COMPARISON OF VERAPAMIL AND CIMETIDINE FOR THEIR EFFECTS ON VOLUME AND ACIDITY OF CARBACHOL INDUCED GASTRIC SECRETION IN FASTING RABBITS

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Background: Peptic ulcer is a common ailment for which over production of gastric acid is the main cause. This study was undertaken to find out the effects of Calcium channel blocker Verapamil and Cimetidine on volume and acidity of Carbacol induced gastric section, free and total acidity of carbachol induced gastric secretion and their effects were also compared. **Methods:** Thirty rabbits of local breed weighing 1-1.5kg were used. The animals were kept on fasting for 48 hours after which the pylorus of each was ligated. Verapamil 10mg/kg, Cimetidine 2.5 mg/kg and Carbachol 600µg/kg body weight were administered intrapertoneally in pylorus ligated rabbits. **Results:** It was found that Verapamil reduced the volume, free and total acidity of gastric secretion, which were statistically highly significant when compared with Carbachol ($P<0.001$). Cimetidine also had the same effects. when the difference of means values brought about by verapamil were compared with those of Cimetidine, all these differences were found statistically non significant, indicating that Verapamil has similar effect as that of Cimetidine on all parameters included in study. **Conclusion:** Verapamil has significant effect on volume and acidity of carbachol induced gastric secretion.

Keywords: Verapamil, Cimetidine, Carbachol, Gastric Secretion, Rabbit, Stomach, Acidity

INTRODUCTION

Peptic ulcer is one of the most common ailments, with which a 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 (ZE) syndrome which is characterized by very high acid secretion.[1] Inhibition of over production of acid is a desirable therapeutic goal in the treatment of peptic ulcer. Cimetidine is capable of reducing gastric acid secretion with usual therapeutic dose.[2] Cimetidine suppresses gastric acid secretion induced by all stimuli.[3].

The calcium channel blocking agents like Verapamil, nifedipine and diltiazem are commonly used in the treatment of hypertension, angina, myocardial infarction and superventricular tachycardia.[4]

Induction of hypercalcaemia through intravenous administration of calcium, is usually associated with increased gastric volume and acidity.[5,6] The acid stimulating ability of calcium; is well known and extreme sensitivity to calcium in patients with ZE syndrome is also documented.[7.8] Calcium channel blocker verapamil may interfere with H^+K^+ ATPase due to its high affinity for the K^+ site H^+K^+ ATPase system which is accessible from luminal side of the stomach.[9] Histamine release from peritoneal mast cells is critically dependent upon extracellular Ca^{++}concentration, so 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 diseases as inhibitors of muscle contraction. In the stomach, motility and acid secretion have been shown to be dependent upon calcium channel blockers. This study was planned to evaluate the effects of calcium channel blocker Verapamil and to compare it with H_2-receptor antagonist cimetidine on the volume and acidity of Carbachol induced gastric secretion.

MATERIAL AND METHODS

Thirty rabbits of local breed were selected for the present study. Healthy animals of both sexes weighing 1-1.5kg were used in the study. All the animals were kept fasting for 48 hours with free availability of water before they were subjected to experimental procedure. The animals were divided into 3 groups each containing 10 animals. Group A was carbachol treated, Group B was Verapamil + carbachol treated and Group C. was Cimetidine + carbachol treated.

The operative procedure was the one adopted by Vischer et al.[10] 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 600µg/Kg body weight were administered to group A, 10mg/Kg body weight

of Verapamil to group B and 2.5 mg/Kg body weight of Cimetidine to group C followed by Carbachol 600µg/Kg body weight after 15 minutes to group B and C. The rabbits were deprived of water for four hours after administration of drugs. Then the rabbits were sacrificed, the thorax and abdomen were opened, oesophagus was 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.[11] One ml of centrifuged and filtered gastric secretion was titrated against 0.1 N NaOH using Topfers reagent for determination of free acidity and 1% phenoplhthalein as indicator for combined acidity. The sum of the two titrations was total acidity. The data was analyzed statistically using student "t" test.

RESULTS

The volume, free acidity and total acidity of gastric secretion in group A (carbachol treated group) was 28.7 ± 0.650ml, 6.39 ± 0.408mEq/dl and 7.64 ± 0.408 mEq/dl respectively. The volume, free acidity and total acidity in group B (Verapamil and Carbachol treated) was 13.64 ± 0.564ml, 2.34 ± 0.195mEq/dl and 3.52 ± 0.264mEq/dl respectively.

Table-1: Comparison between the effect of Verapamil 10 mg/kg and Cimetidine 2.5mg/kg on volume and acidity of Carbachol 600µg/kg body weight induced gastric secretion

Drug	Volume of gastric secretion(ml)	Acidity (m.Eq./dl of gastric secretion) Free	Total
Carbachol	28.7±0.650 (10)	6.39±0.408 (10)	7.64±0.408 (10)
Verapamil+ Carbachol.	13.64±0.564 (10)	2.34±0.195 (10)	3.52±0.264 (10)
P. Values	<0.001	<0.001	<0.001
Cimetidine+ Carbachol	13.12±0.326 (10)	2.04±0.150 (10)	3.2±0.312 (10)
P.Values	<0.001	<0.001	<0.001

Each value represents mean of total observations Figures in parenthesis indicate the number of animals in each group P. values when compared with Carbachol.

These reductions noticed in all the parameters were found to be highly significant when compared with Carbachol (P<0.001). Similarly the volume, free acidity and total acidity in group C (Cimetidine and carbachol treated) was 13.12 ± 0.326ml, 2.04 ± 0.150mEq./dl and 3.21±0.3312 mEq./dl respectively. All these reductions were also found to be statistically highly significant when compared with the Carbachol (P<0.001). All these changes are shown in Table-1 and Figure –1. When we compared the mean values of volume, free and total acidity for Verapamil and Cimetidine it was observed that all these differences in all the three parameters between two groups were found to be non significant. All these changes are shown in Table-1 and Figure –1.

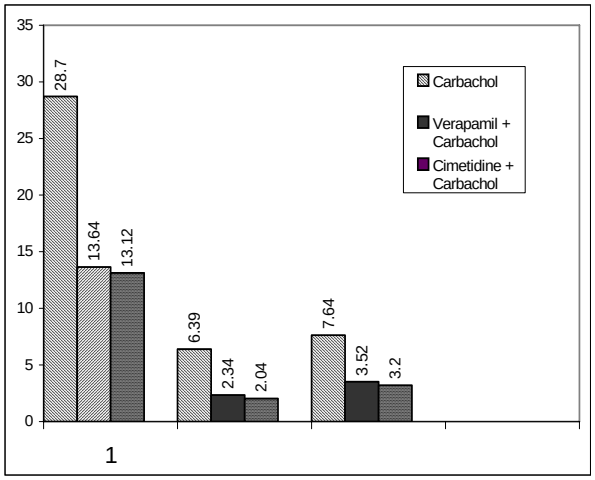

Fig-1: Comparison between effects of Verapamil 10mg/kg and Cimetidine 2.5mg/kg on volume and acidity of Carbachol 600mcg/kg body weight induced gastric secretion

Table-2: Differences in the volume, Free and total acidity produced by Cimetdine 2.5mg/kg and Verapamil 10mg/kg in Carbachol 600µg/kg body weight induced gastric secretion in rabbits

Drug	Volume of gastric secretion (ml)	Acidity (m.Eq./dl of gastric secretion) Free	Total
Verapamil+ Carbachol	13.64±0.564 (10)	2.34±0.195 (10)	3.52±0.264 (10)
Cimetidine+ Carbachol	13.12±0.326 (10)	2.04±0.150 (10)	3.2±0.312 (10)
P.Values	N.S	N.S	N.S

Each value represents mean of total observations. Figures in parenthesis indicate the number of animals in each group. P. values when compared with Carbachol. N.S = 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.[12]

Histamine, acetylcholine or carbachol are potent secretogogues for the paricta cels of gastric mucosa leading to the production of HCl.[11]

Acetylcholine and gastrin act through calcium ions. Carbachol being a cholinomimetic drug increases free intracellular calcium ions. Which,

intern activate protein kinase by phosphorylation and lead to increased production of HCl. In this study we observed that Cimetidine reduced the volume free acidity and total acidity. All these reductions were statistically highly significant when compared with the mean values in Carbachol treated group.

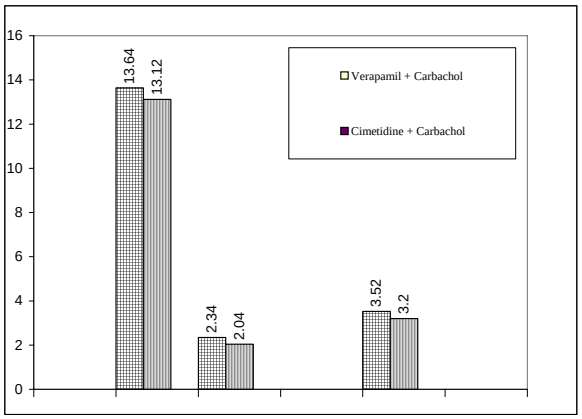

Fig-2: Differences in the volume, free and total acidity produced by cimetidine 2.5mg/kg and verapamil 10mg/kg in carbachol 600µg/kg body weight induced gastric secretion.

Our study correlates with the findings of other workers who observed that Cimetidine significantly reduces the volume and acidity of gastric secretion.[14.15] This is due to well known H_2-receptor antagonistic action of Cimetidine which interacts with H_2-receptor and inhibits the activation of adenyl cyclase and as a result no cyclic AMP is formed which is required for HCL production. Similar reduction were observed using Verapamil. All these reductions were found to be statistically highly significant when compared with Carbachol alone. Our study is in consistent with other workers who concluded that Verapamil significantly reduces gastric acid secretion.[16,17] 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. So leukotriene, the injurous substance is not formed and all the arachidonic acid is metabolized through cyclooxygenase pathway. This will lead to the production of prostaglandin which couples with Gi protein and inhibits adenyl cyclase and thus decrease HCl production.[18]

Release of histamine from mast cells is critically dependent 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 the differences in the mean values of volume, free acidity and total acidity by Cimetidine and Verapamil, they were all found non significant. This indicates that Verapamil is almost as effective as Cimetidine 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 studies in this regard for evaluation of these effects are suggested in human subjects.

REFERENCES

1. Edward CRW, Bouchier IAD, Haslett C. Diseases of the stomach. In: Davidson's Principles and Practice of Medicine. London, Churchill Livingstone ; 1995: p. 425 -34.
2. Mohammed R, Holden RJ, Hearn JB, McKibben BM, Buchanan KD, Crean GP. Effects of eight weeks continuous treatment with oral ranitidine and cimetidine on gastric acid secretion, pepsin secretion & fasting serum gastrin. Gut 1983;24:61-6.
3. Danilewitz M, Tim LO, Hirschowitz B. Ranitidine Suppression of gastric hypersecretion resistant to cimetidine N Engl J Med 1982;306:20-2.
4. Fleckenstein A. History of calcium antagonists. Circ Res 1983;52(1):3-16.
5. Barreras RF. Calcium and gastric secretion. Gastroenterology 1973;64:1168-84.
6. Anderson JR. Diseases of the stomach. In: Muir's Text book of pathology. London, English Language Book Society/Edward Arnold 1985;p.19.18-19.26.
7. Basso N, Materia A, Folini A, Jafe BM. Prostaglandin generation in the gastric mucosa of rats with stress ulcer. Surgery 1983;94:104 -8.
8. Passaro EJr., Basso N, Walsh JH. Calcium challenge in Zollinger-Ellision syndrome, Surgery 1972;72:60-7.
9. Nandi J, King RL, Kaplan DS, Levine RA. Mechanism of gastric proton pump inhibition by Calcium channel antagonists. J Haramacol Exp Ther 1990;252(3):1102-7.
10. Vischer FE, Seay PH, Tazelaar AP, Veldkamp Jr W, Brook MJ. Pharmacology of famine Bromide. J Pharacol Expt Ther 1954;110:188-204.

11. Varley H. Test of gastric function, occult blood. In: Practical clinical biochemistry. London, Willium Meinmann;1962: p 249-77.
12. Shambuerk RD, Schubert ML. Control of gastric acid secretion. Gastroenterol Clin North America 1992;21(3):527-50.
13. Negulescu PA, Matchen, TE. Intracellular calcium regulation during secretogague stimulation of the parietal cells. Am J Physiol 1988;254:P130-40.
14. Domschke W, Lux G, Domschke S. Furan H2-antagonist ranitidine inhibits pentagastrin stimulated gastric secretion. Gastroenterol 1980;79(6):1267-71.
15. Garric T, Goto Y, Buacck S, Guth P. Cimetidine and ranitidine protect against cold restraint induced ulceration in rat by suppressing gastric acid secretion. Dig Dis Sci 1987;32:1261-7.
16. Brogden RN, Carmine AA, Heel RC, Speight TM, Avery GS. Ranitidine: A review of its pharmacology and therapeutic use in peptic ulcer disease and other allied diseases. Drug 1982;24:267-303.
17. Brage R, Cortijo J, Esplugues JK, Esplugues J, Bomnati EM, Rondriguez. Effects of calcium channel blockers on gastric emptying and acid secretion of the rat in vivo. Br J Pharmacol 1986;89(4):627-33.
18. Kirkegaard P, Charistianson J, Peterson B, Olsen PS. Calcium and stimulus-secretion coupling in gastric fundic mucosa: effect of inhibition of calcium transport by verapamil on gastric acid secretion in the isolated guinea pig fundic mucosa and in healthy subjects. Scand J Gastroenterol 1982;17:533-8
19. Rogers C, Pihan G, Szabo S. Role of leukotriens in the pathogeneis of haemorrhagic gastric mucosal lesions induced by ethanol or HCL in the rat. Gastroenterol 1986;90:1797
20. Main IHM, Pearce JB. Effects of calcium on acid secretion from the rat isolated gastric Mucosa during stimulation with histamine, pentagastrin, methacholine, and dibutyrl cyclic adenosine-3,5-monophosphate. Br J Pharmacol 1978;64:359-68.
21. Flekanstein A. Specific pharmacology of calcium in pericardium, cardiac pacemaker and vascular smooth muscles. Ann Rev Pharmacol Toxicol 1977;17:149-66.
22. Latif A, Aamir K, Ali M, Siddiqi N. Deactivation of ripened uterine tissue by calcium channel blocker Verapamil. Pakistan J Pharmacol 2002;19(10):13-7

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