Clinical trial value of trimipramine versus placebo in duodenal ulcer healing

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SUMMARY Thirty-two patients with duodenal ulceration took trimipramine 50 mg or placebo. Fifteen patients on each treatment completed the study. Endoscopy at four weeks showed ulcer healing in seven (46%) patients on trimipramine, compared with only two (15%) on placebo ($P < 0.05$). However, by eight weeks there were eight (53%) patients in both groups with healed ulcers. There were no significant differences between the two groups in ulcer symptoms. Drowsiness was reported by eight patients on trimipramine compared with only one on placebo. Trimipramine 50 mg appears to increase the rate of ulcer healing in the short term. Side-effects at the dose used may limit its long-term usefulness.

Trimipramine, a tricyclic antidepressant, has been shown by Myren and co-workers¹⁻³ to be effective in healing duodenal ulcers. Though its mechanism of action is unclear, trimipramine appears to affect gastric secretion in a manner different from cimetidine or atropine.² In a recent clinical trial trimipramine 25 mg compared favourably with cimetidine 400 mg,⁴ but was less effective than cimetidine 1000 mg. The dose of trimipramine in clinical studies has varied between 25 and 50 mg and sometimes large amounts of antacids have been given in addition.⁴ We therefore looked at the healing rates of duodenal ulcers in patients on trimipramine 50 mg or placebo, who were allowed only limited amounts of mild antacid.

Methods

PATIENTS

Patients were selected from referrals to the endoscopy unit. They were included if they were between 18 and 65 years old, without other systemic disease,

and had not been on anti-ulcer drugs (including antidepressants) in the previous six weeks. Patients gave informed consent to inclusion in the study, which was approved by the hospital ethical committee.

Patients received either trimipramine 50 mg or matching placebo capsules as a single dose at bedtime for eight weeks. The treatments were randomised and the trial conducted double blind. All were given a measured supply of antacid tablets (Rennies) to use symptomatically. Capsules and antacid tablets were dispensed initially and after four weeks. Unused drugs were collected at four and eight weeks and counted.

Endoscopy was performed initially and after four and eight weeks. Each patient was endoscoped by the same clinician on each occasion. Blood pressure, electrocardiogram, full blood count, standard liver function tests, and plasma urea and electrolyte concentrations were recorded initially and after four and eight weeks.

Symptoms were assessed by questionnaire initially and after two, four, six, and eight weeks of treatment. The patients also recorded their symptoms on diary cards for eight weeks.

Statistical comparisons were made using Fisher's exact test to compare ulcer healing in the two groups, and Wilcoxon's rank sum test for comparison of symptoms recorded in questionnaires and diary cards. Student's *t* test was used to compare results of laboratory tests and tablet counts.

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Results

Thirty out of 32 patients completed the study. One patient on placebo withdrew because of ulcer symptoms, and one patient on trimipramine withdrew because of drowsiness which made him unsafe at work (roof tiling). Fifteen patients (four women and 11 men, mean age 42 years, including six smokers) received trimipramine, and an equal number received placebo (five women, 10 men, mean age 51 years, including six smokers). The two groups were well matched in their clinical characteristics.

Complete ulcer healing was noted in 46% of patients on trimipramine compared with 15% on placebo after four weeks. The differences were significant ($P < 0.05$). However, 53% of patients in both groups had complete ulcer healing at eight weeks. (Table 1). Consumption of capsules and antacid was similar in both groups during the first and second four-week periods. There were no significant differences between the groups when questioned initially and at two, four, six, and eight weeks of treatment about occurrence and severity of ulcer pain, sleep disturbance, and change in alertness. Analysis of diary cards similarly showed

Table 1 Trimipramine 50 mg versus placebo in duodenal ulcer healing: endoscopic healing in 30 patients

Duration of treatment (weeks)	Trimipramine (n 15) (no.) (%)		Placebo (n 15) (no.) (%)		P value
4	7	46	2	15	$< 0.05^*$
8	8	53	8	53	NS

*Fisher's exact test.

no differences between the groups with respect to ulcer pain, alertness, and general well-being.

Side-effects were commoner in the trimipramine group. Seven patients (excluding the one patient who withdrew) complained of drowsiness on trimipramine compared with only one patient on placebo. Patients on trimipramine also complained of dizziness (one), leg cramps (one), hot flushes (one), and depression (one). The placebo group complained of dizziness (two), headache (one), palpitations (one), and tiredness (one).

There were no changes in blood pressures, electrocardiograms, and laboratory tests in either group during the treatment period.

Discussion

In this study trimipramine increased the rate of duodenal ulcer healing over a four week period,

Table 2 Trimipramine versus placebo in duodenal ulcer healing: mean ($\pm$ SEM) consumption of trimipramine 50 mg or placebo capsules and antacid (Rennie) tablets

	Active group		Placebo group	
	Trimipramine	Rennies	Placebo	Rennies
Days 1 to 28	27 (± 1)	85 (± 19)	29 (± 0.4)	66 (± 15)
Days 29 to 56	27 (± 1)	80 (± 39)	28 (± 0.4)	60 (± 15)

but was no better than placebo after eight weeks' treatment (Table 2). The 46% ulcer healing on trimipramine in this study is similar to our previously observed four week healing figures for cimetidine and carbenoxolone: 47 and 41% respectively.⁵ The low four-week placebo healing rate was also noted by us in another study.⁶ We are unable to offer an explanation for the more rapid placebo healing rate in the second four week period of this study.

Berstad and colleagues reported duodenal ulcer healing in 86% of patients after six weeks of trimipramine 25 mg daily plus 120 ml antacid (neutralising capacity of 480 mmol).⁴ With trimipramine 50 mg daily Myren and colleagues³ found a duodenal ulcer healing rate of 75% at six weeks. However, the latter multicentre open study lacked a control group or limit on the intake of antacids. These trials have shown no difference in plasma trimipramine concentrations between patients with healed and active ulcers.

Reported side-effects of trimipramine in these trials have been fewer at 25 mg than 50 mg.^{3,4,7} Our finding of drowsiness in 50% of patients on trimipramine is similar to that noted by Myren and colleagues.³ Trimipramine at doses less than 50 mg has not been shown to inhibit gastric secretion in man.⁸ Consequently, the side-effects encountered with 50 mg in various studies would limit its long-term usefulness.

Additional studies are necessary to clarify the role of trimipramine in peptic ulcer healing and to define its usefulness in comparison with existing drugs, but the high incidence of drowsiness will probably prove an important limiting factor.

We thank Professor AE Read for allowing us to study patients under his care and May and Baker Ltd, Dagenham, for supplying trial materials and financial support.

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