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Carbenoxolone Sodium Protects Rat Gastric Mucosa against Ethanol-Induced Necrosis (41080)[1]

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Abstract. Gastric necrosis was induced in the rat by oral administration of absolute ethanol. Carbenoxolone sodium, administered orally, but not intravenously, reduced the severity of ethanol-induced lesions in a dose-responsive manner. Maximum inhibition of lesion formation occurred when carbenoxolone was administered 15 min before ethanol. Our results suggest that carbenoxolone, like prostaglandins, is cytoprotective to the rat gastric mucosa. Similarities in the time response for cytoprotection by these two compounds suggest that they exert their effect by a common mechanism.

The ability of prostaglandins to protect gastric mucosa against a variety of noxious agents has been called cytoprotection. This action of these compounds is unrelated to inhibition of acid secretion (1). Two reviews on the subject have been recently published (2, 3). Prostaglandins of the E type have been shown to protect rat gastric mucosa against the ulcerogenic effects of such diverse irritants as aspirin (2), absolute ethanol, strong acid, strong base, hypertonic salt solution, and boiling water (4). Prostaglandins have also been demonstrated to prevent aspirin-induced fecal blood loss in man (5) as well as accelerate ulcer healing in clinical trials (6, 7). The mechanism of cytoprotection is unknown.

Carbenoxolone sodium, a synthetic derivative of the licorice root substance glycyrrhizinic acid, has been intensively studied and reported to have antiulcer effects in animals and man (8–15). The purpose of the present study was to investigate the effect of carbenoxolone on acute ethanol-induced gastric necrosis in order to determine if carbenoxolone has a cytoprotective action.

Materials and Methods. The method used to induce gastric necrosis with alcohol was similar to that reported by Robert *et al.* (4). Male Sprague–Dawley rats (C.D., Charles River Breeding Laboratories) weighing 175–200 g were fasted for 24 hr and deprived of water for 19 hr prior to the experiment. All animals were housed individually in wire-mesh cages throughout the study. Carbenoxolone or vehicle was administered at a constant volume of 0.5 ml prior to alcohol challenge (specific information on doses, timing, etc., is given in the results section). The suspension vehicle contained methylcellulose (4 mg/ml), benzyl alcohol (9 mg/ml), sodium chloride (9 mg/ml), and polysorbate 80 (5 mg/ml). One hour following oral administration of 1 ml of absolute ethanol, animals were sacrificed by CO_2 asphyxiation. The stomachs were removed, opened along the greater curvature, and the degree of gastric damage was determined. Ethanol-induced lesions, which have been described in detail elsewhere (4), occur in the corpus of the stomach and consist of multiple linear hemorrhagic bands of necrotic tissue. The lesions were measured in millimeters and the total lesion length per stomach was determined. Lesion severity was expressed as the mean total lesion length per group of rats. Student's *t* test was used to determine statistical significance.

Results. *Effect of carbenoxolone on ethanol-induced gastric necrosis.* Carbenoxolone (100 mg/kg) or vehicle was administered orally via gavage or intravenously via a tail vein 30 min prior to ethanol. The effect of this drug on ethanol-induced gastric necrosis is seen in Fig. 1. Results are expressed as a percentage of the mean total lesion length of the

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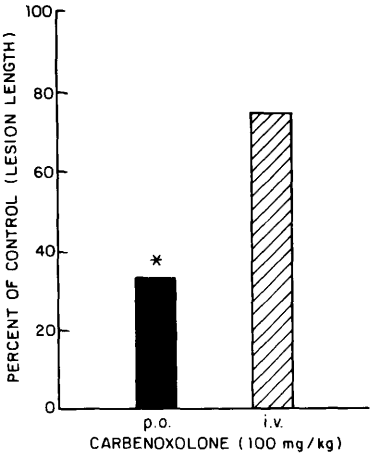

FIG. 1. Severity of ethanol-induced gastric lesions following oral and intravenous administration of carbenoxolone (100 mg/kg) 30 min prior to alcohol challenge. Lesion severity of treated rats is displayed as a percentage of the mean total lesion length of the corresponding vehicle control group. The mean total lesion lengths (±1 SEM) for the p.o. and iv vehicle control groups were 55.1 ± 12.1 and 43.4 ± 7.2 mm, respectively. Each bar represents the result obtained from a group of at least eight rats. Asterisks indicate statistical significance from control. * = $P < 0.01$.

corresponding vehicle control group. Lesion severity was significantly reduced (66.6% inhibition) following oral administration of carbenoxolone ($P < 0.01$). Lesion severity following intravenous administration of the drug was reduced slightly but the difference was not statistically significant.

Effect of varying doses of carbenoxolone on ethanol-induced gastric necrosis. Carbenoxolone was administered orally at various doses 30 min prior to ethanol. Control animals received only vehicle before alcohol. Carbenoxolone significantly reduced the severity of ethanol-induced lesions in a dose-related manner at doses of 30, 100, and 300 mg/kg, p.o. (Fig. 2). Lesion inhibition was nearly complete at the 300 mg/kg dose (95.7%). Lesion severity in rats which received carbenoxolone at a dose of 10 mg/kg was not significantly different from that of control.

Effect of time of administration on the protective action of carbenoxolone. Carbenoxolone was administered orally at a dose of 100 mg/kg at various times before ethanol. The results are shown in Fig. 3.

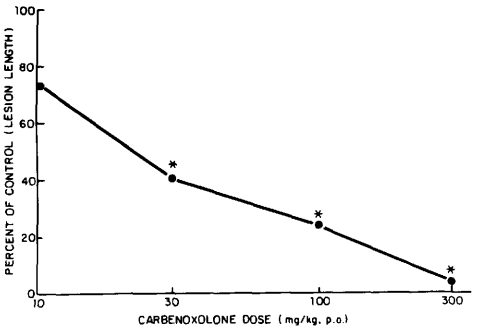

FIG. 2. Severity of ethanol-induced gastric lesions following oral administration of carbenoxolone at various doses 30 min prior to alcohol challenge. Lesion severity of treated rats is displayed as a percentage of the mean total lesion length of the vehicle control group (65.5 ± 6.5 mm). Each point represents the result obtained from 22 rats. Asterisks indicate statistical significance from vehicle control. * = $P < 0.01$.

Lesion severity was significantly reduced when carbenoxolone was administered at 5, 15, 30, and 90 min before ethanol. The drug proved ineffective when given at the same time as or 1 min before the alcohol, and also when given 180 min prior to the alcohol challenge. The greatest inhibition of

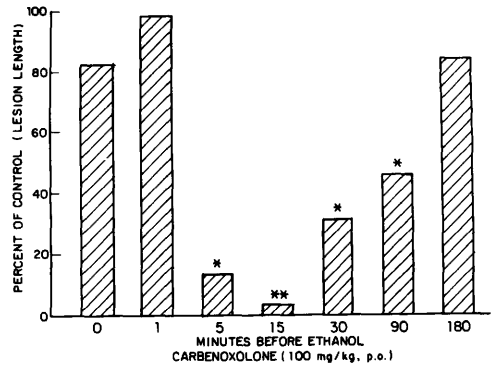

FIG. 3. Severity of ethanol-induced gastric lesions following oral administration of carbenoxolone (100 mg/kg) at times indicated before alcohol challenge. Lesion severity of treated rats is displayed as a percentage of the mean total lesion length of the corresponding vehicle control group. The mean total lesion lengths (±1 SEM) of the 0- to 180-min vehicle control groups were 24.3 ± 10.8, 16.3 ± 6.3, 16.8 ± 4.8, 50.3 ± 12.2, 57.2 ± 13.1, 81.1 ± 14.5, and 109 ± 22.8 mm, respectively. Each bar represents the result obtained from a group of 7–14 rats. Asterisks indicate statistical significance from vehicle control. * = $P < 0.02$, ** = $P < 0.001$.

ethanol-induced damage (96.4%) was observed when carbenoxolone was administered 15 min before ethanol.

Discussion. The results of this study demonstrate that carbenoxolone sodium, when administered orally prior to alcohol challenge, protected the rat gastric mucosa from the damaging effects of absolute ethanol. Since carbenoxolone does not stimulate gastric secretion, it is unlikely that the observed protection resulted from a dilution of the administered alcohol. The lack of protective effect with intravenous administration of this drug suggests that carbenoxolone exerts a local effect on gastric mucosa. Carbenoxolone has been previously shown to reduce formation or increase healing of gastric lesions produced in animals by a variety of methods including stress (restraint) (8–11), electrocautery (12), serotonin (10), acetic acid (10), aspirin (13, 14), and taurocholate (14), as well as an increase in the rate to healing of gastric ulcers in man (15). Our study is the first report that carbenoxolone can reduce gastric damage following acute alcohol challenge in the rat; a model in which lesion formation is unrelated to acid-secretory state of the animal (4).

Prostaglandins have been previously shown to protect the rat gastric mucosa against ethanol as well as other necrotic agents (4). Prostaglandins are more effective when given orally than parenterally and for this reason it has been suggested that they exert a local effect (4). These drugs are cytoprotective when administered as early as 1 min before ethanol with maximum protection occurring when the drug is given 10 to 15 min before alcohol challenge. The protective effect is rapidly lost when greater than 180 min elapses between drug treatment and ethanol administration. Similarities in the time response for cytoprotective activity of both prostaglandins and carbenoxolone suggest that both drugs may increase gastric mucosal resistance through a common mechanism of action.

The mechanism of cytoprotection is unknown. Both prostaglandins and carbenoxolone have been reported to prevent the decrease in transmucosal electrical potential and the increase in acid back diffusion following exposure of the gastric mucosa to various noxious agents (2, 11, 16). This suggests that some way these compounds might strengthen the gastric mucosal barrier. Robert has suggested that a tightening of the gastric barrier may be responsible for the cytoprotective effect observed with prostaglandins (2). Both carbenoxolone and prostaglandins have also been reported to increase mucus production by the gastric mucosa (8, 17–21). These actions could be responsible for increasing the resistance of the gastric mucosa to damaging agents. It remains to be determined if carbenoxolone exerts a direct cytoprotective effect or acts by increasing the levels of endogenous cytoprotective prostaglandins. In any case, our results demonstrate that this drug, which has been shown clinically to enhance the healing of gastric ulcers, shares with the prostaglandins the phenomenon of gastric cytoprotection in the rat.

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