Gastric Antral Ulcers Induced by a Combination of Acid, Indomethacin and Ischemia in Rats

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Accepted March 27, 1985

Abstract—Gastric antral lesions were produced with hemorrhages by vascular ligation-induced ischemia in the prepyloric regions in rats. Additional treatments with intraluminal acid application and indomethacin markedly aggravated the lesions. Histological examination showed that the incidence of ulcers which penetrated the muscularis mucosae was nearly 100% upon treatment with a combination of acid, indomethacin and ischemia. This model provides a useful tool for studying gastric ulcer etiology.

The pathogenesis of gastric ulceration has not been fully elucidated. However, the importance of mucosal circulation (1, 2) and/or endogenous prostaglandins (PGs) (3, 4) to sustain the integrity of the gastric mucosa has been suggested. Recent reports indicated that gastric mucosal blood flow (5) and endogenous PGE levels (6) are decreased in patients with gastric ulcers. Furthermore, the progress of ulcer healing paralleled their recovery. In the present study, we found that severe gastric antral ulcers could be produced by a combination of intraluminal acid, indomethacin and local ischemia in rats.

Male Jcl Sprague-Dawley rats, weighing 200–250 g, were fasted for 24 hr prior to the experiments, but allowed free access to water during the fasting periods. The rats were anesthetized with sodium pentobarbital (50 mg/kg, s.c.). After a midline laparotomy, the prepyloric branches of both the gastric artery and the right gastro-epiploic artery were ligated. The abdominal incision was closed, and the animals were killed with an overdose of ether 24 hr after the operation. The stomachs were removed, fixed in 10% buffered formalin and opened along the greater curvature. The area of each lesion was measured under a binocular microscope (x10) with a 1 mm square-grid eye, and the lesion index was expressed as the sum of the areas of these lesions. Indomethacin (3 mg/kg, i.p., as a suspension in 1% gum arabic) and 150 mM HCl (1 ml/animal by gavage) were administered 1 hr before and immediately after, respectively, the vascular ligation. Statistical analysis was performed using Student’s t-test or the z²-test.

Table 1 summarizes the gastric lesion formation found at 24 hr after the vascular ligation. Macroscopically, the ligation usually produced only one lesion with hemorrhages in the antrum and produced few or no lesions in the corpus. The area of the lesions was markedly increased when the ligation was combined with topical application of acid and injection of indomethacin. No gross lesions were produced by indomethacin alone or in combination with topical acid application in the sham-operated rats.

Histological examination showed that half of the antral lesions had penetrated through the muscularis mucosae extending into the submucosal layer in the group treated with vascular ligation alone. Compared with this, the incidence of the antral ulcers reached to 94% after administration of both acid and indomethacin. Figure 1 shows the typical gastric antral lesions 24 hr after treatment with a combination of acid, indomethacin and vascular ligation.

In humans, gastric ulcers are mostly
located in the antral portions along the lesser curvature (7, 8). Although many experimental models for gastric ulcer have been developed using small laboratory animals, the lesions produced, in most cases, are acute erosions and not ulcers which occur in the acid-bearing portions. The difference between the mucosal blood flow in the corpus and in the antrum may be correlated with the susceptibility of damage. Recently, Murakami et al. (9) and Leung et al. (10) reported that the gastric mucosal blood flow was greater in the antrum than in the corpus in anesthetized rats. Furthermore, Menguy and Masters indicated in a series of their reports that the breakdown of adenosine triphosphate, a key metabolic intermediate of gastric mucosa, was more severe in the
The present paper shows that true antral ulcers could be produced by ischemia restricted to the prepyloric regions. The severity of the lesions increased when both acid and indomethacin were administered, although indomethacin did not induce gastric lesions by itself. This result suggests that the mucosal protection by endogenous PGs may be partly independent of mucosal circulation. Recent studies have shown that gastric antral ulcers could be produced by indomethacin in re-fed rats (13) or by indomethacin in combination with vagus nerve-stimulating secretagogues such as 2-deoxy-D-glucose in rats (14). However, since nearly lethal doses of indomethacin are needed to produce such gastric ulcers, these methods are unsuitable for studying the healing process; animal mortality is high. Preliminary experiments revealed that the ulcers could still be observed on the 30th day after treatment with a combination of acid application, indomethacin and vascular ligation. Experiments are now in progress to study the developing and healing processes of ulcers.

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