J Anesth (1995) 9:303–306

Journal of
Anesthesia

Original articles

Inhibitory effect of prostaglandin E_1 on gastric secretion during general anesthesia in humans

TAKASHI MASHIMO, MASAKI TAKASHINA, YOSHIMI INAGAKI, TOMOYOSHI SETO, YURI TSUDA, and IKUTO YOSHIYA

Department of Anesthesiology, Osaka University Medical School, 2-2 Yamadaoka, Suita-shi, Osaka, 565 Japan

Abstract: The present study was undertaken to clarify the effects of prostaglandin E_1 (PGE_1) on gastric secretion during general anesthesia. Thirty-three patients, 16 with (PGE_1 group) and 17 without (control group) PGE_1 administration, scheduled for selective surgery were studied during general anesthesia with nitrous oxide (67%) and enflurane (1%–2% inspired). PGE_1 was administered at a rate of 50–200 ng·kg^{-1}·min^{-1} when hypotensive medication was required. In the PGE_1 group, gastric juice was collected serially three times before and during administration and 60 min after discontinuation of PGE_1. In the control group, it was collected three times corresponding to those in the PGE_1 group. The pH of gastric juice increased significantly, and the acidity and pepsin activity decreased after the beginning of the administration of PGE_1, and these changes were observed even 1 h after discontinuation. There was significant differences in the pH, acidity, and pepsin activity between the two groups after administration of PGE_1. The results indicate that PGE_1 inhibits gastric secretion at doses that produce a sufficient hypotensive effect under general anesthesia.

Key words: Prostaglandin E_1, Gastric secretion, General anesthesia

Introduction

Gastric stress ulcer is reported to occur sometimes in critically ill patients after surgery [1]. It was speculated to result from an imbalance between aggressive factors, including acid and pepsin, and defensive factors such as mucosal resistance to ulcerogenic stimuli [2]. Drugs such as H_2 antagonists were widely used to decrease the secretion of gastric juice and its acidity during perioperative period [3,4].

Address correspondence to: T. Mashimo
Received for publication on February 28, 1995; accepted on June 20, 1995

Prostaglandin E_1 (PGE_1), which is used for hypotensive anesthesia and management of hypertension during anesthesia, has not only a hypotensive effect but also various other physiologic actions [5–7]. In 1967, Robert et al. [8] reported that PGE_1 suppresses gastric secretion in dogs. Classen et al. [9] also reported that intravenous administration of PGE_1 reduces the volume and acidity of gastric juice in humans when gastric secretion is enhanced by gastric stimulation. However, the effects of PGE_1 on spontaneous gastric secretion during general anesthesia have not been clarified. Therefore, we evaluated changes in the gastric secretion in patients who underwent intravenous infusion of PGE_1 during general anesthesia.

Patients and methods

This study was approved by the Committee for Human Research at our institution and informed consent was obtained from all patients. Thirty-three ASA physical status I–II patients scheduled for elective surgery were studied. Gastric secretion was evaluated during anesthesia in 16 patients administered PGE_1 (PGE_1 group) and 17 controls.

Atropine sulfate (0.5 mg) and hydroxyzine (50 mg) were administered intramuscularly 30 min before induction of anesthesia. Standard monitoring was performed. Anesthesia was induced with thiamylal (4 mg·kg^{-1}) and maintained with nitrous oxide (67%) and enflurane (1%–2% inspired). PGE_1 was administered intravenously by continuous infusion at a rate of 50–200 ng·kg^{-1}·min^{-1} in patients who required hypotensive medication. Saline as a placebo was administered in the control group.

A gastric tube was inserted immediately after induction of anesthesia. In the PGE_1 group, gastric juice was collected serially three times before PGE_1 administration, 60 min after the start of administration, and 60 min after discontinuation. In the control group, it was col-

lected at the same times as in the PGE_1 group. After filtering the gastric juice through absorbent cotton, the pH was determined using a pH tape (Neutralit, Merck, Rahway, NJ, USA), and the remaining sample was frozen until measurement of the acidity and pepsin activity. After the frozen gastric juice sample was thawed, the acidity and pepsin activity were measured in supernatant separated by centrifugation at 3000 rpm for 10 min. The acidity was determined by titration of a dilution of 0.1–1.0 ml of the sample with 50 ml of distilled water against 0.01 N NaOH to an end point of pH 7.0. Titration was made using an automatic titration system (GT-05, Mitsubishi Chemical Industries, Tokyo, Japan). Pepsin activity was determined by a hemoglobin digestion method [10] using 100–200 µl of the sample diluted 3–50 times with 0.04 N HCl. Pepsin values are expressed as micrograms of tyrosine released from the hemoglobin substrate.

Values are expressed as mean ± SD. Parametric data between groups were analyzed by one-way analysis of variance and assessed by Scheffe's test. Parametric data within each group were analyzed by two-way analysis of variance with repeated measures and assessed by paired *t*-test. A *p* value less than 0.05 was considered statistically significant.

Results

Although there were no significant differences in the age or the male-female ratio, the control group showed a significantly lower body weight (Table 1). No significant difference between the two groups was observed in the duration of anesthesia or surgery. The infusion time of PGE_1 was 113.8 ± 47.9 min and the total administration dose was 483.8 ± 232.0 µg in the PGE_1 group. The infusion time of saline was 120 min.

Figure 1A–C shows changes in the pH, acidity and pepsin activity of gastric juice during anesthesia, respectively. In the PGE_1 group, the pH of gastric juice increased significantly and the acidity decreased significantly after the beginning of PGE_1 administration. These changes were observed 60 min after the discontinuation. The pepsin activity of gastric juice tended to decrease during the administration of PGE_1 and decreased significantly after the discontinuation. In the control group, the pH showed as light increase during the administration of saline but the acidity showed no significant change. In contrast, the pepsin activity increased significantly after the administration of saline.

There was no difference in the pH, acidity, or pepsin activity of gastric juice between the two groups before the administration of test drug. The pH was significantly higher in the PGE_1 group than in the control group during the administration and after the discontinuation of PGE_1 (Fig. 1A). The acidity in the PGE_1 group was significantly less than that in the control group after the discontinuation (Fig. 1B). The pepsin activity in the PGE_1 group after the discontinuation was significantly lower than that in the control group (Fig. 1C).

Table 1. Characteristics of subjects

	Control group	PGE_1 group
n	17	16
Sex (M/F)	6/11	9/7
Age (years)	44.5 ± 21.7	50.9± 17.0
Body weight (kg)	51.0 ± 9.4*	58.4 ± 10.5
Duration of surgery (min)	165.6 ± 69.3	220.0 ± 92.5
Duration of anesthesia (min)	230.6 ± 64.3	295.3 ± 98.6

Values are mean ± SD. * $P < 0.05$.
PGE_1, prostaglandin E_1.

Discussion

The pH, acidity, and pepsin activity of gastric juice were all suppressed by PGE_1 at 50–200 $ng \cdot kg^{-1} \cdot min^{-1}$, indicating that PGE_1 inhibits gastric secretion under general anesthesia. The action of PGE_1 to elevate the pH of gastric juice was comparable to that of 20 mg of famotjdine, an H_2 antagonist [4]. The inhibitory action of PGE_1 on gastric secretion persisted for at least 60 min after the discontinuation. Goto et al. [11,12] and Takashina et al. [13] reported that the hypotensive effect of PGE_1 was sustained for more than 1 h after the discontinuation under general anesthesia. Since the blood concentration of PGE_1 has been shown to decrease to the pre-administration level in about 10 min after the discontinuation [12], the reason for prolongation of the effects of PGE_1 remains unclear.

Classen et al. [9] reported that the gastrin-enhanced increase in gastric secretion was suppressed by PGE_1 in healthy adults. However, this result was obtained with a very large dose of 5–7 $\mu g \cdot kg^{-1}$ administered over 30 min. They indicated that no effects on the cardiovascular system such as a reduction in blood pressure were noted at this concentration without anesthesia. Dajani [14] and Brand et al. [15] reported that a PGE_1 analogue administered orally in humans suppressed gastric secretion and was effective as a treatment for peptic ulcer. They speculated that the anti-ulcer effect of PGE_1 is derived from inhibition of gastric acid and pepsin secretion and increase in the gastric mucosal blood flow.

The mechanism of the inhibition of gastric secretion by PGE_1 remains obscure. Nevertheless, the presence of prostaglandins in the gastric mucosal cells has been demonstrated [16–18], and they may play an important physiological role in the mechanism of gastric secretion.

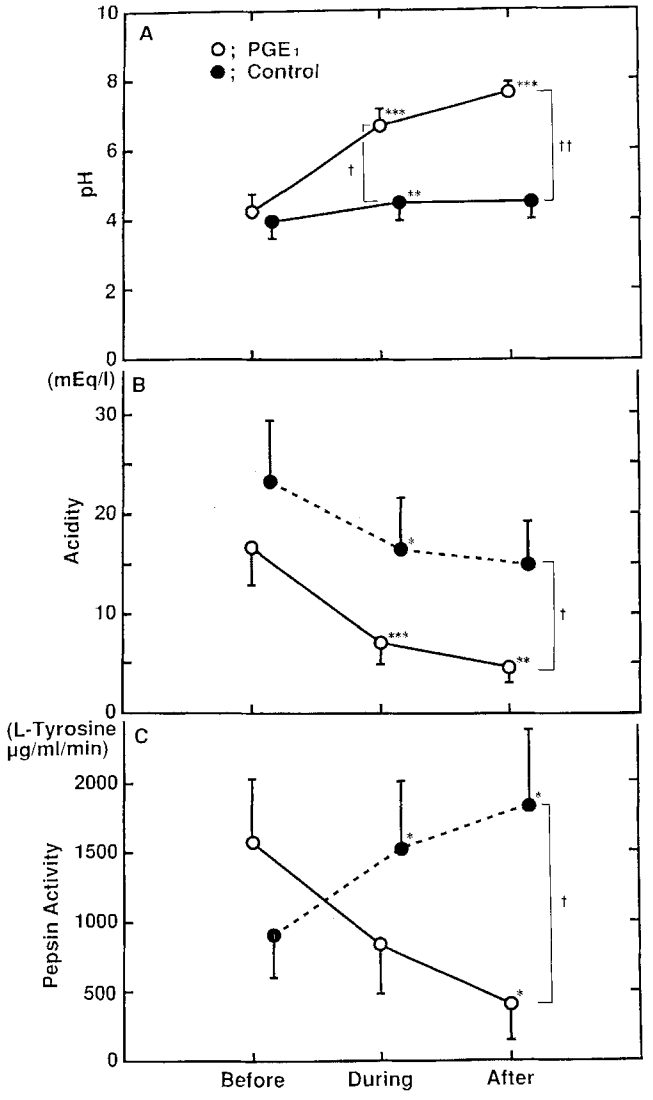

Fig. 1A–C. Changes in the pH (**A**), acidity (**B**), and pepsin activity (**C**) of gastric juice during general anesthesia. The pepsin activity was evaluated in terms of the tryosine release ($\mu g \cdot ml^{-1} \cdot min^{-1}$) from the hemoglobin substrate. Measurements were made before and during the administration and 60 min after the discontinuation of prostaglandin E_1 (PGE_1) in the PGE_1 group. The values of the control group were obtained in samples collected at the same times as in the PGE_1 group. Data are presented as mean ± SD. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ compared with the preadministration value within the group; $^{\dagger}p < 0.05$, $^{\dagger}p < 0.01$ compared with the value in the control group

Coceani et al. [19] clarified in rats that stimulation of the vagus nerve of the gastric wall promotes secretion of gastric juice as well as of PGE_1. Baker et al. [20] reported that pentagastrin and histamine increase gastric acid secretion and promote the release of PGE_2 into the gastric juice. Kobayashi et al. [21] also reported that endogenous prostaglandins inhibit acid secretion in humans. These findings suggest that prostaglandins serve as mediators of the negative feedback in the regulatory mechanism of gastric secretion. Also, PGE_2 is known to bind specifically with porcine gastric wall cells and inhibits the increase in cyclic adenosine monophosphate due to histamine stimulation [22]. Therefore, PGE_1 and PGE_2 are considered to inhibit the H^+ transport mechanism of gastric wall cells by reducing cyclic adenosine monophosphate and, thus, to suppress the secretion of gastric juice [23].

In conclusion, PGE_1 suppressed the pH, acidity, and pepsin activity of gastric juice during general anesthesia. The gastric antisecretory effect of PGE_1 may be promising for the prevention of gastric stress ulcer in the perioperative period.

References

1. Lucas CE, Sugawa C, Riddle J, Rector F, Rosenberg B, Walt AJ (1971) Natural history and surgical dilemma of "stress" gastric bleeding. Arch Surg 102:266–277
2. Ahlquist DA, Dozois RR, Zinsmeister AR, Malagelada JR (1983) Duodenal prostaglandin synthesis and acid load in health and in duodenal ulcer disease. Gastroenterology 85:522–528
3. Coombs DW, Hooper D, Colton T (1979) Preanesthetic cimetidine alteration of gastric fluid volume and pH. Anesth Analg 58:183–188
4. Abe K, Shibata M, Demizu A, Hazano S, Sumikawa K, Enomoto H, Mashimo T, Tashiro C, Yoshiya I (1989) Effects of oral intramuscular famotidine on pH and volume of gastric contents. Anesth Analg 68:541–544
5. Mills DCB, MacFarlane DE (1977) Prostaglandins and platelet adenylate cyclase. In: Silver MJ (ed) Prostaglandins in hematology, Spectrum, New York, pp 219–233
6. Ueda Y, Matsuo K, Kamei T, Kayashima K, Konomi K (1989) Protective effect of prostaglandin E_1 (PGE_1) on energy metabolism and reticuloendothelial function in the ischemically damaged canine liver. Liver 9:6–13
7. Anderson RJ, Berl T, McDonald KM, Schrier RW (1976) Prostaglandins: effects on blood pressure, renal blood flow, sodium and water excretion (Editorial). Kidney Int 10:205–215
8. Robert A, Nezamis JE, Phillips JP (1967) Inhibition of gastric secretion by prostaglandins. Am J Digest Dis 12:1073–1076
9. Classen M, Koch H, Bickhardt J, Topf G, Demling L (1971) The effect of prostaglandin E_1 on the pentagastrin-stimulated gastric secretion in man. Digestion 4:333–344
10. Chiang L, Sanchez-Chiang L, Wolf S, Tang J (1966) The separate determination of human pepsin and gastricsin. Proc Soc Exp Biol Med 12:700–704
11. Goto F, Otani E, Kato S, Fujita T (1982) Prostaglandin E_1 as a hypotensive drug during general anaesthesia. Anaesthesia 37: 530–535
12. Goto F, Otani E, Fujita T (1985) Antihypertensive activity and metabolic rate of prostaglandin E_1 in surgical patients under general anesthesia. Prostaglandins Leukot Med 18:359–366
13. Takashina M, Kamada T, Sasaki S, Mashimo T, Yoshiya I (1990) Effect of prostaglandin E_1 (PGE_1) on skin blood flow and thermoregulation during enflurane anesthesia. Anesthesiology 73:A59
14. Dajani EZ (1987) Perspective on the gastric antisecretory effects of misoprostal in man. Prostaglandins 33:68–77
15. Brand DL, Foufail WM, Thomson ABR, Tapper EJ (1985) Misoprostol, a synthetic PGE_1 analog, in the treatment of duodenal ulcers. A multicenter double-blind study. Dig Dis Sci 30:147s–158s

16. Remwell PW, Shaw JE (1968) Prostaglandin inhibition of gastric secretion. J Physiol (Lond) 195:34–36
17. Bennett A, Friedmann CA, Vane JR (1967) Release of prostaglandin E_1 from the rat stomach. Nature 216:873–876
18. Postius S, Ruoff H-J, Szelenyi I (1985) Prostaglandin formation by isolated gastric parietal and nonparietal cells of the rat. Br J Pharmacol 84:871–877
19. Coceani F, Pace-Ascia KC, Volta F, Worfe LS (1967) Effects of nerve stimulation on prostaglandin formation and release from the rat stomach. Am J Physiol 213:1956–1964
20. Baker R, Jaffe BM, Reed JD, Shaw B, Venables CW (1978) Endogenous prostaglandins and gastric secretion in the rat. J Physiol 278:451–460
21. Kobayashi K, Nakamura H, Arakawa T (1985) Does endogenous prostaglandins inhibit acid secretion? Gastroenterology 88: 1450
22. Tepperman BL, Soper BD (1980) Prostaglandin E_2-binding sites and cAMP production in porcine fundic mucosa. Am J Physiol 242:G313
23. Butcher RW, Baird CE (1968) Effects of prostaglandins on adenosine 3′-5′-monophosphate levels in fat and other tissues. J Biol Chem 243:1713–1717