Prevention of Duodenal Ulcers in Rats by Feeding (35282)

ANDRÉ ROBERT AND JAMES E. DALE

Experimental Biology, The Upjohn Company, and Department of Biology, Western Michigan University, Kalamazoo, Michigan 49001

Duodenal ulcers have been produced in rats by constant subcutaneous infusion of the following secretogogues: histamine, carbachol, and pentagastrin (1, 2). The ulcers are localized in the duodenum, whereas the stomach remains intact. When given alone, however, each of these agents induced duodenal ulcers only in a small proportion of animals. When any two of the secretogogues were combined, synergism was observed so that nearly all animals developed ulcers at low doses of each agent. Since histamine dihydrochloride plus carbachol is a particularly effective combination, it was used in the present study. With this treatment, ulcers appear within 6 hr, and their incidence is maximal after 12 hr. Ulcer severity, however, progressively increases up to 48 hr, at which time mortality and incidence of perforation are the highest.

Since clinical studies have repeatedly shown that the presence of food in the stomach alleviates ulcer symptoms, in the present study, food, in the form of pellets, was offered to rats during constant infusion with ulcerogenic doses of histamine and carbachol to see whether formation of duodenal ulcers would be influenced.

Methods. Female Upjohn rats (formerly Sprague-Dawley) weighing an average of 210 g were divided into four groups: (I) 6 rats, saline, and food; (II) 6 rats, saline, and fasted; (III) 35 rats, histamine plus carbachol, and food; and (IV) 36 rats, histamine plus carbachol, and fasted.

Either saline or the combination of 0.1 mg/kg/min of histamine dihydrochloride and 0.3 μg/kg/min of carbachol was infused subcutaneously from a constant infusion machine at a rate of 13 ml/24 hr, for 48 hr. The animals were placed in perforated stainless steel tubes which allowed some movement, but which prevented them from reaching the infusion tubing. The infusion tubing was made of Tygon, and was connected at one end to a needle introduced subcutaneously and kept in place with a surgical clip. The other end of the tubing was attached to the syringe containing a solution of the secretogogues and mounted on an infusion machine. The dosage was calculated from the body weight taken immediately prior to infusion. The compounds were diluted in saline and mixed in the same syringe. In groups II and IV, food was removed overnight prior to infusion but the animals had access to water; groups I and III were fed *ad libitum* during the same period. During the infusion, groups I and III were constantly supplied with food pellets (Purina Laboratory Chow) and water, while groups II and IV were deprived of food and water for the entire 48 hr. The animals were then killed with chloroform, and the stomach and duodenum were dissected out, opened along the mesenteric attachment for the duodenum and the greater curvature for the stomach. The organs were then coded and mixed to prevent immediate identification, and examined with a binocular magnifier for ulcerations. Incidence of mortality, perforation, and ulcers were expressed as percentages per group, and the average number of ulcers per duodenum in each group was recorded.

Results. At the end of 48 hr, 36% of the fasted treated animals (group IV) were dead, 92% developed duodenal ulcers, and in 53% of the animals the duodenum was perforated (Table I). Several animals died in this group, all with peritonitis consequent to duodenal perforation. On the other hand, there were no deaths among the fed rats (Group III), no perforations, and only 14% developed duodenal ulcers, which were mild. Groups I and II, infused with saline, showed

TABLE I. Effect of Feeding on Duodenal Ulcers and Mortality Due to Infusion of Histamine Plus Carbachol.

	Saline		Histamine + carbachol[a]	
	I Fed	II Fasted	III Fed	IV Fasted
No. of animals	6	6	35	36
Mortality (%)	0	0	0	36
Perforated ulcer (%)	0	0	0	53
Duodenal ulcer	0	0	14	92
No./duodenum	0	0	0.2	2.2

[a] Histamine 0.1 mg/kg/min + carbachol 0.3 μg/kg/min.

no ulcers. Rats given pellets ate much of the food; at autopsy, in Group III, several rats had visible food in their stomach.

Discussion. These results indicate that feeding prevents the formation of duodenal ulcers produced by constant infusion of histamine plus carbachol. This protective action is probably due to the buffering by food of gastric secretion stimulated by the combination of these two secretogogues. A previous study (unpublished) of the effect of histamine plus carbachol on gastric secretion in chronic fistula rats showed that acid concentration and output reached a maximum at 6 to 8 hr of infusion, after which time the values declined below control levels. It is likely that buffering of gastric juice by food, especially during these first few hours of infusion when secretion rate is highest, may be sufficient to protect the duodenum from the ulcerogenic properties of the secretogogue combination.

The protection seen in the present study is reminiscent of the clinical observation that eating alleviates ulcer symptoms. These results suggest that duodenal ulcers produced by infusion of secretogogues represent a useful model for the study of antiulcer agents.

Summary. Duodenal ulcers were produced in fasted rats by constant subcutaneous infusion of histamine dihydrochloride (0.1 mg/kg/min) plus carbachol (0.3 μg/kg/min), two potent gastric secretogogues. These ulcers were perforated in many animals, and 36% of those so treated died of peritonitis. When the animals were given food and water during infusion of the secretogogues, none died nor had duodenal perforations, and only a few showed duodenal ulcers, which were mild. These results are reminiscent of the beneficial effect of feeding on ulcer symptoms in man. Duodenal ulcers produced by the secretogogues used in this study are probably due to excessive secretion of gastric juice, and it is likely that the protection afforded by food results from the buffering of this strongly acid and peptic gastric juice.

1. Robert, A., and Stout, T. J., Fed. Proc., Fed. Amer. Soc. Exp. Biol. **28**, 323 (1969).

2. Robert, A., Stout, T. J., and Dale, J. E., Gastroenterology **59**, 95 (1970).

Received Sept. 2, 1970. P.S.E.B.M., 1971, Vol. 136.