



## Different Antiulcer Activities of Pantoprazole in Stress, Alcohol and Pylorus Ligation-Induced Ulcer Models

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Antiulcer effects of pantoprazole, a proton-pump inhibitor, on water-immersion restraint stress (WIRS)-, alcohol (ethanol)- and pylorus ligation-induced gastric ulcers were investigated in male rats. Rats were orally administered with pantoprazole 30 min prior to exposure to various types of ulcer inducers. In stress-induced ulcer model, rats were subjected to WIRS at 22°C for 4 hours, and the degree of ulcer (in mm) was evaluated. In alcohol-induced ulcer model, rats were orally administered with pure (100%) ethanol (1 mL/kg), and the ulcer lesions were measured 1 hour after ethanol challenge. In pylorus ligation-induced ulcer model, rats were subjected to pylorus ligation, and the degree of erosions and ulcers was scored 17 hours after the operation. Pantoprazole attenuated the ulcer lesions induced by WIRS in a dose-dependent manner, exhibiting a median effective dose (ED<sub>50</sub>) value of 0.78 mg/kg. By comparison, pantoprazole was effective at relatively-high doses for the improvement of ethanol-induced ulcers, showing an ED<sub>50</sub> value of 20.5 mg/kg. Notably, pantoprazole was practically ineffective (ED<sub>50</sub>>50.0) in pylorus ligation model. Taken together, it was confirmed that pantoprazole showed inhibitory activity on gastric ulcers induced by stress and alcohol, but was ineffective on pylorus ligation-induced ulcer. Therefore, the results indicate that proton-pump inhibitors including pantoprazole might reveal highly-different effects according to the type of ulcer inducers, and that the prescription of antiulcer agents should be carefully selected.

**Keywords:** Pantoprazole, gastric ulcer, stress, alcohol, pylorus ligation

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Peptic ulcers are injury of the mucosal area immersed in gastric acid and pepsin, wherein the area is covered normally with mucin secreted from mucus cells (Wallace and Granger, 1996; Neal, 2003). Ulceration results from the imbalance between gastroprotective and aggressive factors (Lou *et al*, 2006). The aggressive factors such as increased gastric secretion and retention, increased generation of reactive oxygen species (ROS) and proinflammatory cytokines such as interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor-necrosis factor- $\alpha$  (TNF- $\alpha$ ) and IL-6, and blood

flow disturbances cause mucosal damages (Hemmer *et al*, 1980; Konturek *et al*, 1990; Das and Banerjee, 1993). An apoptosis is also causative factor for gastric ulceration (Piotrowski *et al*, 1997a, 1997b; Fujii *et al*, 2000). An imbalance between the Bcl-2 family of antiapoptotic protein and apoptotic Bax protein in the early stage of gastric ulcer promotes apoptosis (Slomiany *et al*, 1997; Fujii *et al*, 2000).

Gastric ulcer is a serious injury occurring by spicy food, stress, alcohol, gastric surgery and *Helicobacter (H.) pylori* (Neal, 2003). In many studies, water-immersion restraint stress (WIRS)-, alcohol (ethanol)- and pylorus ligation-induced gastric ulcer models have been used to screen antiulcer compounds, since mechanisms of those models are different (Kitagawa *et al*, 1979; Wallace and Granger, 1996; Shah *et al*, 2003; Isobe *et al*, 2004; Cao *et al*, 2005; Byun *et al*, 2007; Raffin *et al*, 2007). WIRS, a generalized model to induce extreme

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mental and psychological stresses to rodents, stimulates gastric secretion related to central nervous system as well as pituitary-renal hormonal axis (Kitagawa *et al*, 1979; Wallace and Granger, 1996; Neal, 2003; Isobe *et al*, 2004; Cao *et al*, 2005; Byun *et al*, 2007). Ethanol causes not only mucosal stasis, leading to hemorrhage and necrosis, but also lipid peroxidation by triggering radical reactions (Shah *et al*, 2003; Raffin *et al*, 2007). Long-term pylorus ligation induces retention of gastric acid secreted by cholinergic activation and stimulates activity of pepsin, resulting in gastric wall injury (Wallace and Granger, 1996; Neal, 2003).

The enzyme  $H^+/K^+$ -ATPase pumps protons in exchange for potassium ions across the apical membrane to secrete gastric acid by parietal cells (Wallmark *et al*, 1985). Histamine antagonists including cimetidine and ranitidine as well as proton pump inhibitors such as omeprazole and lansoprazole are well known effective drugs for the treatment of peptic ulcers by decreasing the gastric secretion (Neal, 2003). Pantoprazole, a water-soluble benzimidazole, is converted to its active form inside the gastric parietal cells, also improves acid-related, hypersecretory gastrointestinal disorders by irreversibly inhibiting  $H^+/K^+$ -ATPase activity (Lindberg *et al*, 1986; Fitton *et al*, 1996; Jungnickel, 2000; Raffin *et al*, 2007). In addition, pantoprazole has a cytoprotective activity, which might attenuate the gastric mucosal injury (Lou *et al*, 2006; Raffin *et al*, 2007).

It was believed that pantoprazole, as a broad spectrum antiulcer agent, exerts improving effects on various types of gastric ulcer. However, it was assumed that pantoprazole possesses different therapeutic ranges according to the inducers of gastric mucosal injury. Therefore, this study was performed to investigate the comparative antiulcer activities of pantoprazole in WIRS-, alcohol- and pylorus ligation-induced ulcer models.

## Materials and Methods

### Animals

Six-week-old male Sprague-Dawley rats ( $n=10$  per group) weighting 200-220 g were purchased from the Orient Bio Inc. (Gapyeong, Gyeonggi, Korea). The animals were housed in each cage with free access to feed and water under constant environmental conditions ( $22\pm 2^\circ\text{C}$ ; 40-70% relative humidity; 12-hour light-dark cycle; 150-300 lux brightness). All the animal experiments were adhered to the Standard Operation Procedures and approved by the Institutional Animal Care and Use Committee of Chungbuk National University.

### Effect on WIRS-induced gastric ulcer

Rats were fasted 48 hours with only free access to water before performance of the experiment. Each rat was orally administered 6 dose levels (0.625, 1.25, 1.875, 2.5, 5 or 10 mg/kg) of pantoprazole (Sigma-Aldrich; St. Louis, MO, USA) or its vehicle [1% carboxymethylcellulose (CMC), 5 mL/kg]. Thirty min later, the rats were placed in a restraint device and immersed up to their xiphoid process in a  $22^\circ\text{C}$  water bath for 4 hours for the induction of gastric ulcer (Byun *et al*, 2007). After sacrifice of the animals, their stomachs were removed, inflated with 1% formalin (10 mL), and fixed in the formalin solution for 15 min. The stomachs were longitudinally excised along the great curvature. The gastric content was removed by gentle wiping with Kimwipes, and the stomach was unwrapped and fixed on a corkboard with pins. The length of ulcer (hemorrhagic) lesions were measured, in which 5 petechial lesions was calculated as 1 mm. Ulcer index was presented as the total length (mm) of the lesions. The results were expressed as a median effective dose ( $ED_{50}$ ) based on the dose-dependent inhibition rates.

### Effect on ethanol-induced gastric ulcer

After 48-hour fasting, animals were orally administered with 4 dose levels (5, 10, 25 or 50 mg/kg) of pantoprazole or its vehicle (CMC). Thirty min later, the rats were orally administered with 1 mL/kg of ethanol for the induction of gastric ulcer (Kim *et al*, 2008). The animals were sacrificed 1 hour after ethanol administration, and their stomachs were removed. The stomachs were processed and examined as described above.

### Effect on pylorus ligation-induced gastric ulcer

After 48-hour fasting, animals were orally administered with 5 dose levels (2.5, 5, 10, 25 or 50 mg/kg) of pantoprazole or its vehicle (CMC). Thirty min later, the rats were subjected to an operation which was approached from abdominal median incision. The pylorus connected to duodenum was ligated, and the peritoneum and skin were sutured (Shay *et al*, 1945; Cao *et al*, 2005). The animals were sacrificed 17 hours after pylorus ligation, and their stomachs were removed. The stomachs were processed as described above, and the gastric mucosal lesions were examined under a stereomicroscope ( $\times 3$ ). The number and degree of erosions and ulcers were scored in 0-5 levels as described in the Table 1 (Cantarella *et al*, 2005, 2007). The results were expressed as  $ED_{50}$  based on the dose-dependent inhibition rates.

**Table 1.** Score for macroscopic gastric damage evaluation in rats with pylorus ligation

Score	Macroscopic gastric damage
0.0	No lesions
0.5	Diffuse hyperemia
1.0	1 to 2 small erosions
1.5	3 to 6 small erosions
2.0	7 to 10 small erosions
2.5	More than 10 small erosions
3.0	1 marked erosion plus 0 to 4 small erosions
3.5	1 marked erosion plus 5 or more small erosions
4.0	2 marked erosions plus 0 to 4 small erosions
4.5	2 marked erosions plus 5 or more small erosions
5.0	3 or more marked erosions

Small < 2 mm; marked  $\geq$  2 mm.

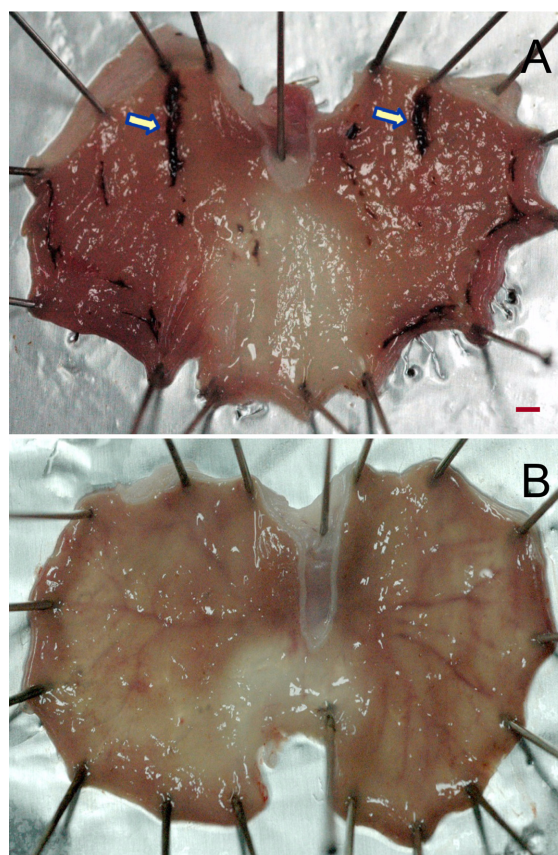
### Statistical analysis

The results are presented as means  $\pm$  standard deviation. The significance of differences of all results was analyzed by one-way analysis of variance followed by the Tukey's test correction. Statistical significance was set a priori at  $P < 0.05$ .

## Results and Discussion

Gastric erosions and ulcers are induced by various factors including gastric oversecretion and retention, weakening and depleting agents of mucin layer, blood flow disturbances, and mucosal injury and inflammation (Wallace and Granger, 1996; Neal, 2003; Isobe *et al*, 2004; Byun *et al*, 2007). The ulcer-inducing agents include non-steroidal antiinflammatory drugs (NSAID) that block production of prostaglandins, leading to mucin depletion and blood flow disturbances (Slomiany *et al*, 1997; Filaretova *et al*, 2002; Cao *et al*, 2004; Rao *et al*, 2004; Kim *et al*, 2005), alcohols (Cao *et al*, 2004; Rao *et al*, 2004; Raffin *et al*, 2007), stresses (Cao *et al*, 2004; Rao *et al*, 2004; Byun *et al*, 2007), gastric oversecretion and retention (Rao *et al*, 2004; Cao *et al*, 2005), gastric hypermotility and acetic acid accumulation (Dias *et al*, 2000; Rao *et al*, 2004; Cantarella *et al*, 2005; Isbil *et al*, 2006; Cantarella *et al*, 2007), and *H. pylori* infection (Wallace and Granger, 1996; Neal, 2003). For the therapy of gastric ulcers, proton-pump inhibitors that block acid secretion from parietal cells, antacids, histamine receptor ( $H_2$ ) antagonists, prostaglandins that strengthen mucin layer, and antibiotics to eliminate *H. pylori* have been used (Wallace and Granger, 1996; Neal, 2003).

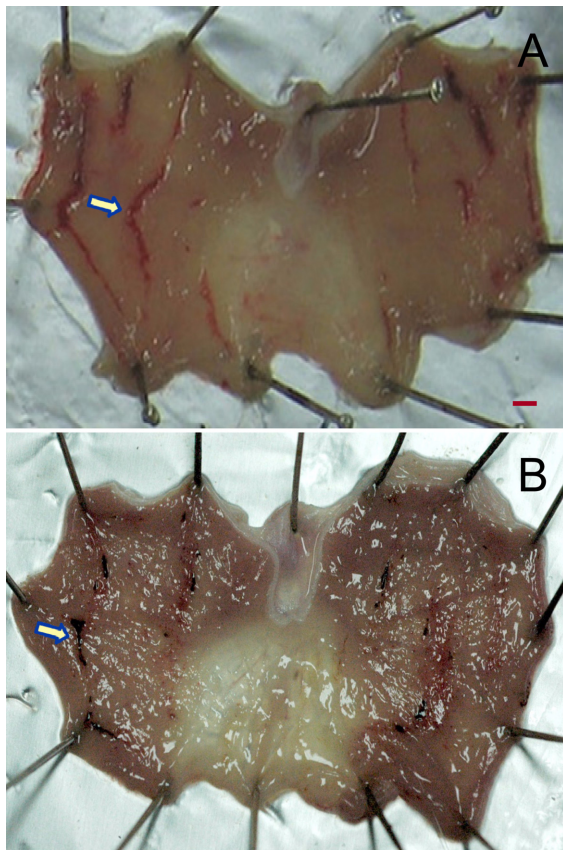
In the present study, the antiulcer effects of pantoprazole, a proton-pump inhibitor, was investigated in WIRS-, ethanol- and pylorus ligation-induced gastric ulcer models, and the comparative efficacies of pantoprazole were evaluated. Four-



**Figure 1.** Representative findings of gastric ulcers (arrows) induced by water-immersion restraint stress. Rats were placed in a restraint device, immersed up to their xiphoid process in a 22°C water bath, and sacrificed 4 hours later for the measurement of ulcer lesions. A, vehicle control; B, 5 mg/kg pantoprazole. Scale bar=1 mm.

hour WIRS produced a linear type of hemorrhagic ulcers (Figure 1A), showing mean ulcer index of 22.3 mm. Such lesions were attenuated by pretreatment with pantoprazole in a dose-dependent manner (Figure 1B). The ulcer index was inhibited to 55.2, 31.1, 26.8, 5.5, and 8.6% of control value by 0.625, 1.25, 2.5, 5 and 10 mg/kg of pantoprazole, respectively, leading to 0.78 mg/kg of  $ED_{50}$  (Table 2). Such an excellent effect of pantoprazole proton-pump inhibitor was expected from the previous results that gastric secretion was facilitated during severe stresses (Kitagawa *et al*, 1979; Wallace and Granger, 1996; Neal, 2003; Cao *et al*, 2004). Furthermore, proton-pump inhibitors including pantoprazole and lansoprazole prevent mucosal cells from cytotoxicity and death induced by indomethacin, stress and ethanol, suggesting that their cytoprotective effect is also an additional key factor for the antiulcer activity (Cao *et al*, 2004; Lou *et al*, 2006; Raffin *et al*, 2007).

Oral administration of ethanol (1 mL/kg) induced many linear hemorrhagic ulcers 1 hour after administration (Figure



**Figure 2.** Representative findings of gastric ulcers (arrows) induced by ethanol (1 mL/kg). Rats were orally administered with 1 mL/kg of pure ethanol, and sacrificed 1 hour later for the measurement of ulcer lesions. A, vehicle control; B, 10 mg/kg pantoprazole. Scale bar=1 mm.

2A), showing mean ulcer index of 53.9 mm. The lesions were attenuated by pretreatment with pantoprazole in a dose-dependent manner (Figure 2B). The ulcer index was inhibited to 63.1, 60.5, 47.0, and 9.8% of control value by 5, 10, 25 and 50 mg/kg of pantoprazole, respectively (Table 2). However, the effective dose was much higher than in stress-induced ulcer model, showing 20.5 mg/kg of ED<sub>50</sub>. Ethanol was reported to facilitate gastric secretion, which may

contribute to some degree to ulceration. Histamine receptor 2 (H<sub>2</sub>)-mediated gastric secretion is not involved in the alcoholic ulcer, since the ethanol-induced lesions are not suppressed by cimetidine (Robert *et al*, 1979; Raffin *et al*, 2007). Instead, it was proposed that mucosal stasis and radical reactions are the main stream cascade for the induction of alcoholic mucosal injury (Shah *et al*, 2003; Raffin *et al*, 2007). Therefore, it is suggested that the effect of pantoprazole comes from the cytoprotective activity, not related to prostaglandins synthesis (Konturek *et al*, 1983; Cao *et al*, 2004). However, the overall effectiveness of pantoprazole was practically low for the alcohol-induced ulcer as shown in the present study.

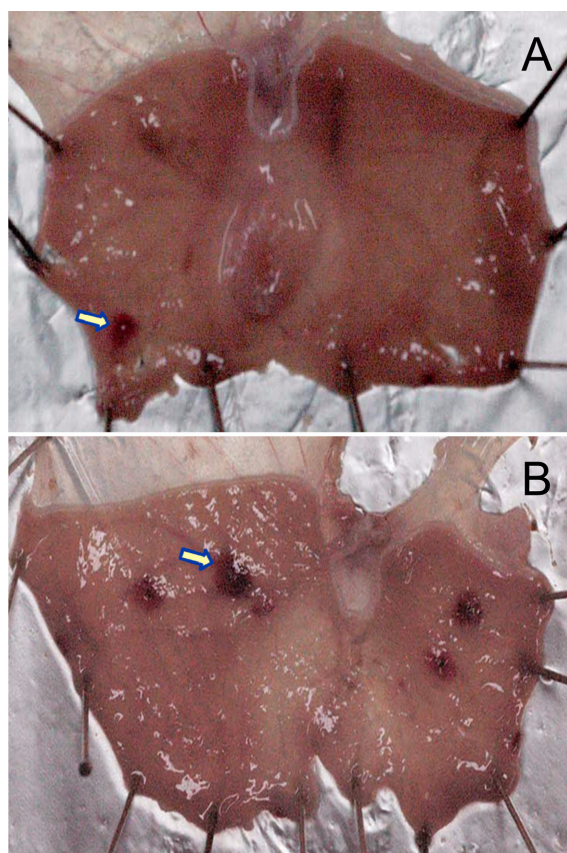
Seventeen-hour pylorus ligation caused focal erosions and petechial ulcers (Figure 3A), showing mean score of 3.94 (maximum score 5.0). Although the lesions were attenuated by 30-min pretreatment with pantoprazole, the effects were obtained by only very high doses without dose-dependent responses at low doses (5-10 mg/kg) (Figure 3B), resulting in an ED<sub>50</sub> of over 50.0 mg/kg (Table 2). In the present study, pantoprazole exhibited biphasic activities, which may be due to its suppression of gastric secretion and direct cytoprotection at low and high doses, respectively (Cao *et al*, 2004, 2005). Notably, pylorus ligation induced mucosal and submucosal hemorrhages, rather than erosions and ulcers (Figure 3), making investigators difficult to measure the length or area of the ulcer lesions. In this context, we adopted a scoring system which has been used in reserpine model (Cantarella *et al*, 2005, 2007), to evaluate more accurately diverse types of the lesions including hemorrhages (petechia and ecchymosis), erosions and ulcers. It is of interest to note that there was a big difference in the effective doses between a previous report (Cao *et al*, 2005) and our present observations. Although the measuring systems were different between the 2 studies (ulcer area versus lesion score), the discrepancy remains to be clarified.

In spite of multiple mechanisms, gastric secretion is one of the main factors for ulceration, because most types of

**Table 2.** Effects of pantoprazole on the gastric ulcer index (mm) and score (maximum score=5.0) induced by water-immersion restraint stress (WIRS), pure ethanol (1 mL/kg) and pylorus ligation

Treatment (mg/kg)		Vehicle	0.625	1.25	2.5	5	10	25	50	ED <sub>50</sub> (mg/kg)
WIRS	Ulcer index (% of control)	22.3±2.6 (100.0)	12.3±3.5* (55.2)	6.9±2.5* (31.1)	6.0±1.7* (26.8)	1.2±0.4* (5.5)	1.9±1.7* (8.6)	ND (-)	ND (-)	0.78
	Ulcer score (% of control)	53.9±3.2 (100.0)	ND (-)	ND (-)	ND (-)	34.0±6.9* (63.1)	32.6±6.5* (60.5)	25.3±6.0* (47.0)	5.3±1.5* (9.8)	20.5
Pylorus ligation	Ulcer score (% of control)	3.94±0.26 (100.0)	ND (-)	ND (-)	3.62±0.34 (91.9)	4.06±0.24 (103.0)	4.39±0.18 (111.4)	3.63±0.36 (92.1)	2.50±0.69* (63.5)	>50.0

Median effective dose (ED<sub>50</sub>) represents an estimated dosage inhibiting the lesions to the half level of control group. ND, not determined. \*Significantly different from vehicle control ( $P<0.05$ ).



**Figure 3.** Representative findings of gastric ulcers (arrows) induced by pylorus ligation. Rats were subjected to an operation of pylorus ligation, and sacrificed 17 hours later for scoring of ulcer lesions. A, vehicle control; B, 25 mg/kg pantoprazole.

the ulcers induced by diverse agents were attenuated by the secretion inhibitors (Cao *et al*, 2004). Activated pantoprazole in parietal cells reduces gastric secretion by irreversibly inhibiting the proton-pump  $H^+/K^+$ -ATPase (Kromer *et al*, 1990; Cao *et al*, 2004; Raffin *et al*, 2007). In addition to gastric secretion, however, several factors such as cell death and recovery, inflammation, stasis and blood flow are involved in the process of ulcer formation (Lou *et al*, 2006). Especially, the effectiveness of pantoprazole was poor in pylorus ligation model. Thus, additional investigations on the effects of pantoprazole using various models remain to be clarified.

In the present study, it was demonstrated that pantoprazole has different improving effects in WIRS-, ethanol- and pylorus ligation-induced gastric ulcer models: i.e., highly effective, practically low effective, and ineffective, respectively. Therefore, it is suggested that the effects of proton-pump inhibitors including pantoprazole might be highly different according to the type of ulcer inducers, and that the prescription of antiulcer agents should be carefully selected.

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