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COMPARATIVE EFFECT OF CIMETIDINE AND GEFARNATE ON NORMAL AND ULCERATED ALBINO RATS

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ABSTRACT

Antiulcerogenic efficacies of cimetidine and gefarnate were compared in the normal, aspirin, acetic acid and stress induced ulcerated albino rata In addition, the[i]r effects on output of gastric acid, pepsin and hexosamine were studied in normal and experimentally ulcerated rata Detonate increased the glucosamine levels in normal and ulcerated rats. A significant reduction in ulcer formation was observed with cimetidine in aspirin, acet[i]c acid and stress induced ulcerous rats. Cimetidine did not reduce acid output in the presence of exogenous hydrochloric acid in aspirin treated rats. A decrease in glucosamine concentration was also observed with cimetidine in aspirin treated rats. Thus cimetidine did not significantly reduced ulcer formation in ulcerated rats. In the present study, planate was found to be more effective than cimetidine because of its effect in normalization of mucus barrier.

Introduction

Ulcer is a disease of both the poor people and those of the affluent society. Exposure to noxious agents like acids, bile, caffeine, tobacco and chilli powder may lead to ulcerogenesis. Levine *et al*. (1979) stated that long transportation, head injuries, severe burn, trauma and physical exertion are some of the etiologic factors which may lead to stress ulceration. According to Guslandi *et al.* (1987), peptic ulcer results when a free balance between the aggressive factors like acids and pepsin and defensive factors collectively called as mucosal resistance is disturbed.

Peptic ulcer is a common condition affecting 5-9% of the population. Treatment of peptic ulcer has been practiced over two thousand years with symptomatic relive (Shreeve *et al*, 1975).

Black *et at.* (1972) classified histaminic receptors as H1 and H2. Cimetidine is the fast H2 receptor antagonist found to be effective for the treatment of ulcer. It inhibits the acid secretory effect.

Adami *et al* (1964) reported an isoprenoid, gefarnate (geranyl ferensyl acetate) extracted from the juice of wild cabbage to stimulate the gastric mucus secretion, promote regeneration and repair the gastric mucosa. The present study was conducted to compare the efficacy of cimetidine and gefarnate in normal and ulcerated rats.

Materials and Methods

Animals used

Albino rats of Sprague Dawley strain of either sex, weighing 224 ± 4 g were used in these experiments. Rats were kept in wire cages and fed with standard diet. Tap water was given *ad-libitum*

Grouping of animals

Experimental animals were divided into four major groups depending upon the procedures of ulcer induced.

Studies on normal rats

Normal healthy albino rats of either sex were treated orally with placebo 10 ml/kg, cimetidine 15 mg/kg and gefarnate 73 mg/kg twice daily for three consecutive days. The rats were fasted for 24 hours with tap water *ad-libitum* and underwent operative procedure on the fourth day. The operative procedure adopted was that of Shay *et al*. (1945).

After pylorous ligation, drinking water was withheld and gastric juices were allowed to collect for a period of four hours. The rats were then killed by an overdose of chloroform and gastric contents were collected through oesophagus, centrifuged at 1800 rpm for 10 min. and analyzed for acid output peptic activity and glucosamine concentration.

Studies on aspirin treated rats

A modified method of Geol *et al* (1985) was used for the production of experimental gastric ulceration in rats by administering them acidified aspirin 0.2 g/kg. The test drugs, cimetidine 15 mg/kg, gefarnate 73 mg/kg and tragacanth 10 ml/kg, were administered 3 hours before aspirin and an equal dose 3 hours after administering aspirin. This regimen was continued for three consecutive days and pylorous ligation was done on the fourth day. As described earlier, the gastric contents were collected and analysed. The stomachs treated with 1% formaline were incised along the greater curvature and examined for lesions.

Studies on stress ulcerous rats (20 hours cold stressing)

Stress ulcer was induced by water immersion according to the methods of Okaba *et al* (1984). Under ether anaesthesia the abdomen of each rat was opened and the pylorous was ligated. The incised abdomen was then closed and covered with

collodion to prevent any leakage of water at the time of water immersion. A dose of the test drugs and placebo were given after pylorous ligation. The temperature of the water bath was maintained at 25°C for 20 hours. After such types of stressing the animals were killed by a blow on the head and stomachs were removed. The gastric contents were collected, centrifuged and analyzed.

Studies on acetic acid induced gastric ulcerous rats

Acetic acid ulcer in rats was induced according to the methods of Keijiro *et al*. (1969). The dosing of test drugs, cimetidine 15 mg/kg, gefarnate 7.5 mg/kg and tragacanth 10 ml/kg were then started one day after the operation for 10 consecutive days, twice daily. Feed was withheld on the 11th day and the animals were sacrified on the 12th day. The stomach was removed and filled with 10 ml of 1% formalin solution for 5 minutes to fix the outer layer of the stomach to facilitate the examination. The stomachs were then cut open along the greater curvature, spread on the pad and examined macroscopically. The ulcer produced was round or oval in shape. The length and width of each lesion was determined. The product of length and width was expressed as ulcer index. The curative ratio was determined by the formula:

$$\text{Curative ratio} = \frac{\text{Control ulcer index - Text ulcer index}}{\text{Control ulcer index}} \times 100$$

Determination of acid output

Acid output was determined by titration with N/100 NaOH using phenolphthalein as an indicator to light pink end point as described by Harold *et al* (1980) and expressed for concentration as millimoles per hour.

Determination of peptic activity

Peptic activity was measured according to the methods of Riggs and Stadie (1943) and expressed as velocity constant per ml of the gastric juice per minute.

Determination of glucosamine concentration

Hexosamines are obligatory components of mucus and their determination has been used for the estimation of mucus contents of gastric juice (John *et al*, 1973). The concentration of glucosamine in gastric juice was determined by the method of Elson and Morgan (1933).

Determination of ulcer index

In aspirin treated and stress ulcerous rats ulcer index was determined by treating the stomachs with 10 ml of 1% formalin solution for 5 minutes in order to fix

the outer layer, incised along the greater curvature and examined for lesions which had developed in the glandular portion. The length of each lesion was determined under dissecting microscope (10x, 4x) and the sum of the length of all lesions in mm for each stomach was expressed as ulcer index [Okaba *et al,* 1976]

Results

In normal (non-ulcerated) rats both the test drugs did not affect the pepsin level However, a significant decrease in acid output was observed with cimetidine, and an increase in glucosamine concentration with gefarnate (Table 1).

In aspirin ulcerated rats the acid output did not change. However, a highly significant decrease in pepsin concentration was observed with both drugs. Gefarnate also significantly increased the glucosamine concentration.

In stress ulcerated rats the pepsin level remains unaffected, but glucosamine concentration was increased by both drugs. A significant decrease in acid output was also found with gefarnate in these rats.

Table 2 indicates that gefarnate has shown a significant decrease in ulcer index in stress ulcerated and acetic acid induced ulcerated rats. No change in ulcer index was found with both drugs in aspirin ulcerated rats. These results are presented in Fig. 1-3.

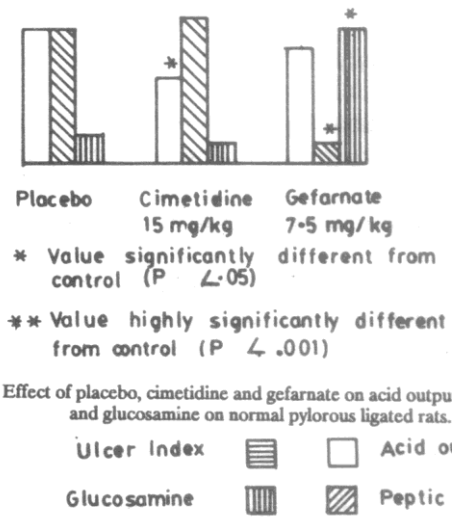

Fig. 1: Effect of placebo, cimetidine and gefarnate on acid output, peptic activity and glucosamine on normal pylorous ligated rats.

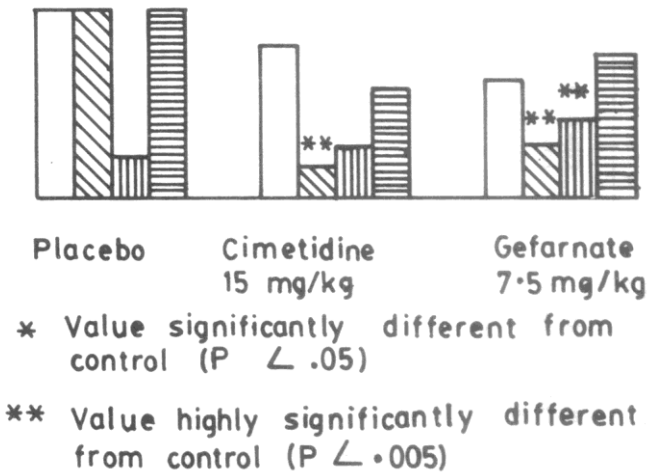

Fig. 2: Effect of placebo, cimetidine and gefarnate on acid output, peptic activity, glucosamine and ulcer index in aspirin ulcerated rats.

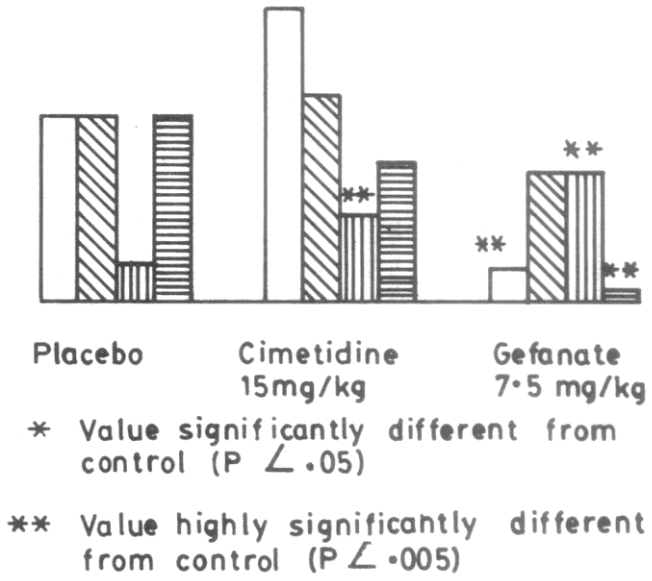

Fig. 3: Effect of placebo, cimetidine and gefarnate on add output, peptic activity, glucosamine and ulcer index in stress ulcerated rats.

Table 1
Effect of Placebo and test drugs (cimetidine and gefarnate) on the acid output, peptic activity and glucosamine concentration in the gastric contents of the normal, aspirin treated and stress ulcerous rats.

Experimental procedure	Treatment	Total oral dosage	Acid output mmol/hr	Peptic activity velocity constant/ml of the gastric juice/min.	Glucosamine concentration ug/100 g/4 hrs.
1. Normal (non-ulcerated rats)	Tragacanth (control)	10 ml/kg	0.10±0.029	0.029±.008	193±32
	Gefarnate	7.5 mg/kg	0.087±0.004	0.004±.0009*	963±82**
	Cimetidine	15.0 mg/kg	0.065±0.005*	0.032±.004	140±16
2. Aspirin treated rats	Tragacanth + Aspirin	10 ml/kg +0.2 mg/kg	0.965±0.14	0.026±.004	637±54
	Gefarnate + Aspirin	7.5 mg/kg +0.2 mg/kg	0.576±0.14	0.007±.002**	1288±21**
	Cimetidine + Aspirin	15 mg/kg +0.2 mg/kg	0.774±0.05	0.004±.0009**	875±118
3. Stress ulcerous rats	Tagacanth	10 ml/kg	0.12±0.005	0.045±.007	265±48
	Gefarnate	7.5 mg/kg	0.02±0.004**	0.032±.009	913±53**
	Cimetidine	15 mg/kg	0.19±0.029	0.049±.007	608±98**

Significant from control * = P <0.05, ** = P <0.001.
N = 6 /group except for tragacanth control (N = 10).

Table 2

Ulcer indices (mean ±S.E.M.) after treatment with placebo and test drugs in aspirin ulcerated stress ulcerous rats and acetic acid induced ulcerous rats.

Experimental procedure	Treatment	Total oral dosage	Ulcer index	% inhibition
1. Aspirin ulcerated rats	a. Tragacanth (control)	10 ml/kg	43±6	Control
	b. Gefarnate	7.5 mg/kg	32±7	25
	c. Cimetidine	15.0 mg/kg	24±11	42
2. Stress ulcerous rats	a. Tragacanth (control)	10 ml/kg	15±5	Control
	b. Gefarnate	7.5 mg/kg	0.77±53**	21
	c. Cimetidine	15.0 mg/kg	11±6	95
3. Acetic acid induced ulcerous rats	a. Tragacanth (control)	10 ml/kg	31±1	Control
	b. Gefarnate	7.5 mg/kg	15±5**	51
	c. Cimetidine	15.0 mg/kg	21±13	31

Significant from control * = $P < 0.05$, ** = $P < 0.005$.
N = 6 /group except for Tragacanth control (N = 10).

Discussion

Cimetidine reduced the gastric acid secretion in normal rats. A decrease in glucosamine concentration was also observed with cimetidine in normal rats. Guslandi (1987) found that cimetidine reduces the protective effect of gastric mucus. Our findings are in agreement with their observations.

Gefarnate has shown a highly significant increase in glucosamine concentration and significant decrease in peptic activity in normal rats.

Both the test drugs were not found to be effective in the inhibition of ulcer formation in the presence of exogenous hydrochloric acid. However, a significant decrease in peptic activity was observed with both drugs either by decreasing the glandular secretion or by binding the pepsin. It would seems that the mechanism of action of gefarnate consists of normalization of the mucus secretion followed by the restoration of normal defensive barrier.

Gefarnate at a dose of 75 mg/kg inhibited the development of the stress ulcer almost completely, reduced acid output and increased glucosamine concentration. Although cimetidine also significantly increased the glucosamine concentration but acid reduction was not observed. Since this is an ideal model for the drugs having inhibitory effect (Barbra *et al,* 1974), it was not found to be effective for stress ulcer prevention.

Gefarnate has been found to enhance the mucus production. A high healing ratio of 51% as compared to 33% of cimetidine was observed with gefarnate in acetic acid induced ulcerous rats. Gefarnate was found to be a better drug in ulcerated animals as compared to cimetidine.

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