

## COMPARISON OF ANTIULCER EFFECTS OF TRICYCLIC ANTIDEPRESSANTS WITH CIMETIDINE AND OMEPRAZOLE IN RATS

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### ABSTRACT

The antiulcer effects of different tricyclic antidepressants (trimipramine, doxepin, imipramine, and amitriptyline) in comparison with those of cimetidine, pirenzepine and omeprazole were investigated in male rats with acute gastric ulcer. Acute gastric ulcer was induced by oral administration of 0.6N HCl solution, 1 mL/rat.

Pretreatment of animals with doxepin, trimipramine, amitriptyline, imipramine (in doses of 10, 25, 40, 50, and 75 mg/kg, SC), cimetidine (in doses of 50, 75, 100, 150 and 200 mg/kg, SC), omeprazole and pirenzepine (in doses of 10, 20, 30, 40 and 50 mg/kg, SC) inhibited the formation of erosions dose-dependently.

The ED<sub>50</sub> of these agents revealed that the most active agents were omeprazole, doxepin and pirenzepine, followed by trimipramine and cimetidine. Imipramine and amitriptyline had slight antiulcer activity.

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### INTRODUCTION

Tricyclic antidepressants are widely used for the treatment of major depression. Recently these agents have been used in treating peptic ulcer.<sup>1</sup>

According to the findings of Mangla et al.<sup>4</sup> doxepin accelerated the healing of duodenal ulcers in man. The acute development of duodenal ulcer in rats has been inhibited by doxepin.<sup>2</sup>

There are several reports about the clinical effects of tricyclic antidepressants on duodenal ulcer. Therefore, this investigation has focused on the experimental effects of these agents on gastric lesions in rats.

The other purpose of the present study is to demonstrate the antiulcer effect of graded doses of tricyclic antidepressants in comparison with those of cimetidine, pirenzepine and omeprazole.

### MATERIALS AND METHODS

Male Wistar rats, weighing 220±25g were used. They were kept in a 12 hr light/dark cycle. The animals were placed in wire-bottomed cages and were starved for 24 hr before the experiments. The following drugs were given to different groups of rats (5 animals per group): doxepin hydrochloride, trimipramine maleate, amitriptyline hydrochloride (Sigma, USA) with doses of 10, 25, 40, 50 and 75 mg/kg (SC); cimetidine hydrochloride (Sigma, USA) with doses of 50, 75, 100, 150 and 200 mg/kg (SC); pirenzepine (Thomae, Germany) and omeprazole (MSD, Germany) with doses of 10, 20, 30, 40 and 50 mg/kg (SC). All of these drugs were injected 60 minutes before the administration of the ulcerogenic agent. The controls were given similar volumes of saline subcutaneously.

Gastric lesions were induced by 0.6N hydrochloric acid

(Merck, Germany) given orally in a volume of 1mL/rat; 1h later, all of the rats were killed, their stomachs were removed, cut open along the greater curvature, rinsed with saline solution and pinned flat onto a plastic board. After removal of hemorrhagic matter, the erosions could be seen. The gastric mucosa of each animal was examined, and the largest diameter of each ulcer was measured; ulcers measuring less than 1 mm were not scored. The value in centimeters of these determinations was considered as an ulcer index for each stomach.<sup>3</sup>

The results were shown in terms of a "preventive index" which is expressed as follows:

$$PI (\text{preventive index}) = \frac{UI (\text{ulcer index})_{\text{control}} - UI_{\text{test}}}{UI_{\text{control}}} \times 100 (\%)$$

For determination of the ED<sub>50</sub> values, however, the percentage change from control values was calculated and the effective dose<sub>50</sub> (the dose that reduced the ulcer to 50% of control value) was estimated graphically after plotting the data. The data were analyzed statistically by Student's t-test.

## RESULTS

Pretreatment of animals with doxepin, trimipramine, amitriptyline and imipramine in doses of 10, 25, 40, 50 and 75 mg/kg (SC) dose-dependently inhibited the formation of erosions by 0.6N HCl solution in the rat. Figs. 1 and 2 show the percent of inhibition of doxepin, trimipramine, imipramine and amitriptyline on gastric lesions. The ED<sub>50</sub> of doxepin and trimipramine was 15.9 mg/kg and 32.5 mg/kg, respectively.

The strongest effect was shown by doxepin, followed by trimipramine, imipramine and amitriptyline.

Fig. 3 shows that cimetidine, in doses of 50, 75, 100, 150 and 200 mg/kg (SC), produced a dose-dependent reduction in gastric lesions. Maximum reduction was produced by 200 mg/kg of the drug with a preventive index of 79.4%. The ED<sub>50</sub> of cimetidine was 114.7 mg/kg.

Fig. 4 shows that omeprazole and pirenzepine, in doses of 10, 20, 30, 40 and 50 mg/kg (SC), inhibited the formation of erosions in a dose-dependent manner. Maximum reduction was achieved by the 50 mg/kg dose of omeprazole and pirenzepine with preventive indices of 65% and 81.7%, respectively. The ED<sub>50</sub> was 2.9 mg/kg for omeprazole and 27.4 mg/kg for pirenzepine.

Plotting the preventive index against log doses of each drug gave the regression with the following equations:

Doxepin:	$y = 58.2x - 20$
Trimipramine:	$y = 84.2x - 77.7$
Imipramine:	$y = 38.9x - 35.6$
Amitriptyline:	$y = 69x - 78.7$

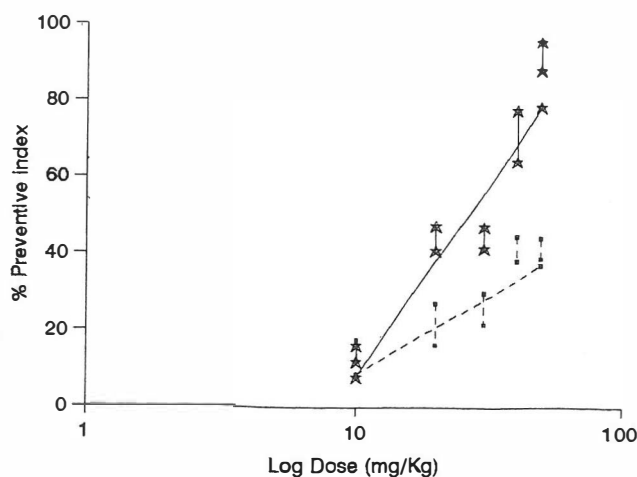


Fig. 1. The effects of different doses of amitriptyline (-----) and trimipramine (—) on gastric lesions induced by HCl. Values are mean (±S.E.M.) of 5 animals per group.

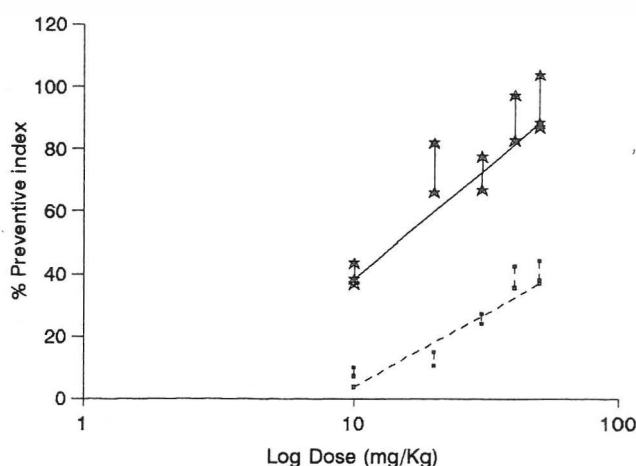


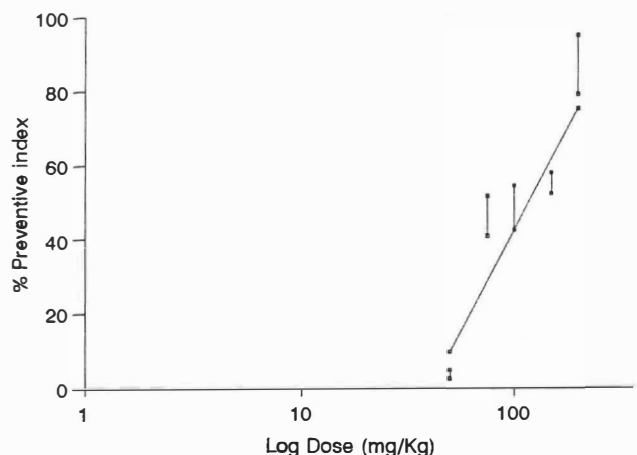
Fig. 2. The effects of different doses of imipramine (-----) and doxepin (—) on gastric lesions induced by HCl. Values are mean (±S.E.M.) of 5 animals per group.

Cimetidine:	$y = 115.4x - 187.7$
Omeprazole:	$y = 11.1x + 44.9$
Pirenzepine:	$y = 83x - 69.3$

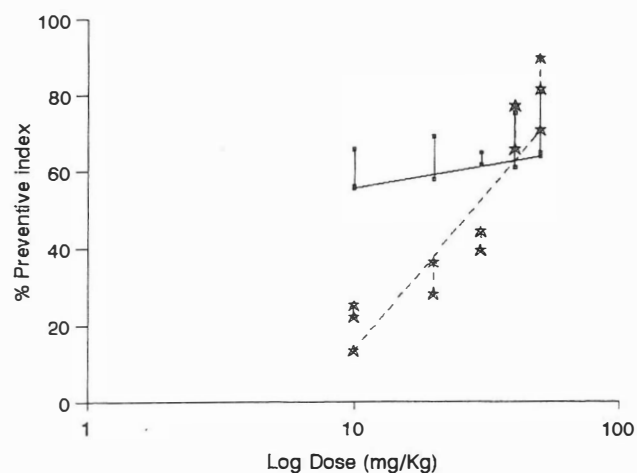
## DISCUSSION

There are several controversial reports concerning the antiulcer effect of tricyclic antidepressants. These drugs have been shown to produce healing of duodenal ulcers in cases where cimetidine had failed,<sup>4</sup> and differences in healing rate between cimetidine and trimipramine were not significant.<sup>5</sup> On the other hand, it has been demonstrated that trimipramine was less effective than cimetidine and no better than placebo.<sup>6</sup>

In light of the above conflicting results about the effects



**Fig. 3.** The effect of different doses of cimetidine on gastric lesions induced by HCl. Values are mean ( $\pm$ S.E.M.) of 5 animals per group.



**Fig. 4.** The effects of different doses of omeprazole (—) and pirenzepine (----) on gastric lesions induced by HCl. Values are mean ( $\pm$ S.E.M.) of 5 animals per group.

of tricyclic antidepressants on peptic ulcers, we studied the antiulcer properties of the tricyclic compounds doxepin, trimipramine, imipramine and amitriptyline. The strongest effect was shown by doxepin and trimipramine, followed by imipramine and amitriptyline.

Our results confirmed those of previous studies<sup>2,7-10</sup> indicating the antiulcer effect of tricyclic antidepressants.

This study also compared the antiulcer effect of tricyclic antidepressants with pirenzepine, omeprazole and cimetidine. The ED<sub>50</sub> of these agents show that the most active agents were omeprazole, doxepin, and pirenzepine, followed by trimipramine and cimetidine; imipramine and amitriptyline showed only slight antiulcer activity.

It has been shown that tricyclic antidepressants block H<sub>2</sub> receptors on parietal cells<sup>11</sup> and in animal brain models.<sup>12</sup> Doxepin also inhibits muscarinic receptors peripherally and

centrally.<sup>13</sup> Based on the above results, both antihistaminergic and anticholinergic effects of doxepin, peripherally and centrally, may contribute to its antiulcer action.

We demonstrated that doxepin had the strongest effect compared with the other tricyclic antidepressants. This is in agreement with the results of other investigators who showed that doxepin had the most potent antihistaminic property in comparison with other available tricyclic compounds.<sup>4</sup> It was also shown that doxepin was as effective as cimetidine in inhibition of histamine H<sub>2</sub> receptors in guinea pig brain.<sup>12</sup>

The antidepressant and sedative effects of tricyclic antidepressants may also contribute to their ability to heal ulcers. It was suggested that trimipramine may have a beneficial effect on masked depression, a condition often found in patients with duodenal ulcers.<sup>1</sup> Additional research is needed to establish the place of tricyclic agents in the overall treatment of peptic ulcer disease.

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