

# A COMPARATIVE STUDY OF THE EFFECTS OF VERAPAMIL AND CIMETIDINE ON ISOLATED RAT STOMACH STRIP

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## ABSTRACT

Effects of verapamil and cimetidine were studied on smooth muscle of rat stomach by using an isolated fundus strip preparation. Verapamil 0.5 ug/ml significantly ( $P < 0.001$ ) reduced acetylcholine (Ach) induced contractions of rat stomach fundus strip. The inhibition was very prolong and dose dependent. On the other hand cimetidine 60 ug/ml significantly ( $P < 0.001$ ) potentiated the Ach-induced contractions, potentiation was dose related. The spontaneous contractions of stomach strip were completely abolished by 8 ug/ml verapamil, whereas 1000ug/ml cimetidine had no effect. It was concluded that verapamil given for cardiovascular disorders would also supplement relief of pain from peptic ulcer and might prevent stress ulcer formation (JPMA 40 : 263 , 1990).

## INTRODUCTION

In the stomach, motility and acid secretion have been shown to be dependent to some extent on calcium ions and are likely to be modified by calcium channel blockers.<sup>1</sup> Verapamil inhibits motility in rat isolated colon by acting on calcium channels in the smooth muscle cell membrane<sup>2</sup>. Gastrointestinal smooth muscle contains both histamine H<sub>1</sub> and H<sub>2</sub> receptors. Stimulation of H<sub>1</sub> receptors leads to contraction and stimulation of H<sub>2</sub> receptors to relaxation of gastrointestinal smooth muscle cells. Histamine<sup>3</sup> H<sub>2</sub> blockers may constitute molecular dependent side effects of gastrointestinal tract<sup>4</sup>. If calcium channel blockers are proved to be effective in reducing peptic ulceration, the undesirable effects of histamine H<sub>2</sub> antagonists may be avoided. The effects of stress which are exerted mostly on cardiovascular<sup>5</sup> and gastrointestinal systems<sup>6</sup> may also be ameliorated with drugs like calcium antagonists which have proved very useful for most of cardiovascular disorders.<sup>7</sup> Verapamil and nifedipine were shown to inhibit gastric acidity in conscious rats<sup>8</sup>. Present study was undertaken to compare the effects of verapamil and cimetidine on smooth muscle of rat stomach.

## MATERIALS AND METHODS

A fundus strip of rat stomach 3-4 cms in length was mounted in an organ bath containing physiological solution, aerated with 100% oxygen flowing at moderate speed with the temperature maintained at 37°C. The composition of solution in mM/L was : NaCl (110) ; NaHCO<sub>3</sub> (24); KCl (5.0); Na<sub>2</sub>HPO<sub>4</sub> 7H<sub>2</sub>O (1.1); CaCl<sub>2</sub> (2.2); Mg SO<sub>4</sub> (1.2) and glucose (5.5)<sup>9,10</sup>. One end of strip was attached to O<sub>2</sub> delivery tube and other to a simple heavy lever writing sideways with ink on a kymograph. An initial resting tension of was applied to each muscle strip and the tissues were allowed to equilibrate for 30 min.<sup>11</sup> In response to the administration of acetylcholine, intensity of each contraction was recorded on kymograph and its amplitude was measured in millimeters. Ach 8 ug/ml, producing submaximal response, was used to test the sensitivity of tissue to verapamil and cimetidine. After instillation of verapamil the tissue recovered slowly, therefore a long duration time cycle of 30 minutes was followed. When antagonist was used it was allowed to act for 5 minutes before the addition of agonist. Effects of

verapamil and cimetidine on Ach induced contractions were studied at 3 and 4 dose levels respectively. Effects of verapamil (8ug/ml) and cimetidine (1000 ug/ml) on spontaneous contractions of rat stomach strip were also observed. A short duration time cycle of 4 mm. was followed. The drugs were allowed to act for 3 mm. before taking the record of tracings on kymograph.

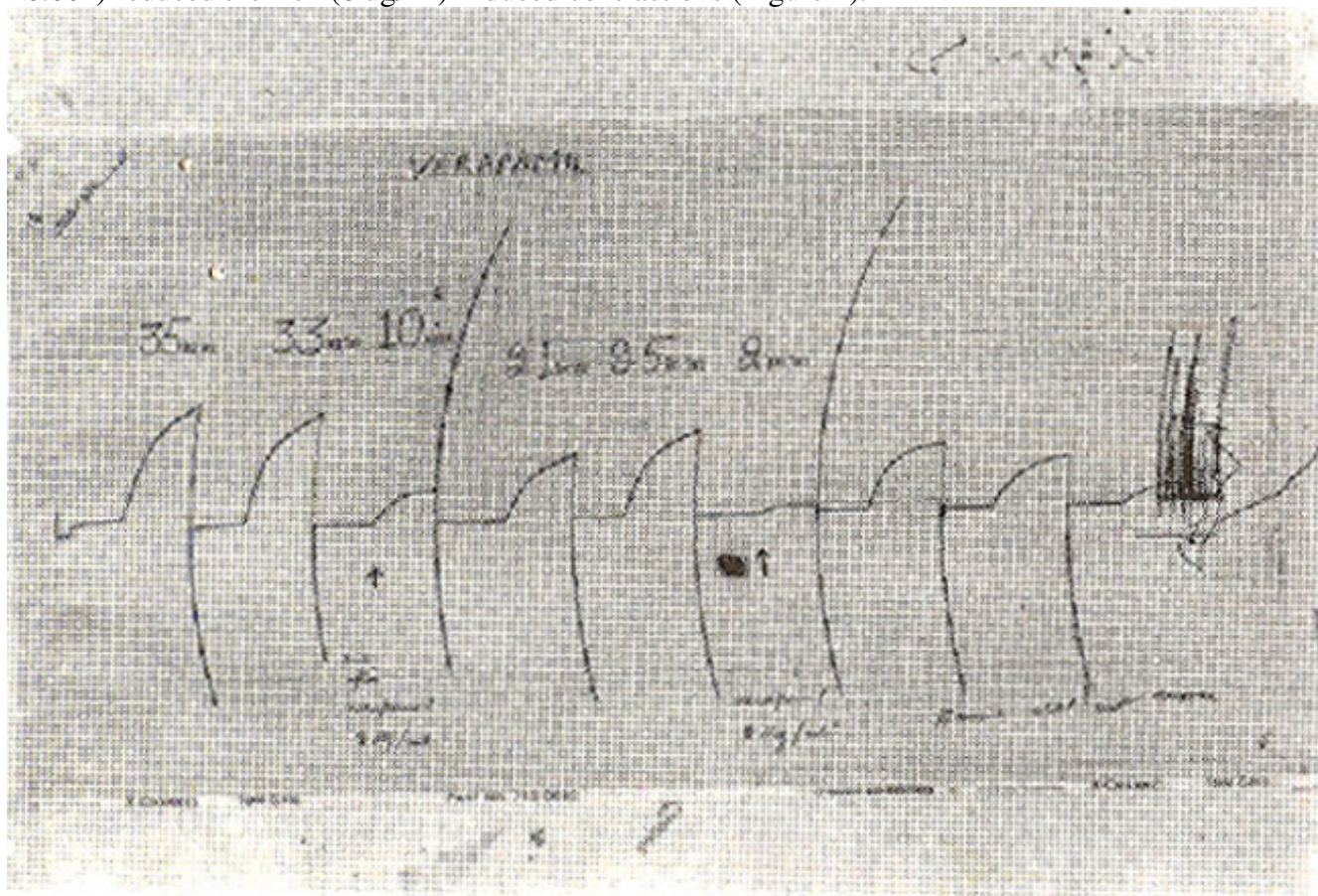
### Statistical analysis

Seven samples of size six each were taken as a self-control to see the effects of three doses of verapamil and four doses of cimetidine. The mean difference before and after the treatment in self-control group were tested using the paired students 't' test for correlated means. The ED50 i.e., medium effective dose (concentration/mi producing 50% change in amplitude of Ach induced response) was calculated from a graph plotted by taking log doses as independent variable and mean percent change as dependent variable.

## RESULTS

### (a) Induced contractions

When allowed to act for 5 minutes verapamil in concentrations of 0.5, 2 and 8ug/ml significantly ( $P < 0.001$ ) reduced the Ach (8ug/ml)-induced contractions (Figure 1).



**Figure 1. Effect of verapamil on Ach-induced contractions of rat fundus strip preparation.**

The intensity of inhibition was concentration dependent (Table 1 and Figure 2).

TABLE I. Effect of drug on Ach-induced contractions of rat stomach fundus strip preparation.

Drugs	Dose ( $\mu\text{g/ml}$ )	n	Mean response with Ach (mm)	Mean response with Ach + drug (mm)	Inhibition	Potentialion
Verapamil	0.5	6	34.8	25.5	$27 \pm 0.6\%$ P < 0.001	
	2.0	6	29.7	18.0	$39 \pm 0.2\%$ P < 0.001	
	8.0	6	32.8	15.5	$53.5 \pm 1.4\%$ P < 0.001	
Cimetidine	60	6	22.7	36.5		$38 \pm 1.2\%$ P < 0.001
	125	6	24.7	44.3		$44 \pm 2.3\%$ P < 0.001
	500	6	21.5	48.5		$55.5 \pm 3.7\%$ P < 0.001
	1000	6	20.0	55.0		$62.5 \pm 5.6\%$ P < 0.001

$\mu\text{g/ml}$  = microgram per milliliter

n = No. of observations

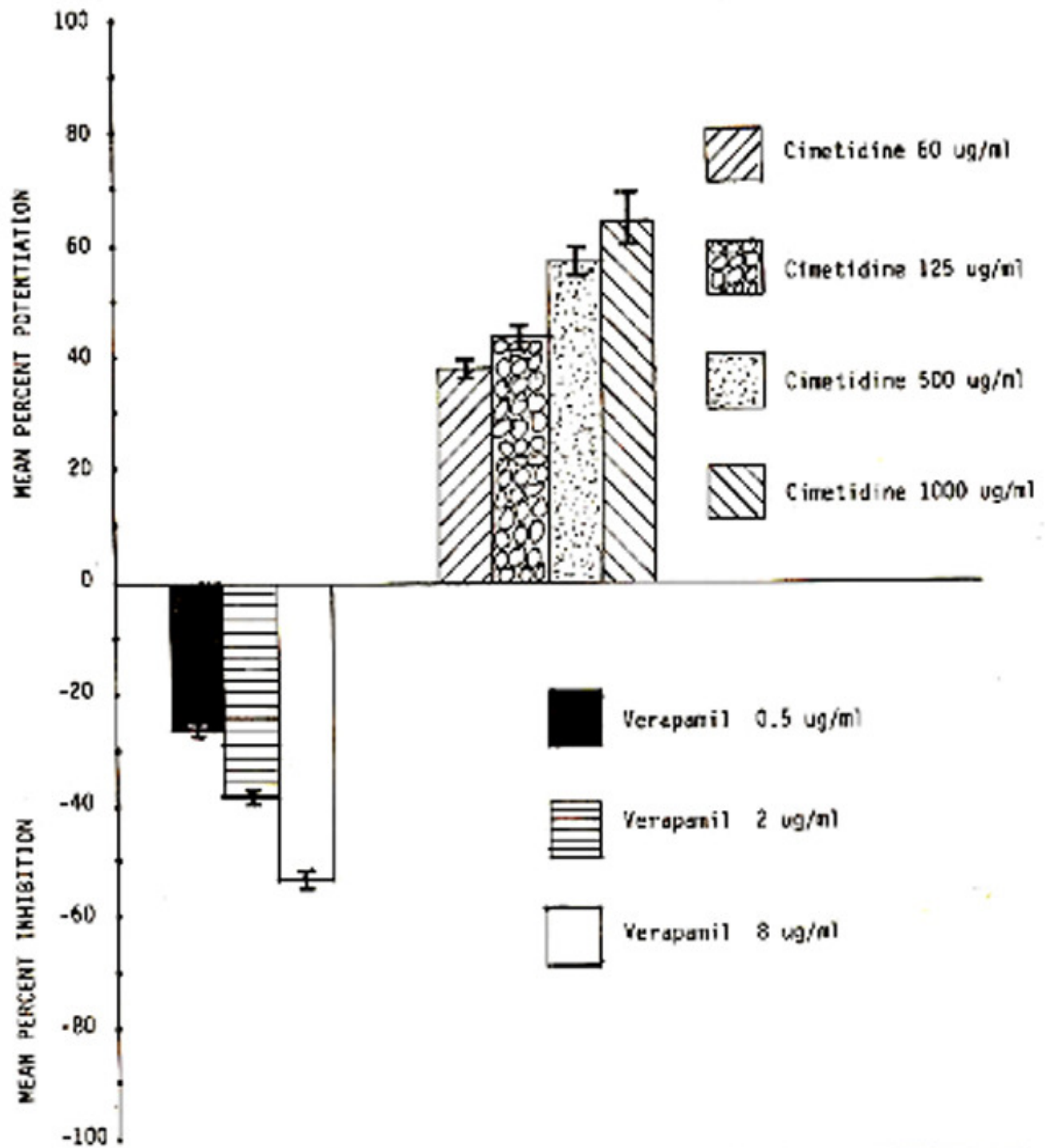
mm = millimeter

Ach = acetylcholine

$\pm$  = Standard error of mean of differences (s.e., m.d.)

p = Probability

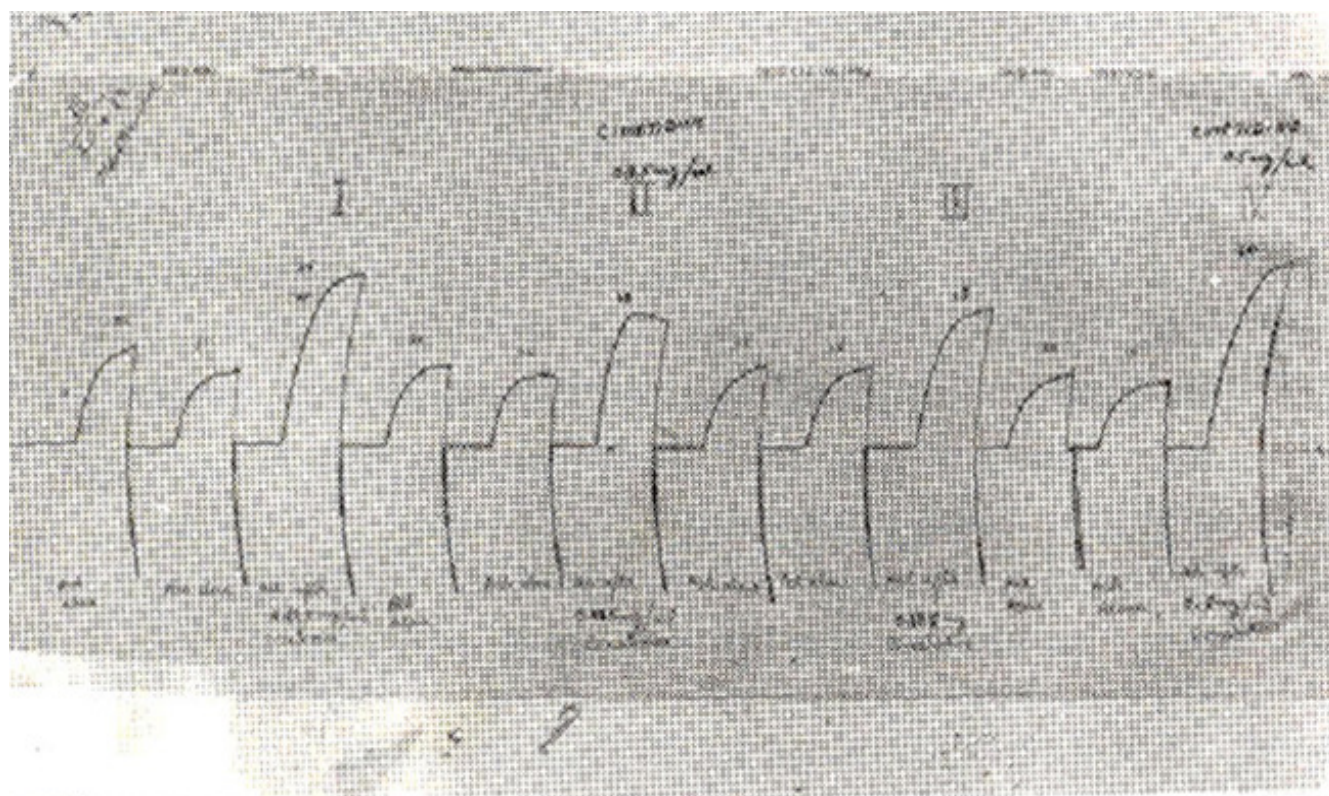
Each dose was tried on a separate tissue for each observation.



**Figure 2. Effect of verapamil and cimetidine on Ach-induced contractions of rat isolated stomach strip.**

Recovery from inhibition was only with very low concentrations. In concentrations producing significant inhibition ( $P < 0.001$ ) recovery was very slow and usually incomplete. Cimetidine in 60, 125, 500 and 1000 ug/ml concentration significantly ( $P < 0.001$ ) potentiated Ach (8 ug/ml) induced contractions (Figure 3).





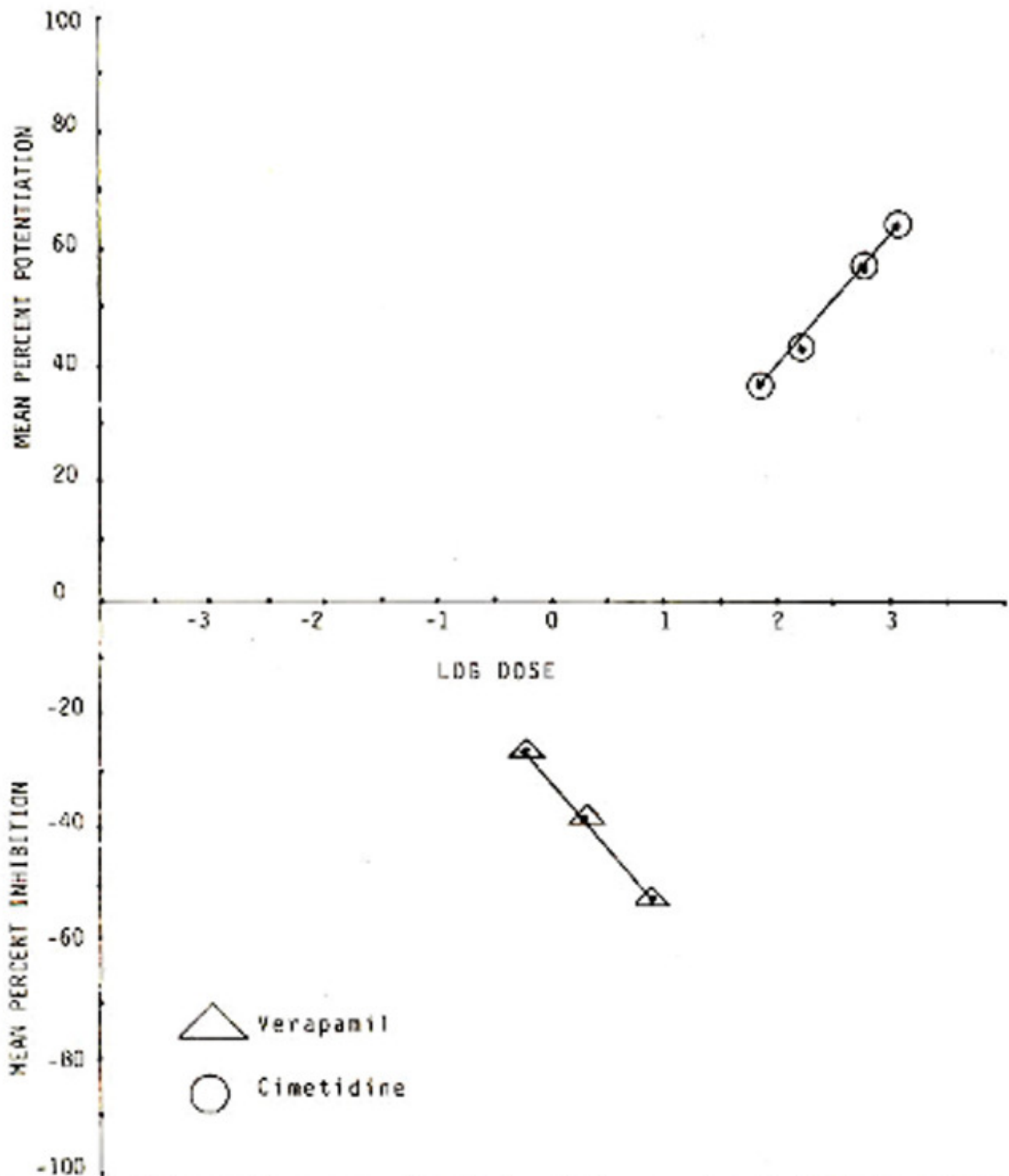
**Figure 3. Cimetidine and dose dependent potentiation of Ach-induced contractions.**

Intensity of potentiation was concentration related (Table II and Figure 2).

**TABLE II. Comparison of effects of Verapamil and Cimetidine on gastric motility in vitro.**

Observations	Verapamil	Cimetidine
1. Effects on Ach-induced Contractions	Inhibition	Potentialiation
2. Dose	Dose related	Dose related
3. Recovery (duration of action)	Very slow and usually incomplete. (prolong)	Moderately slow and complete (short)
4. Dose-response curve	Slope of curve less steep.	Slope of curve like that of Verapamil.
5. ED <sub>50</sub>	5.888 ug/ml	234.423 $\mu$ g/ml
6. Pendular movements of gastric smooth muscle.	Completely abolished with 8 $\mu$ g/ml.	No effect even with 1000 $\mu$ g/ml.

Recovery was moderately slow but complete. The ED<sub>50</sub> of verapamil was about 40 times lower than that of cimetidine. Dose response curve had shown that both drugs will produce ceiling effect with increase in dose (Figure 4).



**Figure 4. Effect of verapamil and cimetidine on Ach-induced contractions in rat isolated stomach strip.**

**(b) Spontaneous contractions**

Verapamil (8 ug/ml) completely abolished the spontaneous contractions of stomach strip. Cimetidine (1000 ug/ml) had no effect.

## DISCUSSION

Increase in gastric motility during stress appears to cause ulcers in stressed pylorus occluded rats<sup>12</sup>. In the present work verapamil inhibited acetylcholine induced contractions of rat stomach in a dose dependent manner. In the past verapamil was shown to prevent acetylcholine induced contractions in guinea pig stomach strip.<sup>13</sup> In another study it prevented stress produced increase in gastric motility in a dose dependent manner in intact rats.<sup>14</sup> Presently  $1.76 \times 10^{-4}$  mol/L verapamil completely abolished the spontaneous contractions of isolated fundus strip of rat stomach. Other investigators found that verapamil  $10^{-3}$  mol/L entirely inhibited isolated toad gastric muscle contractions.<sup>15</sup> Cimetidine 1 mg/ml had no effect on spontaneous contractions of rat stomach strip. Previously 0.3mg cimetidine in 50ml bath was shown to have no effect on spontaneous contractions of rat stomach tissue<sup>9</sup>. Cimetidine  $9.3 \times 10^{-4}$  mol/L produced 50% potentiation (ED<sub>50</sub>) of Ach induced contractions in isolated stomach strip (P < 0.001). Previously  $1.2 \times 10^{-4}$  mol/L and  $4.0 \times 10^{-4}$  mol/L cimetidine had no significant effect on histamine or bethanechol induced contractions of guinea pig isolated ileum. Recently one case of stomach and three cases of esophagus have been reported showing stimulatory response to cimetidine in human. Present work has shown that cimetidine had no effect on spontaneous contractions but potentiates Ach induced contractions. Verapamil inhibits spontaneous as well as acetylcholine induced contractions of rat stomach strip. A physical rubbing of the gastric mucosa after its vitality has been reduced by stress may trigger the formation of stress ulcers in intact rats.<sup>17</sup> Therefore, it is likely that verapamil used for cardiovascular disorders would also have additional benefit of preventing stress ulcer formation.

## ACKNOWLEDGEMENT

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