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COMPARISON BETWEEN THE EFFECTS OF EXTRACT FROM MEDICINAL PLANT "AMMI VISNAGA AND CIMETIDINE ON THE VOLUME AND ACIDITY OF STIMULATED GASTRIC SECRETION IN FASTING RABBITS.

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ABSTRACT

Background: Peptic ulcer is mostly produced due to the over production of gastric acid. This study was undertaken to find out the effects of extract from medicinal plant "Ammi visnaga" (which contains documented natural Calcium channel blocker) and Cimetidine on volume and acidity of Carbachol induced gastric section. Their effects were also compared to find out any difference in their efficacy.
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 animal was ligated. Cimetidine 2.5 mg/kg, Ammi visnaga, 500 mg/kg and Carbachol 600g/kg body weight were administered intraperitoneally.
Results: It was found that Cimetidine reduced the volume, free and total acidity of gastric secretion, which were highly significant when compared with Carbachol ($P<0.001$). The extract also had the same effects. When the difference of mean for Cimetidine was compared with that of extract, all these differences were found non-significant indicating that the extract has similar effect as that of Cimetidine on all parameters included in the study.
Conclusion: The extract from the fruits of Ammi visnaga therefore, be used effectively in the treatment of peptic ulcer and all other conditions like angina, myocardial infarction and hypertension which require calcium channel blockers for their treatment.
Key words: Ammi visnaga, Zollinger-Ellison (Z.E) syndrome

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 (Z.E) 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. Histamine is a potent stimulus for gastric acid secretion. Parietal cells of the stomach contain H_2-receptors & H_2- receptor antagonist Cimetidine effectively blocks gastric acid secretion[2]. Histamine stimulation rises the gastric acid secretion[3]. It has been documented that 38 medicinal plants including Ammi visnaga have natural calcium channel blocker[4]. Khellin and visnagin present in Ammi visnaga have calcium channel blocking mode of action[5]. Methanol extract from the fruit of Ammi visnaga showed significant calcium channel blocking activity[6]. In a study with the help of spectrophotometer and high performance liquid chromatography (HPLC), it was observed that Khelin and visnagin are constitution of fruit of Ammi visnaga[7] The calcium channel blocking agents are commonly used in the treatment of hypertension, angina, myocardial infarction and supraventricular tachycardia[8]. Induction of hypercalcaemia through intravenous administration of calcium, is usually associated with increased gastric volume and acidity[9,10]. The acid stimulating ability of calcium ion is well known and there is extreme sensitivity to calcium in patients with Z.E-syndrome[11,12]. Histamine

release from peritoneal mast cells is critically dependent upon extra cellular 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 CVS as inhibitors of muscle contraction. In the stomach, motility and acid secretion have been shown to be dependent upon calcium ions. So this study was planned to evaluate the effects of extract from the fruits of Ammi visnaga and H_2-receptor antagonist Cimetidine on the volume and acidity of Carbachol induced gastric secretion. Their effects were also compared on these parameters.

MATERIAL AND METHODS

This study was conducted in the department of Pharmacology Saidu Medical College Swat. Approval from Research & Ethical committee was extraction of the extract was done in NIH, Islamabad (CPSP Paper).

Thirty rabbits of local breed were selected for the present study. Healthy subjects of both sexes weighing 1-1.5 kg were used in the study. All the subjects 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 Cimetidine + Carbachol treated and Group C, was Ammi visnaga + Carbachol treated.

The operative procedure was the one adopted by Vischer et al.(1954)[13]. Animals were anaesthetized with ether, abdomen was opened and pylorus was ligated with silk suture. Then abdominal wall was closed with suture clamps and intraperitoneal (I.P) injection of Carbachol 600µg/Kg body weight was administered to group A, 2.5 mg/Kg body weight of Cimetidine to group B and 500 mg/Kg body weight of Ammi visnaga 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, thorax and abdomen were opened, oesophagus was ligated and the stomach was removed quickly. The contents of the stomach were collected. The volume of 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 (1962)[14]. 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% phenolphthalein as indicator for combined acidity. The sum of the two titrations was total acidity. Acidity was calculated by using the formula N1V1=V2v2. 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±0.408 m.Eq./dl and 7.64±0.408 m.Eq./dl respectively. The volume, free acidity and total acidity in group B (Cimetidine and Carbachol treated) was 13.12±0.326ml, 2.04±0.150m.Eq./dl and 3.21±0.312m.Eq./dl respectively. 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 (Ammi visnaga and Carbachol treated) was 13.8±0.578 ml, 2.41±0.216m.Eq./dl and 3.57±0.276m.Eq./dl respectively. All these reductions were also found to be statistically highly significant when compared with the Carbachol group ($P<0.001$). All these changes are shown in Table 1. When we compared the mean values of volume, free and total acidity for Cimetidine and extract, it was observed that these differences in all the three parameters between groups 2and 3 were found to be non significant. All these changes are shown in Table 2.

Table 1
Comparison between the effect of extract from Ammi visnaga 500mg/kg body & Cimetidine 2.5 mg/kg weight and on volume and acidity of Carbachol 600g/kg body weight induced gastric secretion in rabbits.

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)
Cimetidine + Carbachol.	13.12 0.326 (10)	2.04 o.150 (10)	3.21 0.408 (10)
P. Values	<0.001	<0.001	<0.001
Ammi visnaga + Carbachol	13.8 0.578 (10)	2.41 0.216 (10)	3.57 0.276 (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.

Table 2
Differences in the volume, free and total acidity produced by Ammi visnaga 500 mg/kg and Cimetidine 2.5 mg/kg in Carbachol 600g/kg body weight induced gastric secretion in rabbits.

Drug	Volume of gastric secretion(ml)	Acidity (m.Eq./dl of gastric secretion)	
		Free	Total
Cimetidine+ Carbachol	13.12 0.326 (10)	2.04 o.150 (10)	3.21 0.408 (10)
Ammi visnaga+ Carbachol	13.8 0.578 (10)	2.41 0.216 (10)	3.57 0.276 (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 autodiagest the mucosa resulting in the ulceration of oesophagus, stomach and duodenum[15]

Histamine, acetylcholine or Carbachol are potent secretogogues for the parietal cells of gastric mucosa leading to the production of Hcl[16].

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 Ammi visnaga reduced the volume free and total acidity. This is due to the calcium channel blocking activity of natural calcium channel blocker present in the extract. All these reductions were statistically highly significant when compared with the mean values in Carbachol treated group. Similar reductions were observed using Cimetidine. 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 calcium channel blocker Verapamil significantly reduced gastric acid secretion[16.18]. It is due to the fact that calcium channel blocker inhibit the calcium influx, which may be responsible for the observed reductions in volume and acidity of gastric secretion. Besides, calcium channel blocker inhibit lipoxygenase pathway during metabolism of arachidonic acid. So leukotrienes, the injurious 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[19].

Release of histamine from mast cells is critically dependent on external calcium ions, so calcium channel blocker by blocking calcium ions can block histamine release which is a potent agent for HCl secretion[20].

When we compared the differences in the mean values of volume, free and total acidity by Ammi visnaga and Cimetidine, they were all found non significant. This indicates that the extract is almost as effective as Cimetidine in decreasing volume, free and total acidity of gastric secretion. Calcium channel blockers are also used in controlling contraction of cardiovascular smooth muscles[21], allergic reaction[22] and prevention of premature labor[23].

All of these actions are due to the calcium channels blocking activity. As the extract also contains calcium channel blocker, so it can also be used for the treatment of the above mentioned diseases and peptic ulcer because its effects are comparable

with that of standard anti ulcer drug Cimetidine.

CONCLUSION

It is concluded that the extract may be beneficially used as a single drug therapy in patients having peptic ulcer alone or concurrent with angina, myocardial infarction etc that need calcium channel blockers for their treatment. Further studies in this regard for evaluation of these effects are suggested in human subjects.

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