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COMPARISON OF THE EFFECTS OF CAPTOPRIL AND ENALAPRIL ON OXYPHENBUTAZONE AND ETHANOL-INDUCED GASTRIC LESIONS IN RATS

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Abstract : We have compared the effect of the converting enzyme inhibitors, captopril and enalapril, on two models of gastric ulcers, viz; ethanol and oxyphenbutazone-induced lesions in rats. Both captopril and enalapril did not affect ethanol-induced lesions. While captopril significantly protected against oxyphenbutazone-induced lesions, enalapril aggravated the lesions. This difference is probably due to the lack of the protective sulfhydryl group in the chemical structure of enalapril.

Key words : captopril enalapril oxyphenbutazone-induced gastric lesions ethanol-induced gastric lesions sulfhydryl group

INTRODUCTION

Captopril, the angiotensin converting enzyme (ACE) inhibitor has a protective effect on oxyphenbutazone-induced gastric lesions in rats, probably mediated by the prostaglandin pathway; however, captopril failed to protect against ethanol-induced lessions (1).

Sulfhydryls i.e. SH substances in the mucosa, have been proposed as one of the endogenous mediators of gastric cytoprotection (2, 3). Further, it has been reported that exogenous sulfhydryl compounds protect against ethanol-induced gastric lesions (4, 5). On the other hand, depletion of gastric mucosal glutathione (an endogenous sulfhydryl) was cytoprotective (6). These divergent reports, coupled with our observation that captopril, which is a sulfhydryl compound has no effect on ethanol-induced lesions, seem to suggest that the SH group may not have any direct role in gastric cytoprotection. To verify this, we compared the effect of captopril with that of the non-sulfhydryl ACE inhibitor, enalapril, on oxyphenbutazone and ethanol-induced gastric lesions.

METHODS

Male Wistar rats (200-250 g) were deprived of food but not water for 24 hr prior to drug administration and were randomly divided into groups of ten each. Enalapril was administered in doses of 1, 2 and 4 mg/kg ip and captopril in doses of 2.5, 5 and 10 mg/kg ip 30 min before the ulcerogen. A solution of 0.9% Nacl (saline) w/v was injected ip in control animals in the same volume as enalapril (1 ml/kg).

Oxyphenbutazone-induced gastric lesions : Oxyphenbutazone was suspended in 2% gum acacia and administered po in a dose of 150 mg/kg. Two hr later the rats were killed by a blow on the head, the stomachs removed, and the lesions scored as follows:— 0.5 for each ulcer less than 3 mm; 1 for each ulcer more than 3 mm and 5 for perforated ulcer.

Ethanol-induced gastric lesions : 1 ml of 50% ethanol was administered po and rats killed after one hr. The stomachs were opened along the lesser curvature and the area of red haemorrhagic bands

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was measured and summed up for each stomach.

Statistical analysis : All data are expressed as mean ± SEM and analysed by 't' test.

RESULTS

Table I compares the effects of captopril and enalapril on oxyphenbutazone-induced gastric lesions. It can be seem that while captopril has a protective action, enalapril not only failed to protect but actually aggravated the lesions. The table also shows that both captopril and enalapril have no significant effect on ethanol-induced gastric lesions.

TABLE I : Comparison of the effects of captopril and enalapril on oxyphenbutazone and ethanol-induced gastric lesions in rats.

Drug	*Dose mg/kg (ip) n=6*	*Oxyphenbutazone lesions ulcer score Mean±SEM*	*Ethanol lesions Haemorrhagic (mm^2) Mean±SEM*
Saline (control)	1 ml/kg	10.1±0.6	68.4±8
Captopril	2.5 mg/kg	7.2±0.77**	68.0±5
	5.0 mg/kg	5.2±1.4*	68.8±6
	10.0 mg/kg	1.2±0.7**	69.2±8
Enalapril	1.0 mg/kg	10.2±0.3	67.6±2
	2.0 mg/kg	14.2±1.3**	69.9±6
	4.0 mg/kg	19.7±1.5*	74.0±6*

* P value < 0.05, ** P value < 0.01 All other values not significant.

DISCUSSION

Prostaglandins have been proposed as one of the endogenous mediators of cytopretection (7). We have shown (1) that pretreatment with the cyclo-oxygenase inhibitor, indomethacin, prevents the protective effect of captopril, sugggesting the involvement of the prestaglandin pathway. The pretective effect of captopril on oxyphenbutazone-induced gastric lesions is therefore not unexpected as captopril is known to increase prostaglandin levels both in isolated tissue preparations (8) as well as in plasma of patients and experimental animals (9, 10, 11).

However, all ACE inhibitors have indirect effects on prostaglandin production through bradykinin (12, 13). Further, indomethacin has been shown to reduce the antihypertensive action of enalapril (14). It is therefore surprising that enalapril did not protect against oxyphenbutazone-induced gastric lesions like captopril.

The main structural difference between captopril and enalapril is that enalapril lacks the sulfhydryl group present in captopril. Sulfhydryls have been proposed as one of the endogenous mediators of cytoprotection (2, 3). Further it has been shown that exogenous sulfhydryl compounds protect against gastric lesions (4, 5). It thus seems logical to attribute the differences in the effects of the two ACE inhibitors to the sulfhydryl group.

It is to be noted that both the ACE inhibitors, in spite of their effects on prostaglandin release, have failed to protect against ethanol-induced gastric lesions. ACE inhibitors have been shown to augment carragenin-induced inflammation in rats (15, 16) and augment the wheal and flare response to intradermal bradykinin (17). They have also been shown to induce inflammation in the airways propably due to reduced degradation of proinflammatory mediators like bradykinin and substance P (18).

It has been shown that vascular injury with increased vascular permeability and circulatory stasis is a pathogenic factor in ethanol-induced gastric haemorrhagic lesions (19, 20). It is therefore not surprising that the proinflammatory action of ACE inhibitors in the gastric mucosa will tend to aggravate the increased permeability caused by ethanol and negate the gasto-protective effect of the released prostaglandins. However, what is surprising and in fact noteworthy is that the sulfhydryl group which has a protective function in oxyphenbutazone-induced gastric lesions seems to have no role to play in ethanol-induced lesions. This can be deduced from the lack of difference in the effects of captopril and enalapril on ethanol-induced gastric lesions. Thus different mechanisms seem to be involved in the pathogenesis of the two types of gastric lesions.

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