Gastric Antisecretory Activity of 15(R)-15-Methylprostaglandin E\textsubscript{2}, Arbaprostil, in Dogs

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ABSTRACT—The gastric antisecretory activity of 15(R)-15-methylprostaglandin E\textsubscript{2} (arbaprostil) was compared with that of natural prostaglandin (PG) E\textsubscript{2} in Pavlov pouch dogs. Arbaprostil significantly inhibited pentagastrin- and food-stimulated gastric secretion when it was administered directly into the pouch at a dose of 10–30 \mu g/pouch and 30–300 \mu g/pouch, respectively. Natural PGE\textsubscript{2}, however, was inactive up to 1000 \mu g/pouch. The data indicate that arbaprostil is a potent, long-acting orally active antisecretory drug that may be useful for the treatment of peptic ulcer disease.

The inhibition of histamine and food stimulated gastric acid secretion in dogs by prostaglandins (PGs) was first reported by Robert et al. (1). Since then, extensive studies have been performed to determine how naturally occurring and synthetic PGs regulate gastrointestinal function in both animals and humans (2–4). In these experiments, natural PGs have been shown to suppress gastric secretion when given i.v., but are ineffective after oral administration. A possible explanation for the lack of effect of orally administered PGs on acid secretion is their rapid enzyme catalyzed conversion of the 15-hydroxy position in the stomach (5). 15(R)-15-Methyl PGE\textsubscript{2} (arbaprostil), an analogue of PGE\textsubscript{2} which is methylated at carbon 15 of PGE\textsubscript{2} to prevent metabolic conversion, is currently being evaluated as a new antiulcer agent (6–8).

In this investigation, therefore, the effect of topical administration to the gastric mucosa of arbaprostil was compared with that of natural PGE\textsubscript{2} in dogs prepared with a vagus-nerverated Pavlov pouch.

Five mongrel dogs of either sex (8–12 kg) were used. A vagus-nerverated fundic pouch (Pavlov type) was first constructed under pentobarbital general anesthesia (30 mg/kg, i.v.) (9). The Pavlov pouch was cannulated and drained in the left upper quadrant of the abdomen with a stainless steel cannula. This cannula was used as the outlet route for the gastric juice. After this procedure, a Silastic tube (602-205, Dow Corning, MI, U.S.A.), as an inlet tube for perfusion, was inserted 2 cm into the fundic pouch through a tiny incision made in the pouch.

Experiments were carried out under conscious condition 3 weeks after the operation. After an 18 hr fasting period, the pouch was continuously perfused with distilled water (pH was adjusted to 7.0) through the inlet tube by means of a perfusion pump (STC-521, Terumo, Tokyo, Japan) at the rate of 3 ml/10 min. In all studies, the perfusate including gastric secretion was collected from the outlet cannula at 10-min intervals. Gastric secretion was stimulated either by 20 g/kg of commer-
cial dog food (Gaines Meal; 23% protein, 7% fat; Ajinomoto General Foods Corp., Tokyo, Japan) or by a constant i.v. infusion of pentagastrin. Pentagastrin infusion (1.2 μg/kg/hr) in a volume of 10 ml/hr elicited about half the response obtained after feeding. Sixty minutes after the start of pentagastrin infusion or 3 hr after feeding, one of the PGs or the vehicle (0.5% ethanol) was administered into the pouch directly onto the gastric mucosa through the inlet tube in a volume of 7 ml. Then perfusion was stopped, and the outlet cannula was closed for 10 min to keep the drug in the pouch. Ten minutes after administration, the outlet cannula was opened, and perfusion was started again.

The volume of the perfusate secreted every 10 min was measured, and an aliquot of the perfusate was titrated to pH 7.0 with 0.02 N NaOH by electrometric titration (RTS-822, Radiometer, Copenhagen, Denmark). Acid output of each sample was calculated in μEq/10 min. Drug effects were expressed as percent changes from the preadministration level.

Drug used were 15(R)-15-methylprostaglandin E2 (arbaprostil, the Upjohn Company, Kalamazoo, MI, U.S.A.), prostaglandin E2 (Sigma, St. Lois, MO, U.S.A.) and pentagastrin (Sumitomo Pharmaceutical Co., Osaka, Japan). The PGs were first solubilized in absolute ethanol, and then distilled water was added to make a final ethanol concentration of 0.5%.

Data are presented as the mean ± S.E. from 5 dogs per group. Statistical analysis was made by one-way analysis of variance (ANOVA) coupled with Dunnett's test. P values less than 0.05 were considered statistically significant.

I.v. infusion of pentagastrin (1.2 μg/kg/hr) produced gastric secretion, and the value of acid output for the 10 min immediately before 0.5% ethanol administration (control group) was 330 ± 63 μEq/10 min (N = 5). This value was not significantly different from that of each dosing group. Arbaprostil, administered into the pouch 60 min after starting the infusion of pentagastrin, inhibited the acid secretion. At a dose of 10 μg/pouch, it produced a significant effect from 20 min through 50 min after administration. A dose of 30 μg/pouch caused significant inhibition from 20 min through 120 min after dosing (Fig. 1A).

Following feeding, gastric secretion was gradually increased and the maximal acid output was observed 1–2 hr after feeding. This stimulating effect lasted at least for 5–6 hr after the meal. The mean value of gastric acid output for 30 min before 0.5% ethanol administration (control group) was 737 ± 160 μEq/10 min (N = 5). No significant difference was observed in this value between each dosing group and the control group. Arbaprostil, administered into the pouch 3 hr after meal, dose-dependently inhibited gastric secretion. At a dose of 30 μg/pouch, it produced a significant effect from 20 min through 80 min after administration. A dose of 100 μg/pouch caused significant inhibition from 20 min through 100 min after dosing. Acid output was inhibited significantly by 300 μg/pouch of arbaprostil, beginning at 10 min after administration and lasting for more than 2 hr (Fig. 1B).

Natural PGE2, on the other hand, did not have any significant effect on pentagastrin-induced gastric secretion even at the highest dosage examined (1000 μg/pouch) (Fig. 2A). Food-stimulated secretion was significantly inhibited by PGE2 at a dose of 1000 μg/pouch, but this inhibition was less potent than 30 μg/pouch of arbaprostil (Fig. 2B).

Diarrhea as a side effect was not observed in dogs administered arbaprostil or PGE2 in the present experiments.

Thus, in the present study, arbaprostil inhibited pentagastrin- and food-stimulated gastric acid secretion when administered directly onto the gastric mucosa of the Pavlov pouch. On the other hand, only a slight reduction of the gastric secretion induced by pentagastrin or a meal was observed when natural PGE2 was administered.

The fact that topically applied arbaprostil had more prompt and prolonged antisecretory
actions than PGE₂ suggests that methylation at carbon 15 of PGE₂ prevented enzymatic conversion of arbaprostil in the stomach (5). An important requirement for a clinically useful gastric antisecretory agent is to have a good oral activity. The topical activity of arbaprostil raises speculations about the potential mechanism of the antisecretory action after oral administration in clinical settings.

The oxyntic pouch of dogs such as the Heidenhain pouch or the Pavlov pouch allows an assessment of both the topical activity (direct administration to the pouch) and the systemic activity (oral administration without contact with the mucosa in the pouch) of drugs. According to Gaginella et al. (10) and Dajani et al. (11), the synthetic prostanoids Ro 22-6923 and SC-29333 showed 2.5–3 times more potent antisecretory activity when placed

Fig. 1. Dose-related effects of arbaprostil on gastric acid output stimulated by i.v. infusion of pentagastrin (1.2 μg/kg/hr) (A) and by feeding (B) in the Pavlov pouch dog. Either arbaprostil or 0.5% ethanol (control) was placed into the pouch 60 min after the start of pentagastrin infusion (A) or 3 hr after feeding (B). The post-treatment values were expressed as a percentage of changes from the level before drug administration. Each point represents the mean of 5 observations from 5 dogs. Vertical bars show the mean ± S.E. P < 0.05, **P < 0.01, compared with the control group at the same time. A: 0.5% ethanol (○), arbaprostil (●, 3 μg/pouch; ▲, 10 μg/pouch; ■, 30 μg/pouch). B: 0.5% ethanol (○), arbaprostil (●, 30 μg/pouch; ▲, 100 μg/pouch; ■, 300 μg/pouch).
directly into the gastric pouch than when given orally in dogs. These observations suggest that the antisecretory activities of the synthetic PGs are mainly due to a topical action at the gastric mucosa. The mechanisms of topical activities by PGs are yet not fully understood. On the other hand, Soll et al. (12, 13) reported that PGE₂ and its analogue inhibited acid production/secretion by isolated parietal cells in vitro. The effect is thought to involve the activation of PGE receptors which have been shown to be present on the parietal cell membrane (14). These facts suggest that the inhibitory effect on gastric secretion of PGs occurs primarily at the parietal cell, which may be the basis for the potent antisecretory activity of arbaprostil when it is in contact with the gastric mucosa.

According to the present study, arbaprostil more effectively inhibited pentagastrin-stimulated gastric secretion than food-stimulated secretion. This result may be explained by the

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**Fig. 2.** Effects of prostagalandin (PG) E₉ on gastric acid output stimulated by i.v. infusion of pentagastrin (1.2 μg/kg/hr) (A) and by feeding (B) in the Pavlov pouch dog. Either PGE₂ or 0.5% ethanol (control) was placed into the pouch 60 min after starting of pentagastrin infusion (A) or 3 hr after feeding (B). The post-treatment values were expressed as a percentage of changes from the level before drug administration. Each point represents the mean of 5 observations from 5 dogs. Vertical bars show the mean ± S.E. *P < 0.05, compared with the control group at the same time. 0.5% ethanol (○), PGE₂ (●, 300 μg/pouch; ▲, 1000 μg/pouch).
fact that pentagastrin (1.2 μg/kg/hr) elicited gastric secretion to a level only about half that obtained after feeding. In the vagus-innervated Pavlov pouch that we used, the gastric secretory response induced by food-stimulation is a combination of a series of complex and integrated events regulated by many stimulatory factors that include not only gastrin but also vagal cholinergic activation or histamine.

In summary, arbaprostil was shown to possess antisecretory activity when administered directly into the Pavlov pouch in dogs. The reduction of acid secretion is well-known to play an important role in the therapy of gastric and duodenal ulcers (15). This property of arbaprostil, therefore, suggests that it may be useful for the treatment of peptic ulcer disease.

REFERENCES