completion of the first four weeks.

Finally, the majority of patients treated with TDB whose ulcers had healed were reviewed after three months without treatment, or sooner if symptoms recurred, and the endoscopy repeated. The follow-up was continued for up to three years eight months and the endoscopy repeated if symptoms recurred.

At each visit patients were weighed and their blood pressure recorded. The haemoglobin, white cell count, liver function tests, blood urea, and electrolytes were also estimated and the urine examined.

Results

Fifty-six patients entered the trial during the two-year period. Six had to be withdrawn, because of the subsequent discovery of malignancy in three, recurrent haemorrhage in two, and persistent vomiting in one patient.

Of the 50 patients who completed the trial, 25 received TDB (DeNol) and a similar number placebo (Table 1). Patients in the two groups did not differ significantly with regard to their sex, mean age, mean duration of ulcer history, severity of symptoms, occurrence of bleeding, or length of recent hospital admission. Alcohol consumption was also similar but more patients in the placebo group were smokers. A higher proportion of the placebo patients, however, were light smokers, so that their daily cigarette consumption of 18.6 was not significantly different from the 16.8 of the TDB patients who smoked.

There was complete ulcer healing in 18 (72%) of the 25 patients on TDB, but in only nine (36%) of the 25 on placebo (Table 2). The treatment group showed a significant improvement over the placebo group ($p < 0.02$) by Fisher's exact test.

Ulcer healing occurred in all five female patients who received TDB but in only half of those on placebo, but the numbers were too small for this to

Table 2 *Healing of gastric ulcers*

	No.	Healed in	
		1 month	2 months
TDB	25	18 (72%)	24 (96%)
Placebo	25	9 (36%)	—

be statistically significant. The patients' age, smoking habits, length of previous history, recent gastrointestinal bleeding or initial length of in-patient treatment did not appear to be related to ulcer healing.

Twenty-two of the patients in the TDB group and 21 of the placebo group returned completed diaries. The number of days and nights per week in which pain was experienced was less after the first week in the TDB patients and this difference was significant in the third and fourth weeks of the trial ($p < 0.05$, $p < 0.01$ respectively) when analysed by the Mann Whitney test of ranking. Similarly, patients treated with TDB consumed significantly less ($p < 0.01$) gelucil antacids after the first week of the trial (Figs 1 and 2). After one month 18 (72%) of the TDB-treated patients were symptom-free compared with 13 (52%) of the placebo patients.

Symptoms in the patients whose ulcers healed were significantly less after the first week than in those whose ulcers remained unhealed ($p = < 0.02$ in the second week; $p = < 0.05$ third week; $p = < 0.01$ fourth week). All patients whose ulcers healed consumed less than a mean of four antacid tablets per day and all except two consumed less than three per day. Antacid consumption was less in patients whose ulcers healed and this was significant after the second week.

Of the seven gastric ulcers which failed to heal in the TDB group, six healed after a further four weeks of TDB (so that 24 (96%) healed in this group). Ten of the 16 unhealed ulcers in the placebo group healed after four weeks' TDB treatment and two more healed after a further month's therapy. Three of the five whose ulcers remained unhealed eventually responded to cimetidine, while two remained unhealed and were treated surgically.

Table 1 *Details of treatment groups*

	Completed trial	Sex		Mean age (yr)	Recent bleed	Smokers	Mean duration of disease (mth)
		M	F				
TDB	25	20	5	58.9	10	14	59.4
Placebo	25	17	8	59.8	9	20	64.1

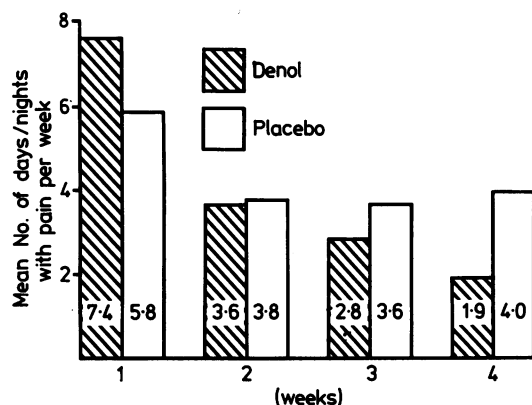


Fig. 1 Mean number of days/nights with pain per week in TDB and placebo groups.

FOLLOW-UP

Twenty-nine of the 36 patients who had received TDB and whose ulcers healed were reviewed after three months. Of the other seven patients, four refused further endoscopy, two died from unrelated causes, and one had been given cimetidine. Nine of the 29 had symptoms at three months and eight (27%) had endoscopic evidence of ulcer recurrence (Table 3). Thereafter, the total numbers of endoscopically proven recurrences were nine (31%) at six months and 12 (41%) at two years. So far, 13 (45%)

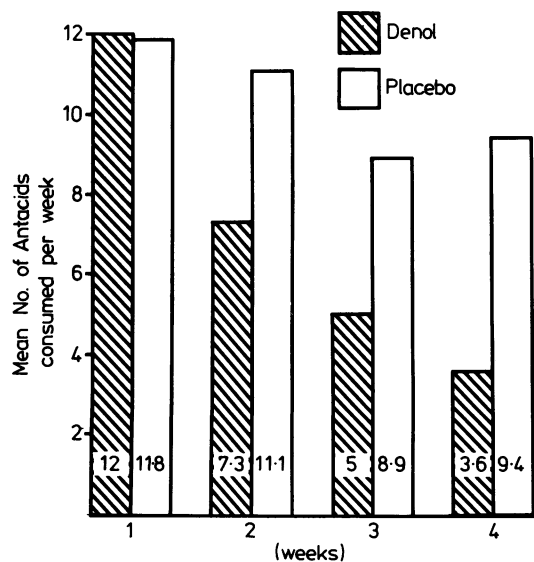


Fig. 2 Mean number of antacids consumed per week in TDB and placebo groups.

Table 3 Cumulative number and percentage relapses after ulcer healing

Patients (no.)	Relapse after ulcer healing (mth)				
	3	6	12	24	Up to 44
TDB	8 (27%)	9 (31%)	10 (34%)	12 (41%)	13 (45%)

ulcers have recurred during the follow-up period of between 24 and 44 months. Sixty-one per cent of the recurrences occurred within the first three months and 12 (92%) occurred within two years. Endoscopy was normal in two patients who had had recent symptoms.

Ulcers recurred in five (83%) of the six patients who required two months' TDB to heal their ulcers, compared with only eight (23%) of 23 who required one month's therapy.

Ulcer recurrence did not appear to be related to the patient's age, sex, smoking habits, previous gastrointestinal bleeding, or to the length of in-patient stay before the start of the trial. Surgical treatment was required for four of the 15 recurrent ulcers and overall for six (12%) of the 50 studied.

Only one patient, who was vomiting before entering the trial, was unable to tolerate TDB.

No patient experienced side-effects. Haematological indices, liver function tests, blood urea, electrolytes, serum creatinine, serum calcium, and urine remained within normal limits during the study.

Discussion

This study has demonstrated that four weeks' treatment with TDB greatly enhanced ulcer healing (72%) in ambulant outpatients when compared with placebo (36%). The healing rate rose to 96% after two months and this length of treatment would seem preferable to the month recommended by the manufacturers. Comparable healing rates of 66% and 90% were obtained in two endoscopically controlled trials published in Australia after four or six weeks' treatment with TDB.^{5,6} TDB-treated patients had significantly more pain-free days and nights during the second two weeks of the trial and consumed less antacids. It appears that TDB is of value in relieving symptoms in gastric ulceration but may not act as rapidly as cimetidine.⁸

Frequent strong antacid consumption may increase healing⁹ but in the present trial only small doses of a relatively weak antacid were used.

Several controlled trials have shown that carben-

oxolone sodium promotes gastric ulcer healing¹⁰ with rates of 37 to 67% after four weeks when compared with the placebo.¹¹ Unfortunately, aldosterone-like side-effects occur sufficiently frequently¹⁵ to limit its usefulness, especially in older patients.

Cimetidine has proved of great value in the management of duodenal ulceration, but its effectiveness in gastric ulceration has been variable, although in comparative studies it proved as effective as carbenoxolone¹² and TDB.⁵ In only two of the five published comparisons with placebo was it shown significantly to increase ulcer healing.⁸

Gastric ulcer recurrence is an important aspect of the treatment with any drug and has not previously been studied after TDB. During the follow-up, 41% of TDB-healed ulcers recurred within two years, which is similar to that reported from the Veterans Administration Co-operative Study¹³ of patients who had mostly received antacids. Recurrence rates of between 30% and 44% after one year have been reported from studies of placebo-treated ulcers with similar relapse rates after carbenoxolone¹¹ and after cimetidine.¹⁴ Asymptomatic ulcer recurrence did not occur in the first three months of follow-up but would not have been detected subsequently because only patients with symptoms were endoscoped. Ulcers which took longer to heal appeared to recur more frequently (83% as against 23%), although the number of patients who required two months' treatment was small. No such difference was found by Gwyn-Morgan *et al* using cimetidine,¹⁴ whose study also suggested that initial hospital treatment may reduce ulcer recurrence. This was not seen in the present study.

The study demonstrated that TDB is a safe, effective drug in reducing symptoms and healing gastric ulcers.

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