Effects of 15(R)-15-Methyl Prostaglandin E2 (Arbaprostil) on Gastric Secretion and Various Gastric Lesions Induced in Rats

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Abstract—We studied the effects of 15(R)-15-methyl prostaglandin E2 (arbaprostil) on gastric secretion and various acute and chronic gastric lesions produced in rats. Arbaprostil significantly inhibited gastric secretion in 4 hr-pylorus-ligated preparations when given intraduodenally in a dose of 30 or 100 µg/kg. The agent, however, significantly stimulated gastric secretion of rats with either a ligated or intact pylorus when given orally in doses of 3–100 µg/kg. Orally administered arbaprostil dose-dependently prevented the development of HCl-ethanol-, histamine-, water-immersion stress-, or indomethacin-induced gastric erosions. Intraduodenally administered arbaprostil also dose-dependently prevented the development of aspirin-induced gastric erosions in pylorus-ligated rats. Arbaprostil, given orally in doses of 1–100 µg/kg twice daily for 2 weeks, had little or no effect on the healing of acetic acid-induced gastric ulcers. However, oral administration of the agent in a dose of 3 or 10 µg/kg twice daily for 4 weeks significantly accelerated the healing of acetic acid-induced gastric ulcers. The increase in doses up to 100 µg/kg twice daily for 4 weeks had no effect on ulcer healing. These results indicate that arbaprostil, at either antisecretory or even acid stimulating doses, is effective in preventing the development of acute gastric erosions and in accelerating the healing of chronic gastric ulcers.

Various prostaglandin analogs have anti-secretory and antiulcer effects both in experimental animals and man, as reviewed by Miller (1). Of these analogs, 15(R)-15-methyl prostaglandin E2 (arbaprostil) or its methyl ester, like other prostaglandins, inhibits gastric secretion of rats, dogs, or man (2–6). In addition, these agents protected the gastric mucosa of rats from acute injury induced by pylorus ligation, aspirin, taurocholic acid or HCl-taurocholic acid (7–9). Arbaprostil also protected the gastric mucosa of man from aspirin-induced injury (10). The mechanism of action of arbaprostil and its methyl ester is postulated to be due to their potent antisecretory effects as well as to the so-called “cytoprotective” activity. In addition, arbaprostil or its methyl ester, promotes the healing of chronic gastric and duodenal ulcers in man (11–14). In most of these clinical studies, the doses of these prostaglandins were antisecretory ones. Whether or not the nonantisecretory doses of prostaglandins also have a beneficial effect on healing of preexisting chronic gastric ulcers was investigated by determining the effect of arbaprostil on gastric secretion and various acute and chronic gastric lesions induced in rats. A part of this work was published earlier (15).

Materials and Methods
Male Donryu rats (220–260 g) were deprived of food but allowed free access to water for 24 hr prior to the experiments, unless otherwise noted.

Gastric secretory studies
Two kinds of experiments were done to determine the effect of arbaprostil on gastric secretion. In the first study, pylorus ligation preparations were used as follows: Under ether anesthesia, the abdomen was incised...
and the pylorus ligated. Four hr after the pylorus ligation, the animals were killed, and the gastric contents were collected and analyzed for volume, acidity and pepsin activity. Acidity was determined by automatic titration of the gastric juice against 0.1 N NaOH to pH 7.0 (Autoburette, Radiometer). Pepsin activity was determined by Anson's method using bovine albumin as a substrate (16). Titratable acid output and pepsin output were expressed as uEq/hr and mg tyrosine/hr, respectively. Arbaprostil (Upjohn, 10–100 µg/kg) or saline as the corresponding vehicle was given either intraduodenally (i.d.) immediately after pylorus ligation or orally (p.o.) by gastric intubation 30 min before pylorus ligation in a volume of 0.5 ml/100 g body wt. In the second study, an animal with the intact pylorus was used. Arbaprostil (1–100 µg/kg) or saline was given p.o. in a volume of 0.5 ml/100 g body wt. The animals were killed 0.5, 4.5 or 7.5 hr later. At autopsy, the esophagus and the pylorus were clamped, and the gastric juice was collected. Gastric samples were analyzed for volume and acidity as described above. Pepsin activity was not determined in this study, because only a small amount of gastric juice was present in the stomach.

Arbaprostil was first solubilized into absolute ethanol (0.1 ml for each milligram); then saline was added.

Gastric lesions

HCl-ethanol-induced erosions: One hundred and fifty mM HCl-60% ethanol (v/v) was given p.o. in a volume of 0.5 ml/100 g body wt. (17). The animals were killed 1 hr later, and the stomach was removed and inflated by injecting 12 ml of 2% formalin to fix the inner and outer layers of the gastric walls. This formalin treatment was performed in all the following experiments. Subsequently the stomach was incised along the greater curvature and examined for erosions. Arbaprostil (0.3–3 µg/kg) or saline alone was given p.o. 30 min before HCl-ethanol administration.

Histamine-induced erosions: Histamine 2HCl (Nakarai), dissolved in saline, was given intraperitoneally (i.p.) in a dose of 100 mg/kg. The animals were killed 4 hr later, and the stomach was examined for erosions. Arbaprostil (3–100 µg/kg) or saline alone was given p.o. 10 min before histamine administration.

Water-immersion stress-induced erosions: Rats not fasted before experiments were placed in a restraint cage (Natsume, Tokyo) (18) and then immersed vertically to the level of xiphoid process in a water bath (23°C) (19). Seven hr later, the animals were killed, and the stomachs were examined for erosions. Arbaprostil (3–100 µg/kg) or saline alone were given p.o. 10 min before stress.

Indomethacin-induced erosions: Indomethacin (Sigma), suspended in 1% carboxymethylcellulose (CMC), was given subcutaneously (s.c.) in a dose of 25 mg/kg. The animals were killed 7 hr later, and the stomach was examined for erosions. Arbaprostil (3–100 µg/kg) or saline alone was given p.o. 10 min before indomethacin treatment.

Aspirin-induced erosions: Under ether anesthesia, the abdomen was incised and the pylorus ligated. Aspirin (Merck), suspended in 1% CMC, was given p.o. in a dose of 150 mg/kg 5 min after pylorus ligation (20). The animals were killed 7 hr later, and the stomach was examined for erosions. Arbaprostil or saline alone was given i.d. immediately after pylorus ligation.

Acetic acid-induced ulcers: An acetic acid-induced gastric ulcer is a chronic ulcer model which penetrates the muscularis mucosa, persists for more than 100 days (21, 22), and is sensitive to antiulcer drugs (23, 24). Therefore, we used this ulcer model to examine the effect of arbaprostil on ulcer healing. Under ether anesthesia, the abdomen of rats not fasted before the experiments was incised and the anterior portion of the stomach was exposed. Then 0.03 ml of 20% acetic acid (v/v) was injected into the submucosal layer in the antrum near its junction with the corpus (21). After closure of the abdomen, the animals were maintained on rat chow and water ad libitum thereafter. Arbaprostil (1–100 µg/kg) or saline alone was given p.o. twice daily (9:00 AM, 6:00 PM) starting from the 5th day after the operation for 2 or 4 weeks to rats with gastric ulcers. The animals were killed 16 hr after the final administration of arbaprostil or saline, and the stomach was examined for ulcers.
Erosion and ulcer index: The length (mm) of each erosion induced by HCl-ethanol, histamine, water-immersion stress, indomethacin, or aspirin was measured under a dissecting microscope with a square grid (×10), summed per stomach, and used as an erosion index. The area (mm²) of the ulcer induced by acetic acid was also measured under a dissecting microscope and used as an ulcer index.

Analysis of data
Data are expressed as the mean±one standard error. Student’s t-test was used to determine the statistical significance of data, and P<0.05 was regarded as significant.

Results

Effects on gastric secretion: Pylorus ligation of control animals for 4 hr resulted in an accumulation of gastric juice, i.e., the volume, acid and pepsin output ranged from 4–8 ml/rat, 50–140 μEq/hr, and 7–20 mg tyrosine /hr, respectively. Armaprostil given i.d. dose-dependently inhibited the gastric secretion (Fig. 1). At 10 μg/kg, there was no alteration in gastric secretion, as compared to

![Graph showing effects of arbaprostil on gastric secretion in pylorus-ligated rats (4 hr). Arbaprostil or saline as a control was given either intraduodenally (i.d.) immediately after pylorus ligation or p.o. 30 min before pylorus ligation.](image-url)
the control values. When 100 μg/kg was given, the inhibition of volume, acid and pepsin output were 47.2%, 63.0% and 60.7%, respectively. In contrast, arbaprostil given p.o. dose-dependently increased gastric secretion in pylorus-ligated rats. At 100 μg/kg, the increase in volume, acid and pepsin output was more than double of the control values.

In intact animals, the gastric contents determined 0.5, 4.5 or 7.5 hr after saline administration were negligible, i.e., about 0.1 ml/animal. Arbaprostil given p.o. practically dose-dependently increased the volume and acid output as compared to the control values (Figs. 2 and 3). At 0.5 hr, the volume and acid output of rats treated with 3 μg/kg of the agent were 0.4±0.04 ml/animal and 18.6±4.7 μEq/0.5 hr, respectively. When 10, 30, or 100 μg/kg of the agent was given, the volume and acid output was 0.6±0.1 ml/animal, 22.4±4.3 μEq/0.5 hr, 1.5±0.2 ml/animal, 47.8±13.0 μEq/0.5 hr, or 2.7±0.2 ml/animal, 81.9±9.5 μEq/0.5 hr, respectively. At 4.5 hr, the volume and acid output of rats treated with 3 or 10 μg/kg were much the same as those seen in the control group. At 100 μg/kg, however, the volume and acid output were 1.2±0.3 ml/animal and 30.9±7.4 μEq/4.5 hr, respectively. At 7.5 hr, arbaprostil at 10, 30 or 100 μg/kg also significantly increased the volume and acid output, although those values were apparently decreased as compared to those observed at 0.5 or 4.5 hr after administration.

Effects on various acute erosions: HCl-ethanol, histamine, water-immersion stress, indomethacin, or aspirin induced multiple, band-like or dotted, elongated erosions in either the corpus or antrum, or both, of control animals at the incidence of 100%. Arbaprostil given p.o. dose-dependently protected the gastric mucosa from injury induced by HCl-ethanol, histamine, water-immersion stress or indomethacin (Fig. 4). HCl-ethanol-induced erosions were significantly inhibited in a dose of 1 or 3 μg/kg of arbaprostil. At 3 μg/kg, the inhibition of erosion formation was 88.8%. Histamine-, water-immersion stress- and indomethacin-induced erosions were also significantly inhibited in doses over 10 μg/kg. At 100 μg/kg, the inhibition of the above erosions was 93.8%, 91.4% and 98.8%, respectively. Arbaprostil given i.d. significantly inhibited aspirin-induced erosions in pylorus-ligated rats (Fig. 5). The inhibition of erosion formation was 44.2%, 50.9% or 54.0% in a dose of 10, 30 or 100 μg/kg, respectively.

Effects on acetic acid-induced ulcers: Submucosal injection of 20% acetic acid

![Graph](image-url)
consistently induced penetrating ulcers by the 5th day after injection; the mean ulcerated area was about 64 mm² (N=20). Nineteen and thirty-three days after injection, the mean ulcerated area in control animals was 7.8±0.9 mm² (N=30) and 5.2±0.7 mm² (N=25), respectively. Arbaprostil given p.o. at 1–100 μg/kg twice daily for 2 weeks had no or little effect on the healing of gastric ulcers (Fig. 6). However, arbaprostil given p.o. at 3 or 10 μg/kg twice daily for 4 weeks significantly accelerated the healing of ulcers: the inhibition in ulcer index being 50.0% or 44.2%, respectively. Increase in doses of arbaprostil up to 30 or 100 μg/kg had no effect on ulcer healing. Unfavorable side effects, such as weight change, were nil during the treatment with arbaprostil.

Discussion

Our observations indicate that while the efficacy of arbaprostil on gastric secretion depends on the route of administration, it does have a beneficial effect on experimentally-induced gastric lesions.

Concerning gastric secretion, we confirmed the antisecretory property of arbaprostil in rats as was already observed in dogs and man (2–6), although the agent was given i.d. in the present study. In contrast to i.d. administration, the p.o. administration of 3–100 μg/kg of arbaprostil significantly increased gastric secretion of rats with a ligated or intact pylorus and the degree of stimulation was more extensive in the pylorus-ligated rats. In rats with an intact
pylorus, this stimulation appeared 0.5 hr after the administration of 3 μg/kg or over of the agent and persisted for up to 4.5 hr when 30 or 100 μg/kg was given. This enhanced secretion then declined 7.5 hr after the treatment, possibly by emptying of the gastric contents into the duodenum. Therefore, it is most likely that arbaprostil stimulates gastric secretion through unknown mechanisms, when applied topically to the stomach.

These results suggest that it is a cytoprotective activity of arbaprostil given p.o. by which the gastric mucosa is kept free from injury induced by either gastric irritants or stress. It is noteworthy that arbaprostil was effective in preventing HCl-ethanol-induced erosions in a dose of 3 μg/kg. This same dose stimulated gastric secretion 0.5 hr after treatment. Since the present study was one of gross inspection, protection of the surface epithelial and deeply located cells against HCl-ethanol-induced damage would have to be studied in detail. Both water-immersion stress and indomethacin will reduce levels of endogenous prostaglandins in the rat stomach (25, 26). Therefore, the effect of arbaprostil on erosion formation may partly involve the replacement of deficient endogenous prostaglandins.

Gilbert et al. (10) reported that arbaprostil given p.o. in an antisecretory dose sig-
significantly inhibited aspirin-induced damage in the stomachs of volunteers. Carmichael et al. (8) demonstrated that 15(R)-15-methyl prostaglandin E2 methyl ester given p.o. at 50 μg/kg significantly inhibited aspirin-induced gastric erosions in rats. We also confirmed that arbaprostil significantly prevented aspirin-induced erosions in rats, although the effects of the agent were weak as compared to those observed in the above 4 erosion models. Since arbaprostil was given i.d., the effect of the agent on aspirin-induced erosions appears to be partly linked to its antisecretory activity. Similar to indomethacin, aspirin also reduces endogenous prostaglandins of the gastric mucosa of rats (27). Thus, the replacement of deficient prostaglandins by arbaprostil might also contribute to the maintenance of mucosal integrity.

Of interest was the finding that while administration of arbaprostil for 2 weeks had little or no effect on healing of acetic acid-induced ulcers, the agent given for 4 weeks significantly accelerated healing of the ulcers. Fung et al. (11) reported that 15(R)-15-methyl prostaglandin E2 methyl ester given p.o. for 2 weeks significantly accelerated the healing of human gastric ulcers. The difference between our data and the clinical data of Fung et al. may be due to the times of administration. They gave the agent 4 times daily in a dose of 150 μg (about 2 μg/kg). It is possible that even in rats the increase in times of administration of arbaprostil may promote the healing of ulcers after 2 weeks treatment. As described above, 4 weeks treatment with arbaprostil led to a significant enhancement of ulcer healing. However, it should be noted that there was an optimal dose for the agent to reveal a beneficial
effect. Even 3 or 10 μg/kg of arbaprostil given twice daily resulted in an enhanced healing. The increase in doses up to 100 μg/kg twice daily conversely decreased its effect in healing ulcers. Ishibashi et al. (28) reported similar results that 15(R)-15-methyl prostaglandin E₂ methyl ester significantly accelerated the healing of acetic acid-induced ulcers in rats when 2 μg/kg of the agent was given twice daily for 12 days. They found that the increase in doses up to 10 μg/kg had no effect on healing of the ulcers. The increase in doses of arbaprostil resulted in parallel increases in efficacy in cases of acute gastric erosions. Why the increase in doses reduced its efficacy in healing the preexisting ulcers is difficult to explain. Stimulation of gastric acid secretion by p.o. arbaprostil may be partly responsible for the reduced effects. We found that 3 or 10 μg/kg of arbaprostil is a dose which stimulates gastric secretion when given p.o. The accelerating effect of arbaprostil, therefore, is likely to occur through mechanisms other than the effect on gastric secretion.

Tarnawski et al. (29) recently reported that while 16,16-dimethyl prostaglandin E₂ in a dose of 5 or 100 μg/kg did not protect the surface epithelial cells against injury induced by absolute ethanol, it did enhance reconstitution of the damaged epithelium. It appears that 3 or 10 μg/kg of arbaprostil accelerates the reconstitution of the surface epithelial cells around the acetic acid-induced ulcers, thereby resulting in enhanced healing. We found that both sucralfate as an antipepsin agent (30) and omeprazole as an anti-secretory and cytoprotective agent (31, 32) dose-dependently accelerated acetic acid-induced ulcers after 2 or 8 weeks treatment (33). Whether these agents and arbaprostil act on the ulcers through the same mechanism remains unknown.

We conclude that while arbaprostil given p.o. stimulates gastric secretion, the agent potently protects the gastric mucosa from various types of acute injury and accelerates the healing of chronic gastric ulcers at cytoprotective doses.

References
1 Miller, T.A.: Protective effects of prostaglandins against gastric mucosal damage; Current knowledge and proposed mechanisms. Am. J. Physiol. 245, G601–G623 (1983)
2 Robert, A. and Magerein, B.J.: 15-methyl PGE₂ and 16,16-dimethyl PGE₂: Potent inhibitors of gastric secretion. Adv. Biosci. 9, 247–253 (1973)
3 Robert, A. and Yankee, E.W.: Gastric anti-secretory effect of 15(R)-15-methyl PGE₂, methyl ester and 15(S)-15-methyl PGE₂, methyl ester. Proc. Soc. Exp. Biol. Med. 148, 1155–1158 (1975)
4 Robert, A., Schultz, J.R., Nezamis, J.E. and Lancaster, C.: Gastric antisecretory and antiulcer properties of PGE₂, 15-methyl PGE₂, and 16,16-dimethyl PGE₂. Intravenous, oral and intrajejunal administration. Gastroenterology 70, 359–370 (1976)
5 Karim, S.M.M., Carter, D.C., Bhana, D. and Ganesan, P.A.: Effect of orally and intravenously administered prostaglandin 15(R)-15-methyl E₂ on gastric secretion in man. Adv. Biosci. 9, 255–264 (1973)
6 Johansson, C., Befrits, R., Wonen, O. and Kallner, A.: Effect of graded 15(R)15 methyl prostaglandin E₂ and of indomethacin on the gastric secretory and plasma gastrin response to modified shamfeeding. Acta Physiol. Scand. 122, 421–426 (1984)
7 Carter, D.C., Ganesan, P.A., Bhana, D. and Karim, S.M.M.: The effect of locally administered prostaglandin 15(R)15 methyl-ethyl ester on gastric ulcer formation in the Shay rat preparation. Prostaglandins 5, 455–463 (1974)
8 Carmichael, H.A., Nelson, L., Russell, R.I., Chandra, V., Lyon, A. and Cochran, K.M.: The effect of prostaglandin 15(R)15 methyl-E₂ methyl ester on asprin and taurocholic acid-induced gastric mucosal hemorrhage in rats. Gut 17, 33–36 (1976)
9 Carmichael, H.A., Nelson, L., Russell, R.I., Lyon, A. and Chandra, V.: The effect of the synthetic prostaglandin analog 15(R)15 methyl-PGE₂ methyl ester on gastric mucosal hemorrhage induced in rats by taurochollic acid and hydrochloric acid. Dig. Dis. Sci. 5, 411–414 (1977)
10 Gilbert, D.A., Surawicz, C.M., Silverstein, F.E., Weinberg, C.R., Saunders, D.R., Feld, A.D., Sanford, R.L., Bergman, D. and Washington, P.: Prevention of acute asprin-induced gastric mucosal injury by 15-R-15 methyl prostaglandin E₂: An endoscopic study. Gastroenterology 86, 339–345 (1984)
11 Fung, W.P., Karim, S.M.M. and Tye, C.Y.: Effect of 15(R)-15-methyl prostaglandin E₂ methyl
ester on healing of gastric ulcers. Controlled endoscopic study, Lancet 2, 10–12 (1974)

12 Fung, W.P. and Karim, A.M.M.: Effect of 15(R)-15-methyl prostaglandin E$_2$ on the healing of gastric ulcers—double blind endoscopic study. Med. J. Aust. 2, 127–128 (1976)

13 Rybicka, J. and Gibinski, K.: Methyl-prostaglandin E$_2$ analogues for healing of gastroduodenal ulcers. Scand. J. Gastroenterol. 13, 155–159 (1978)

14 Vantrappen, G., Janssens, J., Popieila, T., Kulig, J., Tytgat, G.N.J., Huibregtse, K., Lambert, R., Pauchard, J.P. and Robert, A.: Effect of 15(R)-15-methyl prostaglandin E$_2$ (Arbaprostil) on the healing of duodenal ulcer. A double-blind multicenter study. Gastroenterology 83, 357–363 (1982)

15 Jino, H., Hayashi, Y., Hiraoka, H., Tanaka, H. and Okabe, S.: Protective effects of 15(R)-15-methyl PGE$_2$ (Arbaprostil) on acute gastric lesions in rats (Abs.). Gastroenterology 88, 1434 (1985)

16 Anson, M.L.: The estimation of pepsin, trypsin, papain and cathepsin with hemoglobin. J. Gen. Physiol. 22, 79–89 (1938)

17 Mizui, T. and Doteuchi, M.: Effect of polyamines on acidified ethanol-induced gastric lesions in rats. Japan. J. Pharmacol. 33, 939–945 (1983)

18 Takagi, K. and Okabe, S.: The effects of drugs on the production and recovery processes of the stress ulcer. Japan. J. Pharmacol. 33, 939–945 (1983)

19 Takagi, K., Kasuya, Y. and Watanabe, K.: Studies of the drugs for peptic ulcer, a reliable method for producing stress ulcer in rats. Chem. Pharm. Bull. (Tokyo) 12, 465–472 (1964)

20 Okabe, S., Takeuchi, K., Nakamura, K. and Takagi, K.: Pathogenesis of gastric lesions induced by aspirin in the pylorus-ligated rat. Japan. J. Pharmacol. 24, 363–371 (1974)

21 Takagi, K., Okabe, S. and Saziki, R.: A new method for the production of chronic gastric ulcer in rats and the effect of several drugs on its healing. Japan. J. Pharmacol. 19, 418–426 (1969)

22 Okabe, S. and Pfeiffer, C.J.: Chronicity of acetic acid ulcer in the rat stomach. Am. J. Dig. Dis. 11, 619–629 (1972)

23 Okabe, S., Takeuchi, K., Kunimi, H., Kanno, M. and Kawashima, M.: Effects of an antulcer drug, sucralfate (a basic aluminum salt of sulfated disaccharide), on experimental gastric lesions and gastric secretion in rats. Dig. Dis. Sci. 28, 1034–1042 (1983)

24 Yamamoto, O., Okada, Y. and Okabe, S.: Effects of a proton pump inhibitor, omeprazole, on gastric secretion and gastric and duodenal ulcers or erosions in rats. Dig. Dis. Sci. 29, 394–401 (1984)

25 Basso, A., Materia, A., Forlini, A. and Jaffe, B.M.: Prostaglandin generation in the gastric mucosa of rats with stress ulcer. Surgery 94, 104–108 (1983)

26 Whittle, B.J.R.: Temporal relationship between cyclooxygenase inhibition, as measured by prostacyclin biosynthesis, and the gastrointestinal damage induced by indomethacin in the rat. Gastroenterology 80, 94–98 (1981)

27 Ligumsky, M., Golanska, E.M., Hansen, D.G. and Kaufman, G.L.: Aspirin can inhibit gastric mucosal cyclo-oxygenase without causing lesions in rat. Gastroenterology 84, 756–761 (1983)

28 Ishibashi, A., Kasuya, Y., Takeuchi, K. and Okabe, S.: Effects of 15(S)-15-methyl-PGE$_2$ methyl ester on healing of chronic gastric and duodenal ulcers in rats. Japan. J. Pharmacol. 29, 807–810 (1979)

29 Tarnawski, A., Hollander, D., Stachura, J., Krause, W.J. and Gergely, H.: Prostaglandin protection of the gastric mucosa against alcohol injury—A dynamic time-related process. Role of the mucosal proliferative zone. Gastroenterology 88, 334–352 (1985)

30 Nagashima, R., Yoshida, N. and Terao, N.: Sucralfate, a basic aluminum salt of sucrose sulfate. II. Inhibition of peptic hydrolysis as it results from sucrose sulfate interaction with protein substrate, serum albumins. ArzneIMITTforsch. 30, 73–76 (1980)

31 Olbe, L., Haglund, U., Leth, R., Lind, T., Cederberg, C., Ekenveld, G., Elander, B., Fellenius, E., Lundborg, P. and Wallmark, B.: Effects of substituted benzimidazole (H 149/94) on gastric acid secretion in humans. Gastroenterology 83, 193–198 (1982)

32 Mattsson, H., Andersson, K. and Larsson, H.: Omeprazole provides protection against experimentally induced gastric mucosal lesions. Eur. J. Pharmacol. 91, 111–114 (1983)

33 Miyake, H., Fukuda, K., Masuda, Y. and Okabe, S.: Effects of a proton pump inhibitor, omeprazole, on healing of acetic acid-induced gastric ulcers in rats (Abs.). Gastroenterology 88, 1504 (1985)