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

Muhammad Jan, Muhammad Azhar Mughal*, Ramesh Kumar Tanwani**, Kausar Aamir***, Mehar Ali**

Departments of Pharmacology Saidu Medical College Swat, *Sir Syed Medical College Karachi, ** Jinnah Medical College Karachi, ***BMSI, JPMC, Karachi

Background: This study was conducted to observe the effect of H_2-receptor antagonist Ranitidine and calcium channel blocker Verapamil on the volume, free and total acidity of carbachol induced gastric secretion. Methods: Twenty four albino rats of Sprangue Dawley strain weighing 150-200 grams were used. Animals were divided into Four groups. After fasting for 48 hours, pylorus of each animal was ligated, verapamil 10mg/Kg, ranitidine 0.5 mg/Kg and carbachol 600 µg/Kg body weight were administered intraperitoneally. Results: It was observed that ranitidine significantly reduced both the volume and acidity ($p<0.001$). Similarly Verapamil also significantly reduced the volume, free and total acidity when compared to carbachol alone. When verapamil was used in combination with ranitidine 15 minutes before carbachol, there was further inhibition of volume and acidity as compared to ranitidine alone. This reduction was statistically highly significant ($p<0.001$). Conclusion: Our study suggests that combined therapy of verapamil and ranitidine may have clinical usefulness in the management of severe peptic ulcer and Zollinger Ellison Syndrome.

Keywords: Verapamil, Raniditine, Carbachol, Gastric Secretion

INTRODUCTION

Peptic Ulcer is one of the most common ailments the physician comes across in the clinical practice. Increased acid production from the gastric mucosa is responsible for peptic ulceration in majority of the patients. Ulcers are not found in achlorhydric patients and almost always occurs in patients with Zollinger Ellison Syndrome which is characterized by very high acid production[1]. Inhibition of production of HCl is a desirable therapeutic goal in the4 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 quite commonly being used in the treatment of hypertension, angina, myocardial infarction and supraventricular tachycardia[2]. 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 hypercalcemia with intravenous administration of calcium is usually associated with increased gastric secretion and acidity[3,4]. The acid stimulating ability is well known and extreme sensitivity to calcium in patients with Zollinger Ellison Syndrome is also documented[5,6].

Calcium channel verapamil may interfere with 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[7]. Histamine release from the peritoneal mast cells is critically dependent upon external Ca^{++} concentration, non-availability of Ca^{++} may cause reduced effects of Histamine on acid production in the stomach. Calcium channel blockers have been mainly used in cardiovascular system as inhibitors of muscle contraction, and muscle contraction is not the only event in which they play an important role. In stomach, motility and acid secretion, which have been shown to be dependent upon calcium ions, are likely to be modified by calcium channel blockers. The routine dose of Ranitidine for peptic ulcer is 150-300 mg daily but for severe ulcers and Zollinger Ellison Syndrome 600-900 mg may be required. Use of calcium channel blocker may be helpful in reducing the dose of Ranitidine used in combination and it may reduce the toxic effects associated with the use of very high doses of Ranitidine. The present study was planned to evaluate the effects of

calcium channel blocker, verapamil in combination with H2-receptor antagonist, Ranitidine, on the volume and acidity of carbachol induced gastric secretion.

MATERIALS AND METHODS

Twenty four rats belonging to Sprangue Dawley strain were selected for the present work. Healthy animals of both sexes weighing 150 – 200 gms were obtained from the 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 experiments. The animals were divided into four groups comprising of six rats each.

A carbachol Treated (Control)

B Verapamil + carbachol treated

C ranitidine + carbachol treated

D verapamil + ranitidine + carbachol treated

The operative procedure was the one adapted by Visscher et al[8]. The animals were anaesthetized with ether, abdomen opened and the pylorus was ligated with silk suture. The abdomen was closed with suture clips. Intraperitoneal injection of carbachol 600 µg/Kg was given to group A. 10 mg/Kg body weight verapamil to group B, 0.5 mg/Kg body weight ranitidine to group C and verapamil + ranitidine to group D was given intrperitoneally. Carbachol 600 µg/Kg body weight was given to group B, C and D after 15 minutes. The rat6s were kept alive and deprived of water for four hours after administration of the 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 the estimation of free and total acidity. For the determination of acidity the method described by Varley[9] was used. One ml of centrifuged and filtered gastric secretion was titrated against o.1 N NaOH using Topfer's reagent (pH 5range 2.9 – 4.4) as an indicator for determination of free acid and 1% Phenolphthaline as indicator for determination of combined acidity. The sum of the two titration was the total acidity. The data was analyzed statistically using student's 't' test.

RESULTS

The mean values for the volume of gastric secretions with carbachol was 9.00 $\pm$ o.58 ml, for free and total acidity were 8.339 $\pm$ 0.21 and 13.22 $\pm$ 0.27 m.Eq/dl respectively. We observed that when verapamil was injected to group B 15 minutes before carbachol, the inhibition produced regarding the volume free and total acidity was 36.11%, 62.62% and 38.53% respectively when compared with carbachol (Table 1). This inhibition was statistically highly significant ($p < 0.001$). Ranitidine injected to group C reduced the volume, free and total acidity by 40%, 64.40% and 43.22% respectively when compared with carbachol (Table 1). This inhibition was statistically highly significant ($p < 0.001$).

Likewise when the animals received combination of verapamil and ranitidine 15 minutes before carbachol, the volume was reduced by 61.11%, free acidity by 75.80% and total acidity by 59.59% when compared with carbachol (Table 1). This inhibition was statistically highly significant ($p<0.001$).

DISCUSSION

The secretion of acid in the stomach is controlled at a variety of levels by neuronal, hormonal and paracrine mechanisms. When these regulator mechanisms malfunction, acid and pepsin autodigest the mucosa resulting in the ulceration of oesophagus, stomach and duodenum[10].

Table-I: Effects of Verapamil + Ranitidine on volume and acidity of carbachol induced gastric secretion

Drugs	Volume of gastric secretion (ml)			Acidity (mEq/dl)					
				Free			Total		
	Mean	% reduction	P Value	Mean	% reduction	P Value	Mean	% reduction	P Value
Carbachol	9.00 ± 0.58	---	---	8.399 ± 0.210	---	---	13.220 ± 0.270	---	---
Verapamil + Carbachol	5.750 ± 0.280	36.11%	‹ 0.001	3.139 ± 0.270	62.62%	‹ 0.001	8.126 ± 0.490	38.53%	‹ 0.001
Ranitidine + carbachol	5.40 ± 0.23	40.00%	‹ 0.001	2.99 ± 0.26	64.40%	‹ 0.001	7.506 ± 0.830	43.22%	‹ 0.001
Verapamil + ranitidine + carbachol	3.50 ± 0.31	61.11%	‹ 0.001	2.03 ± 0.43	75.80%	‹ 0.001	5.36 ± 0.39	59.43%	‹ 0.001

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. We observed that ranitidine reduced the volume and acidity of gastric secretion and these reductions were highly significant when compared with the mean values in carbachol treated rate (control). Our study correlates with the work of Domskey et al[11] on the human subjects, Garric et al[12] on rats, Daly et al[13] and Brogden et al[14] on animals and human subjects. All these workers observed that ranitidine reduces the volume and acidity of gastric secretion. This due to well known H_2-receptor antagonistic action of ranitidine.

The gastric acid secretion is induced by gastrin, vagal stimulation and local Cholinergic effects. All these processes require calcium ions. Verapamil. A well known calcium channel blocker, inhibits the calcium influx, which may be responsible for the observed reduction in volume and acidity of gastric secretion. Besides, verapamil inhibits lipoxygenase pathway during metabolism of arachidonic acid, so leukotriens, the injurious substance is not formed and all the arachidonic acid is metabolized through cycloxygenase pathway and leads to the production of prostglandins which couple with Gi protein, inhibits adenyl cyclase and thus decreases the acid production[15]. Similarly verapamil being a vasodilator improves gastric blood flow and inhibits ischemic necrosis during stress due to vasoconstriction[16].

Verapamil directly inhibits H^+-K^+ ATPase and reduces gastric acid secretion. Release of histamine by the mast cells critically depends upon external calcium ions so verapamil by blocking calcium ions blocks histamine release which is potent agent for HCl secretion. The observations in our study are almost similar to the work of Brage et al[17] on rats. Similar results were also obtained by Kirkagaard et al[18] using verapamil 10 mg/Kg body weight in human subjects. Levine et al19 also observed that there was no effect on blood pressure in normotensive patients using verapamil for reduction of gastric acid secretion. In our study when we administered verapamil + ranitidine 15 minutes before carbachol there was highly significant reduction in volume and total acidity. This reduction was more than that produced by ranitidine alone

CONCLUSION

The combination of verapamil with ranitidine can be effectively used in severe peptic ulcer and Zollinger Ellison syndrome. This may be spatially very beneficial in the patients who have peptic ulcer as well as one of the conditions like angina, myocardial infarction, supraventricular tachycardia or bronchial asthma because verapamil has its use in all these conditions. Further human studies on this line of approach are suggested.

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Address for Correspondence:

Dr. Muhammad Jan, Associate Professor, Department of Pharmacology, Saidu Medical College, Swat.