COMPARISON OF EFFECTS OF VERAPAMIL AND RANITIDINE ON VOLUME AND ACIDITY OF CARBACHOL INDUCED GASTRIC SECRETION

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SUMMARY

Peptic ulcer is a common ailment for which gastric acid secretion is the main cause. This study was conducted to observe the effects of histamine H₂-receptors antagonist ranitidine and calcium channel blocker verapamil on the volume, free acidity and total acidity of carbachol induced gastric secretion. Eighteen albino rats of Sprague Dawley strain weighing 150-200 grams were used. After fasting for 48 hours, pylorus of each animal was ligated, verapamil 10 mg/Kg, ranitidine 0.5 mg/Kg and carbachol 600 ng/Kg body weight were used intraperitoneally. It was observed that ranitidine reduced both the volume and acidity of gastric secretion which were statistically highly significant when compared with carbachol (p < 0.001). Similarly verapamil also reduced volume, free acidity and total acidity which were highly significant when compared with carbachol. When the differences of means brought about by ranitidine were compared with those of verapamil, all these differences were statistically non significant indicating that verapamil has got similar effect to that of ranitidine on the inhibition of volume and acidity induced by carbachol and it may be used effectively in the treatment of peptic ulcer.

INTRODUCTION

Peptic ulcer is one of the most common ailments, the physician comes across in the clinical practice. Increased acid production from gastric mucosa is responsible for peptic ulceration in majority of the patients. Ulcers are not found in achlorhydric patients and almost always occur in patients with Zollinger Ellison (Z.E.) syndrome which is characterized by very high acid secretion. Inhibition of over production of acid is a desirable therapeutic goal in the treatment of peptic ulcer. Suppression of gastric acid secretion with histamine H₂-receptor antagonist ranitidine is used very commonly in Zollinger Ellison syndrome and other conditions with peptic ulceration.

The calcium channel blocking agents like verapamil, nifedipine and diltiazem are commonly used in the treatment of hypertension, angina, myocardial infarction and supraventricular tachycardia.

There is evidence that a raised calcium level in blood promotes an increase in gastric secretion and this may account for high incidence of peptic ulceration in patients with hyperparathyroidism. Induction of hypercalcaemia with intravenous administration of calcium is usually associated with increased gastric volume and acidity. The acid stimulating ability of calcium is well known and extreme sensitivity to calcium in patients with Z.E. syndrome is also documented.
**TABLE - I**

EFFECT OF RANITIDINE AND VERAPAMIL ON THE VOLUME AND ACIDITY OF CARBACHOL INDUCED GASTRIC SECRETION

<table>
<thead>
<tr>
<th>Drug</th>
<th>Volume (ml)</th>
<th>Free acidity (mEq/dl)</th>
<th>Total acidity (mEq/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbachol</td>
<td>9.00±0.58</td>
<td>8.399±0.21</td>
<td>13.22±0.27</td>
</tr>
<tr>
<td>(Control)</td>
<td>(6)</td>
<td>(6)</td>
<td>(6)</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>5.40±0.28</td>
<td>2.99±0.26</td>
<td>7.506±0.83</td>
</tr>
<tr>
<td></td>
<td>(6)</td>
<td>(6)</td>
<td>(6)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Verapamil</td>
<td>5.75±0.28</td>
<td>3.139±0.27</td>
<td>8.126±0.49</td>
</tr>
<tr>
<td></td>
<td>(6)</td>
<td>(6)</td>
<td>(6)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Each value represents mean of total observations.
Figures in parenthesis indicate number of animals.
P value when compared with carbachol group.

![Graph 1](image1)
![Graph 2](image2)

**Fig. 1.** Effect of ranitidine and verapamil on the volume and acidity of carbachol induced gastric secretion in fasting rats. Verapamil was administered 10 mg/kg body weight, ranitidine 0/5 mg/kg and carbachol 600 μgm/kg body weight (I.P.).

**Fig. 2.** Differences in volume, free acidity and total acidity produced by ranitidine and verapamil in carbachol induced gastric secretion in fasting rats. Ranitidine was administered 0.5 mg/kg body weight and verapamil 10 mg/kg body weight (I.P.).
### TABLE II
DIFFERENCES IN VOLUME, FREE ACIDITY AND TOTAL ACIDITY PRODUCED BY RANITIDINE AND VERAPAMIL IN CARBACHOL INDUCED GASTRIC SECRETION

<table>
<thead>
<tr>
<th>Drug</th>
<th>Volume (ml)</th>
<th>Free acidity (mEq/dl)</th>
<th>Total acidity (mEq/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranitidine</td>
<td>3.50±0.60</td>
<td>5.408±0.296</td>
<td>5.714±0.944</td>
</tr>
<tr>
<td>Verapamil</td>
<td>5.75±0.28</td>
<td>3.139±0.27</td>
<td>8.126±0.49</td>
</tr>
</tbody>
</table>

Each value represents mean of difference of total observations.
Figures in parenthesis indicate number of animals.
± indicates standard error.
P values for significance of difference between verapamil and ranitidine.
N.S. Non significant.

Calcium channel blocker verapamil may interfere the H+, K+ ATPase due to its high affinity for K+ site of H+K+ ATPase system which is accessible from luminal side of the stomach. Histamine release from peritoneal mast cells is critically dependent upon external Ca2+ concentration, so non-availability of Ca2+ may cause reduced effects of histamine on acid production in the stomach. Calcium channel blockers have been mainly used in CVS as inhibitors of muscle contraction. In the stomach, motility and acid secretion which have been shown to be dependent upon calcium ions, are likely to be modified by calcium channel blockers so this study was planned to evaluate the efficacy of calcium channel blocker verapamil and to compare it with H2-receptor antagonist ranitidine.

### MATERIAL AND METHODS

Eighteen (18) rats belonging to Sprague Dawley strain were selected for the present work. Healthy animals of both sexes weighing 150–200 gms were used in the study. The animals were obtained from animal house of JPMC, Karachi and all the experiments were performed in the Department of Pharmacology and Therapeutics, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi. All the animals were kept fasting for 48 hours with free availability of water before they were subjected to the experiment. The animals were divided into 3 groups comprising of 6 rats each.

A-Control group carbachol treated.
B-Ranitidine + carbachol treated.
C-Verapamil + carbachol treated.

The operative procedure was the one adopted by Visscher et al. Animals were anaesthetized with ether, abdomen opened and pylorus was ligated with silk suture. Then abdominal wall was closed with suture clips and intraperitoneal (IP) injection of carbachol 600 μg/Kg body weight to group A, 0.5 mg/Kg body weight, ranitidine to group B and 10 mg/Kg body weight verapamil to group C followed by carbachol 600 μg/Kg body weight after 15 minutes to group B and C were administered. The rats were deprived of water for four hours after administration of drugs. Then the rats were sacrificed with chloroform anaesthesia, the thorax and abdomen opened, oesophagus
ligated and the stomach was removed quickly. The contents of the stomach were collected. The volume of the gastric juice was measured. Then the contents were centrifuged, filtered and subjected to titration for estimation of free and total acidity by the method described by Varley. One ml of centrifuged and filtered gastric secretion was titrated against 0.1 N NaOH using Topfer’s reagent (pH range 2.9-4.4) for determination of free acid, and 1% phenolphthalein as indicator for determination of combined acidity. The sum of the two titration was total acidity. The data was analysed statistically using student “t” test.

RESULTS

The volume, free acidity and total acidity of gastric secretion in group A (carbachol treated control) was 9.0±0.58 ml, 8.39±0.21 mEq/dl and 13.2±0.27 mEq/dl respectively. The volume, free acidity and total acidity in group B (ranitidine and carbachol treated) was 5.4±0.23 ml, 2.9±0.26 mEq/dl and 7.50±0.83 mEq/dl respectively. The reductions noticed in all the parameters were found to be highly significant (P < 0.001). Similarly the volume, free acidity and total acidity in group C (verapamil and carbachol treated) was 5.75±0.28 ml, 3.13±0.27 mEq/dl and 8.12±0.49 mEq/dl respectively. All these reductions were also found to be statistically highly significant when compared with the control (P < 0.001) Table I.

For the comparison of effects of two drugs ranitidine and varapamil on volume and acidity of carbachol induced gastric secretion, the differences produced by the two drugs were analysed statistically (Table II). The mean values for differences of means for volume, free acidity and total acidity in ranitidine treated group were 3.5±0.6 ml, 5.408±0.286 mEq/dl, 5.71±0.944 mEq/dl respectively, and the value for the same parameters in varapamil treated group were 3.30±0.52 ml, 5.26±0.303 mEq/dl and 5.09±0.608 mEq/dl. The differences in all the three parameters between two groups were found to be non significant.

DISCUSSION

Acid secretion in the stomach is controlled at a variety of levels by neural hormonal and paracrine mechanisms. When these regulatory mechanisms malfunction, acid and pepsin autodigest the mucosa resulting in the ulceration of oesophagus, stomach and duodenum.

Histamine, acetylcholine or carbachol are potent secretagogues for the parietal cells of gastric mucosa leading to the production of HCl.

Acetylcholine and gastrin act through calcium ions. Carbachol being a cholinomimetic drug increases free intracellular calcium ions which activate protein kinases by phosphorylation and lead to increased production of HCl. In this study we observed that ranitidine reduced the volume, free acidity and total acidity. All these reductions were statistically highly significant when compared with the mean values in carbachol treated rats (control). Our study correlates with the work of many workers who observed that ranitidine significantly reduces the volume and acidity of gastric secretion. This is due to well known H$_2$-receptor antagonistic action of ranitidine which interacts with H$_2$-receptor and inhibits the activation of adenylate cyclase and as a result no cyclic AMP is formed which is required for HCl production. We observed almost similar reductions using verapamil. All these reductions were found to be statistically highly significant when compared with control. Our study correlates with other workers who concluded that verapamil significantly reduces gastric acid secretin. Calcium may induce gastric secretion other than by gastrin release including vagal stimulation, local
cholinergic effects, increased sensitivity to acetylcholine and calcium dependent acetylcholine release and enhancement of intracellular spread of excitation promoting the coupling between exterior excitation. Verapamil, a well known calcium channel blocker inhibits the calcium influx, which may be responsible for the observed reductions in volume and acidity of gastric secretion. Beside this, verapamil inhibits lipoxygenase pathway during metabolism of arachidonic acid that so leukotriene, the injurious substance is not formed and all the arachidonic acid is metabolized through cyclooxygenase pathway and leads to the production of prostaglandin which couple with Gi protein and inhibits adenylate cyclase and thus decrease HCl production.\(^{19}\)

Release of histamine from mast cells critically depends on external calcium ions, so verapamil by blocking calcium ions can block histamine release which is a potent agent for HCl secretion.\(^{19}\)

When we compared differences produced in the mean values of volume, free acidity and total acidity by ranitidine and verapamil, they were all non significant. This indicates that verapamil is almost as effective as ranitidine in decreasing volume, free and total acidity of gastric secretion. Verapamil is also used in controlling contraction of cardiovascular smooth muscles,\(^{20}\) allergic reaction\(^{21}\) and prevention of premature labor.\(^{22}\)

**CONCLUSION**

It is concluded that verapamil may be beneficially used as a single drug therapy in patients having peptic ulcer concurrent with angina, myocardial infarction, prevention of premature labor or bronchial asthma. Further human studies in this regard for evaluation of these effects are suggested.

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