Gastric Lesion-Preventing or -Potentiating Activity of Clonidine in Rats

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Abstract—The dual effects of clonidine on gastric experimental damage have been studied in the rat. At lower doses, clonidine prevents gastric lesions induced by oxotremorine plus neostigmine, probably through an α2-agonist mechanism; at higher doses, the compound potentiates dimaprit-induced gastric damage, probably through an H2-agonist mechanism.

Publications on the effects of clonidine on gastric acid secretion have appeared (1, 2). The overall results indicated that clonidine has both inhibitory and excitatory effects on gastric acid secretion. The inhibitory effect appears to be mediated through the activation of presynaptic α2-receptors that modulate the release of acetylcholine from the vagus nerve, while the excitatory action seems to be due to histamine-like properties of the drug. The influence of clonidine on gastric lesions has been much less studied. The aim of the present study was to elucidate this aspect in rats. First of all, the study used gastric damage caused by oxotremorine plus neostigmine. This model has been shown to be based on activation of muscarinic receptors (3).

Female albino Sprague Dawley rats, fasted 24 hr before the test but allowed free access to water were used for all studies. Neostigmine (Sigma), 3 mg/kg, was given orally. Fifteen min later, clonidine (Sigma) or atropine (BDH) was given intravenously; 30 min later, oxotremorine (Sigma) (0.650 mg/kg, i.v.) was administered. Animals were killed for autopsy 60 min after oxotremorine, and gastric lesions were then evaluated.

Ten rats each were used for the control and drug-treated groups. The compounds were freshly dissolved in 0.9% w/v NaCl solution (saline). Doses were expressed as free bases. Controls were given the same amount of aqueous vehicle.

As can be observed in Fig. 1, both clonidine and atropine were effective against gastric damage induced by oxotremorine plus neostigmine, and this activity was dose-related. The mechanism of anti-ulcer activity was further investigated. To examine the role of the alpha-2 sympathomimetic effects of clonidine in protecting against gastric damage, the anti-ulcer properties of clonidine or atropine were evaluated in the presence of an alpha-1 adrenergic receptor blocker, prazosin (ICN, K≈K), and an alpha-1 and alpha-2 adrenergic receptor blocker, phentolamine (ICN, K≈K), given 45 min before the antiulcer agent. Phentolamine, at a dose of 10 mg/kg, p.o., which had no effect "per se" on oxotremorine plus neostigmine-induced damage, prevented the anti-ulcer activity of clonidine, but not that of atropine. On the contrary, prazosin given at the same dose and by the same route did not modify the anti-ulcer activities of either compound (Fig. 1).

The last part of the paper shows the hyper-ulcerogenic properties of clonidine when dimaprit is the ulcerogenic agent. Dimaprit is an H2-histamine receptor agonist (4) and induces gastric lesions which are based on H2-receptor activation (5).

Clonidine or ranitidine (Glaxo) was injected intravenously into 24-hr fasted rats; 15 min later, dimaprit (kindly supplied by Smith Kline & French) (50–100 mg/kg, i.v.) was given; and the autopsy was done 60 min after the H2 agonist. The numbers of animals'
way of dissolving compounds and way of expressing doses were as described above. Clonidine (0.3–1.0 mg/kg, i.v.) significantly increased the effect of dimaprit on gastric mucosa in a dose-related manner (Table 1). Ranitidine was effective in inhibiting

![Graph](https://via.placeholder.com/150)

**Fig. 1.** Effects of atropine and clonidine on gastric damage induced by neostigmine (3 mg/kg, p.o.) + oxotremorine (650 μg/kg, i.v.) in the rats untreated or pre-treated with an alpha-adrenergic blocker. *P* < 0.05 as compared to the control group. • Ulcerated/treated rats (ten animals for each group).

The percentage incidences of gastric damage in the experimental groups were compared to those in controls and the significance of the differences analyzed by the $\chi^2$ test corrected for continuity (6).

**Table 1.** Effects of clonidine on dimaprit-induced gastric damage in the rat

| Treatment | Ulcerated/treated rats |
|-----------|------------------------|
| Dimaprit (100 mg/kg, i.v.) | 10/10 |
| Dimaprit (50 mg/kg, i.v.) | 2/10 |
| Clonidine (0.3 mg/kg, i.v.) + Dimaprit (50 mg/kg, i.v.) | 7/10a |
| Clonidine (1.0 mg/kg, i.v.) + Dimaprit (50 mg/kg, i.v.) | 10/10a |
| Ranitidine (0.3 mg/kg, i.v.) + Dimaprit (100 mg/kg, i.v.) | 0/10b |
| Ranitidine (0.3 mg/kg, i.v.) + Dimaprit (50 mg/kg, i.v.) | 0/10c |
| Clonidine (0.3 mg/kg, i.v.) | |

$a = P < 0.05$ as compared to low dose dimaprit group, $b = P < 0.05$ as compared to high dose dimaprit group, $c = P < 0.05$ as compared to clonidine+dimaprit group. Statistical analyses as described in Fig. 1.
ulcerogenic processes induced by both dimaprit and dimaprit plus clonidine at the same dose (0.3 mg/kg, i.v.).

In conclusion, these data strongly suggest that, as it does for secretory processes, lower doses of clonidine inhibit gastric lesions by a mechanism involving an alpha-2 mechanism and higher doses potentiate gastric damage by stimulation of H₂ receptors.

References
1 Cheng, H.G., Gleason, E.M., Nathan, B.A., Lachmann, P.J. and Woodward, J.K.: Effects of clonidine on gastric acid secretion in the rat. J. Pharmacol. Exp. Ther. 217, 121–126 (1981)
2 Del Tacca, M., Soldani, G., Bernardini, C., Martinotti, E. and Impicciatore, M.: Pharmacological studies on the mechanisms underlying the inhibitory and excitatory effects of clonidine on gastric acid secretion. Eur. J. Pharmacol. 81, 255–261 (1982)
3 Daniotti, S. and Del Soldato, P.: Comparative studies of the effects of some antimuscarinic agents on gastric damage and pupillary reflex in the rat. Br. J. Pharmacol. 82, 305–307 (1984)
4 Parsons, M., Owen, D., Ganellin, C. and Durant, G.: Dimaprit—[S-3-(N,N-dimethylamino) propyl isothiourea]—a highly specific histamine H₂ receptor agonist. I. Pharmacology. Agents Actions 7, 31–37 (1977)
5 Del Soldato, P.: Studies with specific agonists and antagonists of the role of histamine H₁- and H₂-receptor activation in the pathogenesis of gastric lesions in rats. Agents Actions 14, 139–142 (1984)
6 Snedecor, G. and Cochran, W.: Statistical Methods. p. 209–210, Iowa State University Press, Iowa City (1972)