PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 163, 228–232 (1980)

# Prostacyclin-Induced Gastric Mucosal Vasodilation and Inhibition of Acid Secretion in the Dog (40752)

K. M. WALUŚ, W. PAWLIK, AND S. J. KONTUREK

*Institute of Physiology, Medical Academy, Kraków, Poland*

Several studies demonstrated that the gastric mucosa is able to synthesize and release various prostaglandins (PGs), particularly of E series, which have been suggested to exert local negative feedback inhibition of gastric secretion and to act as modulators of functional vasodilation in the gastric mucosa (1–4). Prostacyclin ($PGI_2$), a potent vasodilator and inhibitor of platelet aggregation originally discovered in the arterial wall (5, 6), was recently found to be a major product of arachidonate metabolism in the gastric mucosa (6, 7) and to protect the gastric mucosa against the damage from many ulcerogens (8, 9).

This study was designed to determine the action of $PGI_2$ and its breakdown product, 6-keto-$PGF_{1\alpha}$, given directly into the artery supplying the stomach or into the portal or systemic venous circulation and on gastric secretion and mucosal blood flow (MBF), and to compare these effects to those obtained by "classical" antisecretory PG, $PGE_2$.

*Materials and Methods.* Thirty-six mongrel dogs of both sexes weighing from 8 to 14 kg were deprived of food for at least 18 hr before experimentation. The animals were anesthetized with intravenous (i.v.) chloralose and ethyl carbamate injection (1 ml/kg of a solution containing 9.25 g chloralose and 92.5 g ethyl carbamate in 150 ml of normal saline). After endotracheal intubation, ventilation was maintained by a positive pressure respiratory pump (Medipan, Poland). A femoral artery was cannulated and connected to a pressure transducer (Statham) for continuous monitoring of systemic arterial blood pressure. Both femoral veins were also cannulated for infusion of drugs and drawing blood samples.

Following a midline laparotomy, the stomach was exposed and all splenic vessels were ligated. A polyethylene catheter was introduced into a branch of the splenic artery so that normal saline, $PGI_2$, $PGE_2$ or $PGF_{1\alpha}$ could be administered into the left gastroepiploic artery, and therefore, directly to the stomach tissue. Another catheter was placed in the tributary of the superior mesenteric vein to introduce the drug into the portal circulation.

An *in vivo* stomach chamber preparation of the oxyntic gland area with intact blood supply was made as previously described (10, 11). A part of the stomach supplied by the gastroepiploic artery was excised and clamped between rings of a double-lumen lucite chamber. The mucosal surface of each part of the segment was bathed with 10 ml of isotonic saline maintained at about 37°. The effluent from the chamber was collected every 15 min and titrated (Radiometer autoburette, Copenhagen) to pH 7.0 to determine the rate of acid secretion. Gastric MBF was estimated by the aminopyrine clearance method (12) adapted for this preparation (13). The ratio value (R) reflecting the relationship between MBF and the rate of gastric secretion was calculated.

Basal gastric secretion was collected for two 15-min periods and then submaximal stimulation of acid secretion was obtained by i.v. infusion of histamine dihydrochloride in a constant dose (80 μg/kg/hr) given through a femoral vein. The dose of histamine was expressed as a weight of its salt. After 1 hr of histamine administration, either normal saline (control tests) or one of the PGs was infused intraarterially (i.a.) in graded doses increased every 30 min by a factor of 10.

In separate series of experiments the effects of $PGI_2$ infused either into the femoral vein or into the portal circulation (i.p.) via the superior mesenteric vein, on acid secretion and MBF were determined. In these tests, $PGI_2$ was administered in graded doses, each dose being infused for a period of 30 min and then increased by a factor of 10.



0037-9727/80/020228-05$01.00/0

A stock solution of $PGE_2$ and $PGI_2$ (1 mg/ml) was made up freshly in 1 *M* Tris buffer (pH 9.6). Dilutions were made immediately prior to use in ice-cold isotonic sodium bicarbonate solution (1.25% w/v; pH 8.8) and instilled with peristaltic pump (Unipan, Poland).

All values reported here are the means ± standard errors of the means (SEM). Results were evaluated statistically using the Mann–Whitney U test (14) accepting statistical significance at the 5% level.

*Results.* Intravenous administration of a constant dose of histamine alone resulted in an increase of gastric acid secretion, MBF, and R value reaching peak values within the first hour and then followed by a well-sustained plateau for the entire period of histamine stimulation. Saline infused i.a. did not affect significantly any of the parameters examined (control tests) and these results are omitted for the clarity of presentation. $PGE_2$ infused i.a. in doses ranging from 0.001 to 1.0 μg/kg/hr resulted in a dose-dependent inhibition of acid secretion; the $ID_{50}$ (dose causing 50% inhibition) was about 0.01 μg/kg/hr. At a dose 1.0 μg/kg/hr acid secretion was almost completely inhibited. The MBF and R value showed a marked fall already at the lowest dose of $PGE_2$ and remained at the same level for the rest of the experiment when graded doses of this compound were administered (Fig. 1).

Intraarterial infusion of $PGI_2$ in doses ranging from 0.01 to 100.0 μg/kg/hr also caused a dose-dependent inhibition of acid secretion with $ID_{50}$ of about 1.0 μg/kg/hr. At the dose 100.0 μg/kg/hr the acid response to histamine was almost completely inhibited. The MBF showed a dose-dependent increase during $PGI_2$ administration reaching about 185% of the control value at a dose of 1 μg/kg/hr. With further rise in the dosage of $PGI_2$, there was a considerable fall in MBF toward the control level. The R value showed changes similar to these of MBF (Fig. 2).

Interarterial infusion of 6-keto-$PGF_{1\alpha}$ in doses identical with those of $PGI_2$ did not cause any significant alteration in either gastric secretion or MBF. Detailed results of $PGF_{1\alpha}$ administration are omitted for the clarity of presentation.

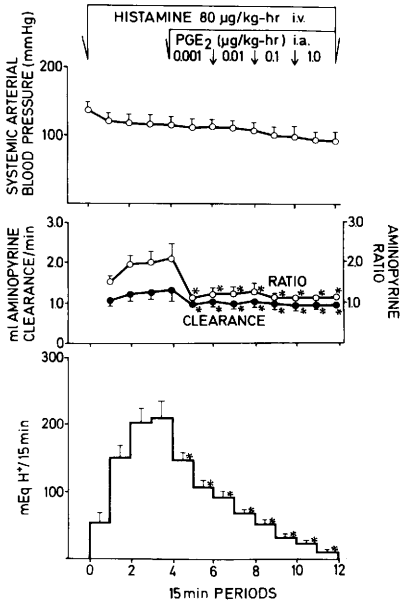


FIG. 1. Effect of intraarterial infusion of $PGE_2$ on histamine-induced gastric acid secretion, mucosal blood flow, and systemic arterial blood pressure. Mean values ± SEM for six dogs. In this and subsequent figures asterisks indicate statistical significance ($P < 0.05$).

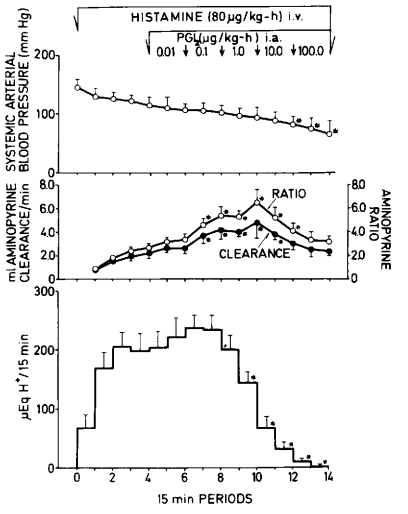


FIG. 2. Effect of intraarterial administration of $PGI_2$ on histamine-induced gastric acid secretion, mucosal blood flow, and systemic arterial pressure. Means ± SEM for six dogs.

Mean systemic arterial pressure was about 145 mm Hg under basal conditions and declined to 120 mm Hg during histamine infusion. In tests with i.a. infusion of $PGE_2$ or 6-keto-$PGF_{1\alpha}$, the arterial pressure remained virtually unchanged but in experiments with i.a. administration of $PGI_2$ it tended to fall reaching the nadir of about 65 mm Hg at the highest dose of $PGI_2$ (Figs. 1 and 2).

$PGI_2$ administered i.v. in doses gradually increasing from 0.1 to 1000.0 μg/kg/hr resulted in a significant decrease in acid secretion only at the highest doses (100.0 and 1000.0 μg/kg/hr). MBF considerably rose at the doses of 10.0 and 100.0 μg/kg/hr and then dramatically decreased at the highest dose (1000.0 μg/kg/hr) of $PGI_2$. The changes in R value paralleled those of MBF. Systemic arterial pressure showed a dose-dependent decline during i.v. administration of $PGI_2$ reaching the lowest value of about 5 mm Hg at the highest dose (Fig. 3).

$PGI_2$ given i.p. at doses identical to those given i.v. failed to affect gastric acid secretion or MBF but caused a gradual fall in the arterial pressure with the lowest value of about 40 mm Hg recorded at a dose of 1000.0 μg/kg/hr (Fig. 4).

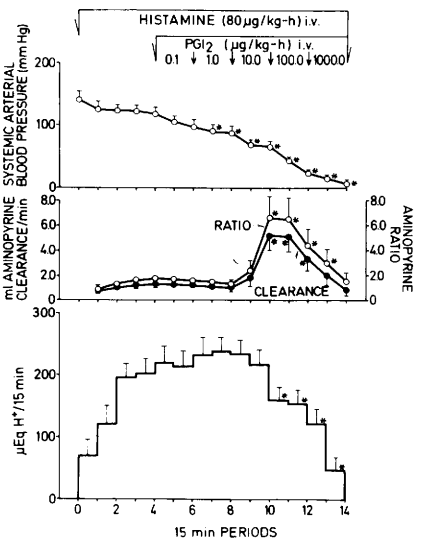


FIG. 3. Effect of intravenous infusion of $PGI_2$ on histamine-stimulated acid secretion, mucosal blood flow, and systemic arterial pressure. Means ± SEM for six dogs.

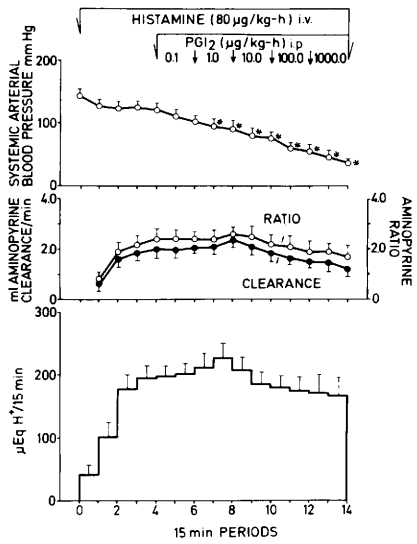


FIG. 4. Effect of intraportal infusion of $PGI_2$ on histamine-induced acid secretion, gastric mucosal blood flow, and systemic arterial blood pressure. Means ± SEM for six dogs.

*Discussion.* This study demonstrates that $PGI_2$ causes a dose-dependent inhibition of gastric acid secretion accompanied by a rise of the gastric MBF. When given i.a. directly to the stomach, $PGI_2$ was less effective in inhibiting gastric secretion than $PGE_2$ and it resulted in a marked and dose-dependent rise in the MBF of the histamine-stimulated gastric mucosal microcirculation. These different effects of $PGI_2$ and $PGE_2$ on MBF result probably from the fact that $PGI_2$ is a much stronger vasodilator of the gastric microcirculation but weaker inhibitor of gastric secretion than $PGE_2$. $PGE_2$ might also dilate gastric mucosal vessels but because of the potent inhibitory action on gastric secretion it results in a secondary reduction in the MBF (15). On the contrary, $PGI_2$, even in relatively small doses, induced such strong mucosal vasodilatation that the increased MBF persisted even during gastric secretory inhibition. Only at the highest doses of $PGI_2$ when systemic arterial pressure was dramatically decreased, below 70 mm Hg, the fall in the MBF was also observed. Thus, for the most part of the dose–response curve of $PGI_2$, a dissociation between inhibition of acid secretion and the

changes in the MBF was observed. The antisecretory effect of $PGI_2$ probably resulted from a direct action on the oxyntic glands since $PGI_2$ is effective also *in vitro* stomach preparation whereas its major breakdown product, 6-keto-$PGF_{1\alpha}$ is not (8), nor does it lower blood pressure.

Our results are in partial agreement with a recent report of Whittle *et al.* (8) showing that in rats, $PGI_2$ increases the MBF while suppressing gastric secretion. The higher activity of $PGI_2$ relative to $PGE_2$ in inhibiting gastric secretion in rats observed in their study could be attributed at least in part to different routes of PG administration. When given i.v. these compounds have to pass the pulmonary circulation where $PGE_2$, but not $PGI_2$, is rapidly inactivated (17, 18) so that the latter reaches the stomach presumably in larger amounts. Because of pulmonary inactivation of $PGE_2$, but not $PGI_2$, and because of the possible role of both $PGE_2$ and $PGI_2$ as local modulators of gastric secretion and mucosal microcirculation (1, 2, 7), the comparison of the intrinsic potency of these compounds was performed in our study by direct intraarterial administration.

The inhibition of histamine-stimulated gastric secretion was also demonstrated when $PGI_2$ was given i.v. but in contrast to i.a. infusion, the reduction in acid secretion was observed only at very high doses of $PGI_2$. This difference in $PGI_2$ inhibitory potency could be explained in part by the dilution of this compound in the circulation so that only minute fraction of the total dose can be delivered to the stomach. In addition, i.v. infusion requires longer time for the compound to reach the stomach and because of a very short half-life of $PGI_2$ in the circulation (18), most of the $PGI_2$ infused i.v. may have been metabolized before acting on the oxyntic glands.

It is of interest that the fall in the systemic arterial pressure after i.v. $PGI_2$ was much greater than that after i.a. administration, whereas the gastric inhibitory effect was many times more pronounced following i.a. than i.v. infusion. This may indicate that $PGI_2$ is strongly inactivated during gastric and/or hepatic transit. In contrast, $PGE_2$ given i.a. appears to be a very effective inhibitor of gastric secretion but does not affect the systemic blood pressure. This can be attributed to weaker vasodilator properties of $PGE_2$ and stronger inactivation of this PG in the pulmonary circulation (17). $PGI_2$ administered into the portal circulation did not influence acid secretion or MBF but the systemic blood pressure fell although not as much as after i.v. infusion. This seems to indicate that $PGI_2$ is strongly inactivated during the hepatic transit, a finding in agreement with previous observation of Dusting *et al.* (18) who found that liver removes about 75% of $PGI_2$ from the portal circulation. The observation that $PGI_2$ given i.p. retains its pressure-depressive effect but not the gastric inhibitory action suggests a much greater sensitivity of $PGI_2$ for the vascular system than for the stomach.

*Summary.* Intraarterial infusion of $PGI_2$ or $PGE_2$ causes a dose-dependent inhibition of histamine-stimulated gastric acid secretion in an *in vivo*-chambered stomach, $PGI_2$ being less potent inhibitor than $PGE_2$. While $PGE_2$ decreases gastric mucosal blood flow, $PGI_2$ causes a marked and dose-dependent increase in mucosal blood flow. $PGI_2$ is also secretory inhibitor after intravenous, but not after intraportal administration. 6-Keto-$PGF_{1\alpha}$, a breakdown product of $PGI_2$, has no effect on gastric secretion or gastric mucosal circulation. $PGI_2$ lowers systemic arterial blood pressure, the effect being more pronounced after intravenous than intraarterial or portal administration. This suggests a marked inactivation of this PG during the liver transit.

This work was supported by Research Grant 10-RMZ-I.

1. Baker, R., Jaffe, B. M., Reed, J. D., Shaw, B., and Venables, C. W., J. Physiol. (London) 278, 451 (1978).
2. Robert, A., Schultz, J. R., Nezamis, J. E., and Lancaster C., Gastroenterology 70, 359 (1976).
3. Coceani, F., Pace-Asciak, A., Volta, F., and Wolfe, L. S., Amer. J. Physiol. 213, 1056 (1967).
4. Bennet, A., Friedman, C. A., and Vane, J. R., Nature (London) 216, 873 (1967).
5. Moncada, S., Gryglewski, R. J., Bunting, S., and Vane, J. R., Nature (London) 263, 663 (1976).
6. Gryglewski, R. J., Bunting, S., Moncada, S.,

Flower, R. J., and Vane J. R., Prostaglandins **12**, 687 (1976).
7. Moncada, S., Salmon, J. A., Vane, J. R., and Whittle B. J. R., J. Physiol. (London) **275**, 4P (1978).
8. Whittle, B. J. R., Boughton-Smith, N. K., Moncada, S., and Vane, J. R., Prostaglandins **15**, 955 (1978).
9. Robert, A., Hanchar, A. J., Lancaster, C., and Nezamis, J. E., Fed. Proc. **37**, 4030 (1978).
10. Moody, F. G., and Durbin, R. P., Amer. J. Physiol. **209**, 122 (1965).
11. Konturek, S. J., Pawlik, W., Waluś, K. M., Coy, D. H., and Schally, A. V., Proc. Soc. Exp. Biol. Med. **158**, 156 (1978).
12. Jacobson, E. D., Linford, R. H., and Grossman, M. I., J. Clin. Invest. **45**, 1 (1966).
13. Chou, A. C., Jacobson, E. D., and Shanbour, L. L., Circ. Shock **2**, 13 (1974).
14. Siegel, A., "Non Parametric Statistics for the Behavioral Sciences." McGraw–Hill, New York (1957).
15. Jacobson, E. D., Proc. Soc. Exp. Biol. Med. **133**, 516 (1970).
16. Armstrong, J. M., Lattimer, N., Moncada, S., and Vane, J. R., Brit. J. Pharmacol. **62**, 125 (1978).
17. Ferreira, S. H., and Vane, J. R., Nature (London) **216**, 868 (1967).
18. Dusting, G. J., Moncada, S., and Vane, J. R., Brit. J. Pharmacol. **64**, 315 (1978).

---

Received September 7, 1979. P.S.E.B.M. 1980, Vol. 163.