Marked Healing-Promoting Action of Cimetidine on Acetic Acid-Induced Ulcer in Rats with a Limited Food-Intaking-Time

Mikio ITO, Tamio TSUKAHARA and Yoshio SUZUKI
Department of Pharmacology, Faculty of Pharmacy, Meijo University,
Tenpaku-ku, Nagoya 468, Japan

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Abstract—The effect of cimetidine on ulcer healing was investigated in rats with acetic acid induced ulcer who were permitted to intake food only between 9:30–10:30 a.m. and 6:00–7:00 p.m. When evaluated on the 15th and 21st days after operation, cimetidine (100 mg/kg x 2/day, p.o.) markedly decreased the ulcer index and the defective area of the ulcerated region. Moreover, this agent pronouncedly increased the decreasing index of exposed ulcer floor and the mucosal regeneration index. On the 21st day, the thickness of the ulcer base was decreased by this agent, the involution of granulation being indicated. Thus, marked healing-promoting action of cimetidine on acetic acid-induced ulcer was observed by limiting the food-intaking-time.

Histamine H2-receptor antagonists are well-known to strongly inhibit gastric acid secretion and markedly promote healing of human peptic ulcers (1, 2). However, the healing-promoting action of this kind of agent on experimental chronic ulcers in rats is not as marked as that on human peptic ulcers (3, 4). These experimental animals are usually permitted to intake food freely all through the experimental period. As a result, the stomachs of the animals unlike those of humans are never completely empty whenever they are cut open. Furthermore, the ulcerated part may not directly exposed to HCl and pepsin due to the presence of food. We have already reported that the healing of acetic acid-induced ulcer in rats is significantly delayed by limiting the food-intaking-time (5). In the present study, the healing-promoting action of cimetidine, a histamine H2-receptor antagonist, was assessed by using a model of acetic acid-induced ulcer in rats with a limited food-intaking-time.

Gastric ulcer was induced in male Sprague-Dawley rats weighing approx. 180 g by injection of 0.05 ml of 20% acetic acid into the serosal layer in the glandular part of the stomach in accordance with the method described by Takagi et al. (6). These animals were permitted to intake commercial food pellets freely only between 9:30–10:30 a.m. and 6:00–7:00 p.m. every day from 3 days prior to acetic acid injection. However, tap water was always supplied ad libitum. Cimetidine was suspended in 1% gum arabic and administered orally, twice a day (at 11:00 a.m. and 7:30 p.m.), in a volume of 0.5 ml per 100 g of body weight for 14 or 20 consecutive days after operation. Control animals were given 1% gum arabic only instead of the test drug. On the 15th or 21st day, the animals were sacrificed by rapid decapitation. The stomachs were removed and filled with 5 ml of 10% formalin. After 5 min, the stomachs were cut open along the greater curvature. The longitudinal and abscissal lengths of the upper-opened part of the ulcer were measured under observation with a stereoscopic microscope setting a micrometer, and the product of both lengths (mm2) was expressed in terms of the ulcer index. After measuring the ulcer size, histological measurements were performed by light micrography of hematoxylin and eosin-stained preparations by the method reported previously (4). Moreover, the degree of development of collagen fibers was evaluated under light microscopic observation.
of Masson trichrome-stained preparations (4, 7). Drug evaluation was carried out according to the following parameters: the thickness of the ulcer base, the defective area in the ulcerated region, the decreasing index of exposed ulcer floor, the mucosal regeneration index and the development index of collagen fibers. The results obtained were statistically analyzed by Student's t-test.

The results are given in Fig. 1. When evaluated on the 15th day after operation, cimetidine (100 mg/kg x 2/day, p.o.) markedly decreased the ulcer index and the defective area in the ulcerated region by 66.7% and 53.6%, respectively. In addition, this drug caused potent increasing actions of 48.7% and 118.4% on the decreasing index of exposed ulcer floor and the mucosal regeneration index, respectively. However, the thickness of the ulcer base and the development index of collagen fibers were little affected by this drug. The assessment on the 21st day revealed that the effects of cimetidine were almost similar to those on the 15th day. In addition, the thickness of the ulcer base was decreased 34.1% by this drug.

Our previous study on acetic acid-induced ulcer in rats with a limited food-intaking-time indicated that the ulcerated part may be exposed to acid for a long time at night due to gastric emptying (5). On the other hand, the stomachs of food-intaking-time non-limited rats were filled with the digested food whenever they were cut open. It is well-known that the intragastric pH elevates after meals by the diluting action and the buffering action of digested food. Therefore, it is assumed that histamine H₂-receptor antagonists having a potent inhibitory action on gastric secretion can not exert a great effect when examined by using rats whose stomachs are constantly filled with digested food. However, it cannot be concluded only from the above findings that the marked

![Graph](image-url)

**Fig. 1.** Effects of cimetidine on the healing of acetic acid-induced ulcer in rats. Each column denotes the mean value with S.E. (N=8–10). Ul: Ulcer index. BT: Thickness of ulcer base. DA: Defective area in ulcerated region. EDI: Decreasing index of exposed ulcer floor. MRI: Mucosal regeneration index. CDI: Development index of collagen fibers. *P<0.05, **P<0.01, ***P<0.001, compared with the control.
healing-promoting action of cimetidine on acetic acid-induced ulcer in rats with limited food-intaking-time may be attributed to inhibition of the gastric secretion. Further investigation is needed to examine the effect of cimetidine on gastric secretion and to assess the effects of different types of gastric secretory inhibitors (i.e., anti-muscarine agents and anti-gastrin agents) on the ulcer healing in this model in order to clarify this problem.

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