The effect of a new gastric proton pump inhibitor on serotonin-induced gastric mucosal lesions in rats

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Summary: The anti-ulcer effect of NC-1300, a new proton pump inhibitor, and its effect on gastric mucosal blood flow were studied in rats. Acute gastric mucosal lesions were induced by the subcutaneous administration of serotonin, 20 mg/kg. Using the electrolytically generated hydrogen gas clearance technique, it was determined that such gastric ulceration resulted mainly from a decrease in gastric mucosal blood flow. These lesions could be inhibited to a statistically significant extent by the intravenous administration of NC-1300, 20 mg/kg, which markedly inhibited gastric acid secretion. However, the serotonin-induced decrease in gastric mucosal blood flow could not be prevented by pretreatment with 20 mg/kg of NC-1300. It was concluded that protection against serotonin-induced gastric ulceration can be achieved by markedly inhibiting gastric acid secretion. Gastroenterol Jpn 1988;23:501–505

Key Words: Gastric acid secretion, Gastric mucosal blood flow, Gastric ulcer, Proton pump inhibitor, Serotonin-induced ulcer

Introduction

Gastric mucosal blood flow (GMBF) is important to the defense mechanism of the gastric mucosa. Accordingly, it is useful to examine the pathophysiology and treatment of peptic ulcer through an experimental model in which ulcers were induced mainly by decreasing the GMBF. Gastric mucosal lesions induced by serotonin were studied because it was thought that this agent might decrease the GMBF and lead to acute gastric mucosal lesions.

We previously reported that the proton pump inhibitor, omeprazole, had no effect on GMBF. In this paper, we examine the effect of a new proton pump inhibitor on GMBF in serotonin-induced gastric mucosal lesions.

Materials and Methods

Male Wistar strain rats weighing approximately 200 g were deprived of food but not water for 20 hours before each experiment. Animals were anesthetized by the subcutaneous injection of 1 g/kg of ethyl carbamate.

1. Confirmation of the ulcerogenic effect of serotonin

Serotonin creatinine sulfate (serotonin) at a dose of 2 mg/kg or 20 mg/kg was administered subcutaneously to rats. Animals were sacrificed four hours later, and their stomachs were resected. To quantify gastric mucosal hemorrhagic lesions, both the cardia and the pylorus were ligated, and 5 ml of 1% formalin solution was introduced into the stomach. The resected stomach was immersed in 1% formalin solution.
for about 30 minutes. Following this light fixation, the stomach was opened along the greater curvature and the length (mm) of the gastric mucosal lesions was measured with a ruler. The sum of the length of the individual lesions was defined as the ulcer index. Then, following complete fixation in 10% formalin solution and staining with hematoxylin and eosin, specimens of the gastric mucosa were examined microscopically.

2. Effect of serotonin on gastric secretion

To examine the effect of serotonin on gastric secretion, gastric juice was collected according to the method of Shay, et al.2. Following laparotomy performed through a mid-line incision, the stomach was lavaged clean by 5 ml of saline delivered through an oro-gastric tube and subsequently removed by suction. The pylorus was then ligated carefully without damaging the blood vessels, and serotonin, 2 or 20 mg/kg, or saline (1 ml) as control, was administered subcutaneously. Four hours later, the cardia was ligated and the stomach was resected. Gastric juice was collected from the resected stomach for measurement of acid concentration and pepsin activity.

3. Effect of serotonin on GMBF

To determine the effect of serotonin on GMBF, we measured this parameter by an electrolytically generated hydrogen gas clearance technique as we previously described1. Following laparotomy, a single needle-type electrode was inserted into the anterior wall of the corpus ventriculi. After administration of 0.5 ml of saline through the tail vein, the GMBF was measured. This was taken as the apparent GMBF baseline value (Fa). Fifteen minutes after the saline injection, serotonin, 2 or 20 mg/kg, was injected subcutaneously, and the apparent GMBF (Fa) was measured 30 and 60 minutes later. After those measurements, 2 ml of 5% KCl solution was injected intravenously to induce cardiac arrest. Fifteen minutes after sacrifice, the apparent blood flow (Fd) was measured as indicated by the simple diffusion of hydrogen gas. The true GMBF (Ft) at each point was then calculated according to the equation,

\[ Ft = Fa - Fd. \]

4. Effect of proton pump inhibitor on gastric secretion

We examined the effect of a new proton pump inhibitor, 2-[(2-dimethylaminobenzyl) sulfinyl] benzimidazole (NC-1300), synthesized by Okabe, et al.3, on gastric acid and pepsin output. We used the sodium salt of NC-1300 (NC-1300 Na) which can be administered intravenously. To confirm its inhibitory effect on gastric secretion, 2 or 20 mg/kg of NC-1300 Na or 1 ml of saline as a control were administered through the tail vein, and 4 hours later gastric juice was collected by the pylorus ligation method. Acid and pepsin output were then measured.

5. Effect of NC-1300 Na on GMBF

Using the electrolytically generated hydrogen gas clearance technique, GMBF was measured before, immediately after, and again at 15 and 30 minutes following the intravenous administration of 2 or 20 mg/kg of NC-1300 Na.

6. Effect of NC-1300 Na on serotonin-induced ulcer

To elucidate the effect of NC-1300 Na on serotonin-induced ulcer, 2 or 20 mg/kg of NC-1300 Na were administered through the tail vein followed by the subcutaneous injection of serotonin, 20 mg/kg. The ulcer index was measured by macroscopic observation four hours after administration of serotonin.

Under subcutaneous administration of serotonin at a dose of 20 mg/kg, the effect of NC-1300 Na at a dose of 20 mg/kg on the gastric juice secretion was studied using the pylorus ligation method described. Gastric juice was collected for 4 hours. Acid and pepsin output were then measured.

The effect of NC-1300 Na pretreatment on the serotonin-induced decrease of GMBF was studied using the electrolytically generated hydrogen gas clearance technique. The GMBF