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ANTIULCER ACTIVITY AND THE MECHANISM OF ACTION OF MAGALDRATE IN GASTRIC ULCERATION MODELS OF RAT

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Abstract : The present study was undertaken to investigate the mechanism of cytoprotective effects of magaldrate in aspirin plus pylorus–ligation model and ethanol–induced gastric ulcer model in rats.

Magaldrate (60 mg/kg, p.o.) produced a significant reduction in the ulcer index and significant increase in mucus content in ethanol–induced gastric ulceration in rats. In aspirin plus pylorus–ligation model magaldrate produced significant decrease in ulcer index, total acidity and protein content (PR). It did not produce any significant change in volume of gastric secretion. However, it produced significant increase in total carbohydrate (TC) level but not in ratio between TC and proteins. It also produced a significant decrease in lipid peroxidation (as expressed by thiobarbituric acid reactive substance).

Our data suggests the cytoprotective action of magaldrate on gastric mucosal cells which may be due to protection of gastric mucosa from lipid peroxidation

Key words : magaldrate, anti–ulcer activity, lipid-peroxidation, cytoprotection

INTRODUCTION

Antacid therapy had enjoyed a period of success in the treatment of the gastro–oesophageal reflux disease (GORD), acute stress ulcer syndrome and pregnancy related reflux disease as well as prophylaxis during delivery (1). It raises a number of fundamental questions regarding the therapeutic mechanism of antacids. There are evidences that aluminium–containing antacids are cytoprotective, because they protect gastric mucosa against various ulcerogenic and necrotising agents including alcohol. It is reported that gastric mucosal necrosis produced by alcohol is independent of luminal acid and it cannot be reduced by H_2 receptor antagonists, the protective action of antacid may be accomplished by mechanism other than acid neutralising

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ability (2). The protective mechanism is believed to be related to increased endogenous production of sulfhydryl containing compounds (3). Magaldrate has been reported to produce cytoprotective and antiulcer activity in some models of rat (4). In the present investigation we have investigated antiulcer activity using aspirin plus pylorus ligation model and ethanol-induced gastric ulcer model in rats. In addition we also report its effect on TC:PR ratio and lipid peroxidation to further elucidate the mechanism of action.

METHODS

Albino rats of either sex weighing between 150–200 g fed with standard chaw diet were used for the experiment. They were divided into groups of six each. Animals were starved for 36 hour before ulcerogenic treatment, in cages with grating on floor to prevent coprophagy. Anti-ulcer activity of the drug was evaluated against experimentally induced gastric ulcer models: ethanol induced gastric ulcer model in rats and aspirin plus pylorus ligation model in rats.

Ethanol induced gastric ulcers in rats

Ethanol was administered orally in the dose of 1 ml of 80% to the 36 hrs. fasted animal. In treated group, magaldrate (60 mg/kg) was administered orally 1 hour before the administration of ethanol. Two hours after administration, animals were sacrificed, stomachs were removed, opened along greater curvature and subjected to measurement of ulcer index. The stomach was subjected to the measurement of mucus content as per the method of Corne et al (5).

Aspirin plus pylorus ligated model in rats

Suspension of aspirin in 1% carboxymethylcellulose in water was administered orally in the dose of 200 mg/kg to non fasted rats once daily for 5 consecutive days. Magaldrate (60 mg/kg) was administered orally 30 min before the aspirin treatment. On fifth day, food was withdrawn from the animals but water was given *ad libitum*. On sixth day pylorus was ligated as per the method of Shay et al (6) under light ether anesthesia. Four hrs. after pylorus ligation, animals were sacrificed giving high dose of ether. The stomach was removed carefully and opened along greater curvature. Contents were drained in the test tube, which subjected to biochemical analysis for the volume of gastric content, total acidity, pepsin activity (7), total carbohydrates (TC) (8) and protein content (PR) (9). Ulcer index was measured as per the method of Ganguli and Bhatnagar (10). Stamach tissue was subjected to lipid peroxidation for measurement of malondialdehyde (MDA) content (11).

The data was analysed by unpaired student's 't' test. The value of p less than 5% ($p<0.05$) was considered as statistically significant.

RESULTS AND DISCUSSION

Oral administration of absolute ethanol produced blackish elongated bands of haemorrhagic lesions in the corpus mucosa, along the long axis of stomach within 2 hrs. Single dose treatment of magaldrate (60

mg/kg) produced significant decrease in ulcer index value as compared to control group (Table 1). Ethanol and several NSAIDs, such as aspirin irritate the gastrointestinal mucosa of both human and animals and may, therefore, cause injury and bleeding (12). Studies focusing on the pathogenesis of ethanol induced gastric mucosal injury suggest that an initial event is disruption of the vascular endothelium resulting in increased vascular permeability, oedema formation and epithelial lifting (12). Protection in ethanol induced gastric ulceration in the present investigation suggests involvement of cytoprotective action of magaldrate. This is further substantiated by their action on mucus content. One of the important criteria to determine the status of mucosal resistance is the status of mucus secretion. Mechanism of mucosal gel from gastric mucus induced by ethanol was examined using basic dye alcian blue which combines with acidic mucopolysaccharides (13). Hence the effective protection afforded to the gastric mucosa against the insults of necrotising agents suggests either the involvement of endogenous prostaglandin or reinforcement of gastric ulcer model in rats (Table 1).

TABLE I: Effect of magaldrate on ulcer index and mucus content against ethanol induced gastric ulcer model.

Parameters	*Control*	*Magaldrate (60 mg/kg) treated*
Ulcer index	2.80±0.32	0.45±0.49***
Mucus content (µg alcian blue/g wet tissue)	0.06±0.01	0.09±0.01*

*Significantly different when compared with control group ($P<0.05$)
***Significantly different when compared with control group ($P<0.001$)
n = 6 in each group

In the aspirin plus pylorus ligation model it has been proposed that because of pylorus ligation, the digestive effect of accumulated gastric juice and interference of gastric blood circulation are responsible for the induction of ulceration (14). Magaldrate produced significant decrease in ulcer index as compared to control group (Table 2). Pylous ligation for 4 hour after pretreatment with aspirin resulted in accumulation of gastric secretary volume and increase in total acid and pepsin output of gastric juice of control group (Table 2). Magaldrate produced significant decrease in total acidity, total acid output and pepsin activity. Volume of gastric acid secretion was not altered significantly by magaldrate (Table 2). There was a marked increase in TC in magaldrate treated rats as compared to control group. Pretreatment with magaldrate produced marked decrease in PR as compared to control group. The ratio between TC and PR was significantly increased by magaldrate (Table 2). The reduction in mucin activity might be responsible for weakening of mucosa causing back diffusion of protons. Magaldrate pretreatment showed marked increase in TC and decrease in PR content of gastric juice leading to improved mucin activity indicating strengthening of mucosal barrier. Decreased PR content has been suggested to represent decrease exfoliation and shedding of gastric mucosal cells induced by the ulcerogenic agents. There is general convention that alteration in acid secretion by drugs is always accompanied with alteration in pepsin secretion (15). Thus, the gastroprotrective effect of magaldrate as evident from significant reduction in

TABLE II: Effect of magaldrate on ulcer index and lipid peroxidation against aspirin plus pylorus ligation model.

Parameters	*Control*	*Magaldrate (60 mg/kg) treated*
Ulcer index	0.16±0.01	0.01±0.003***
MDA content (mM/100 mg wet tissue)	138.26±16.26	116.75±10.28**
Total acidity (mEq/L)	45±8.29	8.66±2.72**
Total acid output (mEq/4h)	44.98±5.53	25.99±2.76*
Volume of gastric content (ml/4h)	2.626±0.324	3.575±0.897
Pepsin activity (µg/ml)	337.5±20.73	55.5±8.67***
Total carbohydrates (µg/ml)	430±1.414	4110±897.37***
Protein content (µg/ml)	900±70.71	96±5.18***
TC/PR ratio	0.483±0.0364	41.75±7.02**

*Significantly different when compared with control group ($P<0.05$)
**Significantly different when compared with control group ($P<0.01$)
***Significantly different when compared with control group ($P<0.001$)
n = 6 in each group.

ulcer index values, appear partly due to reduction of total acid and pepsin output of gastric juice.

Oxygen derived free radicals such as the superoxide anion and the hydroxyl radical, are cytotoxic and promote tissue injury (16). Studies in the rat show that oxygen derived free radicals are directly implicated in mechanism of acute and chronic gastroduodenal ulceration and that scavenging them stimulated the healing of ulceration (17). Because aspirin and ethanol injure the gastrointestinal mucosa and because oxygen derived free radicals mediate injury of this mucosa, oxyradicals may play an important role in the ethanol and aspirin induced erosive gastritis. In the process of lipid peroxidation, the MDA content was significantly reduced by magaldrate against aspirin plus pylorus ligation model in rats, which indicates the scavenging effect of the drug upon oxygen derived free radicals within gastric mucosa. Pretreatment with and magaldrate (60 mg/kg) for 5 consecutive days produced a significant decrease in ulcer index values as compared to control group. The decrease in ulcer index was accompanied by significant decrease in MDA content, the result of lipid peroxidation (as expressed by thiobarbituric acid reactive substance assay) by magaldrate as compared to control group (Table 2). In conclusion, our data suggests the cytoprotective action of magaldrate on gastric mucosal cells. Further, our study also provides evidence that it also protects gastric mucosa from lipid peroxidation.

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