Comparison of Prostaglandin E_1 and Norepinephrine on the Gastric Mucosal Circulation (34509)

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Gastric secretion and mucosal blood flow are directly related (1–3). When secretion is increased or decreased, mucosal perfusion is altered in the same direction. However, it is also possible to change mucosal blood flow without altering secretion. Thus, isoproterenol can be administered in a dose which fails to inhibit gastric secretion but retains its dilator effect on the gastric mucosal circulation (1). It should also be noted, however, that when isoproterenol is administered in a dose which inhibits gastric secretion, there is a decline in mucosal blood flow.

Recently, Robert and his associates (4) observed that prostaglandin E_1 (PGE_1) inhibited gastric secretion. Like isoproterenol, PGE_1 has pronounced dilator properties in many local circulatory areas. Since limitation of blood flow is one mechanism whereby gastric secretion could be inhibited, it was of some interest to assess the effects of PGE_1 on the gastric mucosal circulation.

The matter of dissociation of gastric secretion and blood flow is of importance beyond the question of the action of PGE_1 on the stomach. It is not known, for example, whether vasoconstrictor and vasodilator agents which inhibit gastric secretion act differently on the gastric mucosal circulation. For these reasons, we compared the actions of norepinephrine and PGE_1 on gastric secretion and blood flow.

Methods. Experiments were conducted on five mongrel dogs of both sexes weighing 12–18 kg. Each animal had been prepared with a gastric fistula at least 3 months before initiating the present investigation. In each dog secretory responsiveness was determined to both histamine and a gastrin-like peptide (pentagastrin) administered by constant infusion into a saphenous vein. Drug dosage was progressively doubled until no further increase in secretory rate could be achieved. Doses of histamine or pentagastrin, which stimulated a response in acid output approximating one third of the maximal secretion from the gastric fistula of each dog, were then employed for all subsequent experiments. For histamine (histamine acid phosphate) the doses used in the five dogs varied from 0.25 to 1.0 mg/hr of the base. For pentagastrin (Peptavlon, Ayerst Laboratories) the doses were 5 to 10 μg/hr.

Secretion from the gastric fistula was collected at 15-min intervals. The volume of juice was measured, and the acid concentration was determined electrometrically with an automatic titrator (Radiometer) to a pH of 7.0. Acid output was calculated from concentration and volume and was expressed as millequivalents per 15-min period.

Gastric mucosal blood flow in these conscious animals was determined by means of aminopyrine clearance (1). A loading dose of aminopyrine (20 mg/kg) was injected rapidly into a foreleg vein and was followed by a continuous hourly maintenance dose (5 mg/kg) throughout each experiment. The maintenance dose of aminopyrine and constant dose of the secretory stimulants were administered in physiological saline solution at slow rates (0.5 ml/min) via a constant-infusion pump (Harvard Apparatus Company) connected to a saphenous vein throughout all experimental periods. Concentrations of aminopyrine in plasma and in gastric juice were determined colorimetrically (5). The clearance was calculated in milliliters per minute. Experiments were begun no sooner than 90 min after starting the maintenance

TABLE I. Effect of PGE_1 Inhibition of Pentagastrin- and Histamine-Stimulated Stomachs Comparing *R* Values, Clearances, and Secretory Rates during Successive Periods of Control, Low Dose, High Dose, and Recovery from PGE_1.[a]

	Control	Low dose ($0.1\ \mu g\ kg^{-1}\ min^{-1}$)	High dose ($1.0\ \mu g\ kg^{-1}\ min^{-1}$)	Recovery
PGE_1–Pentagastrin				
Ratio	35.8 ± 4.5	41.5 ± 4.0	41.0 ± 3.0	38.2 ± 3.7
Clearance (ml/min)	34.7 ± 3.6	39.5 ± 4.1	25.8 ± 3.7[c]	36.7 ± 3.9
Secretion (meq/15 min)	2.1 ± 0.2	2.1 ± 0.2	0.8 ± 0.1[c]	1.8 ± 0.2
PGE_1–Histamine				
Ratio	38.8 ± 9.8	45.7 ±10.8	54.0 ±14.8[c]	49.5 ±10.6[b]
Clearance (ml/min)	51.2 ± 8.4	49.2 ± 8.5	39.4 ± 2.4[b]	51.2 ± 9.0
Secretion (meq/15 min)	2.6 ± 0.2	2.3 ± 0.2	1.2 ± 0.2[c]	2.8 ± 0.3

[a] Mean ± standard error values are shown.
[b] $p<.05$.
[c] $p<.01$.

dose of aminopyrine to insure stable plasma levels of the weak base.

In previous studies of the relationship between gastric secretion and mucosal blood flow (1), it was noted that a constant infusion of secretory stimulant, *e.g.*, histamine would maintain secretory rate, aminopyrine clearance, and *R* values at stable levels for hours after the initial changes. Therefore, we designed the present study with each animals to serve as his own control. After a suitably prolonged control period, the inhibitory agents to be studied were added to the infusion. Two doses of either PGE_1 or norepinephrine were employed, 0.1 and 1.0 $\mu g\ kg^{-1}\ min^{-1}$. Thus, each experiment consisted of four intervals, namely, control (2.5 hr), low dose of the secretory inhibitor (1 hr), high dose of the inhibitor (1 hr), and recovery (1 hr).

Secretory rate and mucosal blood flow were determined every 15 min during each of the four experimental intervals. Gastric juice was collected every 15 min, and a venous blood sample was obtained each hour. Secretory and clearance values of the last two 15-min periods were averaged in each experimental interval when stability was maximal. These average values were used in the statistical analysis.

Each animal was tested with PGE_1 and with norepinephrine during stimulation with histamine and during stimulation with pentagastrin. On a given test day, only one secretagogue and one inhibitor was used. Only two tests were performed in 1 week on any animal owing to the potential toxicity of aminopyrine. Hematocrit values were determined in each dog once per month and showed no significant or persistent declines.

The raw data from this study consisted of acid output and clearance values at successive 15-min intervals over 5 hr. In addition, we were able to calculate the ratio (*R*) of aminopyrine concentrations in gastric juice and plasma. *R* is equivalent to the ratio of mucosal blood flow to the volume rate of gastric secretion (1). Statistical comparison of these parameters during the test periods with values obtained during control periods was performed using Duncan's New Multiple Range Test (6) calculated on an IBM 1800 computer.

Results. PGE_1 (Table I). The high dose of PGE_1 significantly decreased secretion and mucosal blood flow with either secretory stimulant. This inhibitor also increased *R* values with histamine. During recovery, *R* remained elevated in the histamine-stimulated stomachs. The low dose of PGE_1 did not significantly affect these parameters.

Norepinephrine (Table II). *R* values, clearance, and secretion were decreased significantly by the high dose of norepinephrine with either secretory stimulant. The low dose of the catecholamine decreased all mea-

TABLE II. Effect of Norepinephrine Inhibition of Pentagastrin- and Histamine-Stimulated Stomachs Comparing *R* Values, Clearances, and Secretory Rates during Successive Periods of Control, Low Dose, High Dose, and Recovery from Norepinephrine.[a]

	Control	Low dose (0.1 μg kg^{-1} min^{-1})	High dose (1.0 μg kg^{-1} min^{-1})	Recovery
Norepinephrine–Pentagastrin				
Ratio	45.7 ± 2.6	34.5 ± 3.2	21.8 ± 4.9[b]	53.3 ±13.6
Clearance (ml/min)	43.5 ± 1.9	25.0 ± 2.4[c]	6.8 ± 1.2[c]	26.2 ± 3.9[c]
Secretion (meq/15 min)	2.4 ± 0.4	1.7 ± 0.2[b]	0.3 ± 0.1[c]	0.6 ± 0.1[c]
Norepinephrine–Histamine				
Ratio	32.2 ± 3.2	22.8 ± 2.0[c]	20.7 ± 1.1[c]	39.5 ± 3.3[b]
Clearance (ml/min)	59.8 ± 9.9	34.2 ± 2.8[c]	13.8 ± 2.0[c]	38.5 ± 5.8[c]
Secretion (meq/15 min)	4.3 ± 0.4	3.4 ± 0.2[b]	1.3 ± 0.2[c]	2.0 ± 0.2[c]

[a] Mean ± standard error values are shown.
[b] $p<.05$.
[c] $p<.01$.

surements during histamine stimulation. During recovery from norepinephrine clearance and secretory rate remained depressed but *R* values with histamine were increased.

Discussion. A gastric secretory inhibitor could act upon the mucosa by one of several mechanisms to diminish stimulated secretion. One mechanism would involve constriction of mucosal perfusion, whereby the declining blood supply would limit secretion. Under these circumstances we would expect to see a decreased mucosal clearance of aminopyrine with the secretory inhibitor. Alternatively, a different kind of secretory inhibitor could act directly upon oxyntic cells to slow secretion. Since secretion and blood flow are linked (in that a decrease in secretion is accompanied by a directionally corresponding decrease in mucosal perfusion), we would also expect to find a decrease in blood flow with the second kind of secretory inhibitor. In a recent preliminary report, Wilson and Levine (7) concluded that a diminished clearance of aminopyrine during secretory inhibition with PGE_1 signified that the mechanism involved was constriction of the blood supply. Since secretory inhibition of either kind reduces aminopyrine clearance, the diminished clearance does not alone identify the mechanism involved.

The ratio (*R*) of clearance to secretory rate is a more helpful guide to the mechanism of secretory inhibition. With an agent known to constrict blood vessels generally and also to inhibit gastric secretion, such as norepinephrine, one would anticipate that the drug would decrease not only secretion and blood flow, but also depress the *R* values. This would indicate that the primary effect of the agent was upon the circulation, *i.e.*, the fall in blood flow exceeded the decrease in secretory rate, so that blood flow became a limiting factor for secretion. This effect of norepinephrine was observed with either dose of the drug. During recovery, both secretion and blood flow remained depressed, but *R* exceeded control values, probably reflecting local circulatory factors involved in reactive hyperemia. The dramatic responses of all three measurements to two widely differing doses of norepinephrine make it likely that the catecholamine acts on the gastric mucosa to diminish secretion by restricting the blood supply upon which secretion ultimately depends.

With PGE_1 the story was different. At the low dose, when secretion was unaffected, the drug did not decrease either clearance or the ratio of blood flow to secretion. Even with the high dose, when secretory rate had declined, the ratio of blood flow to secretion was not decreased compared with control. Indeed, with histamine as the stimulant, *R* values increased with the high dose of PGE_1. These are the findings one would expect with a secretory inhibitor whose major documented

action on the circulation is to dilate arterioles and increase local blood flow (8, 9). Furthermore, PGE_1 has been found to decrease secretory rates in isolated gastric mucosa where blood flow is not a factor (10). It seems likely that the mechanism whereby PGE_1 inhibits gastric secretion is by direct action on secreting cells rather than by vasoconstriction.

Thus, norepinephrine acts as an agent which diminishes gastric secretion by limiting mucosal blood flow, whereas PGE_1 seems to act by some other primary mechanism, and the decreased blood flow appears secondary to the declining secretory activity.

These studies suggest that an additional assessment of gastric secretory inhibitors might be worth pursuing, namely, the vasodilator or vasoconstrictor properties of these agents in the gastric mucosa. If a drug inhibits its secretion by constricting mucosal arterioles directly, the desired therapeutic control of hypersecretion may be obtained at the expense of creating gastric mucosal ischemia. Such agents are ulcerogenic (11). A preferable inhibitor is one which acts primarily on oxyntic cells to reduce secretory activity, a situation in which blood flow reduction lags behind the fall in acid production, as indicated by no decrease in R values.

Summary. Secretion, mucosal blood flow, and the ratio (R) of blood flow to secretory rate were measured in conscious dogs provided with a gastric fistula. Secretion was stimulated to steady rates about one third of maximal with either pentagastrin or histamine. Prostaglandin E_1 (PGE_1) or norepinephrine was administered in doses of 0.1 or 1.0 $\mu g\ kg^{-1}\ min^{-1}$. With the high dose of either agent, secretion was decreased, whether stimulated by histamine or pentagastrin, but the ratio of blood flow to secretory rate was decreased only with norepinephrine. It is concluded that norepinephrine operates to reduce secretion by limiting mucosal blood flow. On the other hand, PGE_1, which is a powerful vasodilator, reduces secretion by a primary mechanism other than restricting gastric mucosal blood flow. The decrease in blood flow seen with PGE_1 appears to be the result and not the cause of gastric secretory inhibition.

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1. Jacobson, E. D., Linford, R. H., and Grossman, M. I., J. Clin. Invest. **45**, 1 (1966).

2. Jacobson, E. D., Swan, K., and Grossman, M. I., Gastroenterology **52**, 414 (1967).

3. Harper, A. A., Reed, J. D., and Smy, J. R., J. Physiol. London **194**, 795 (1968).

4. Robert, A., Nezamis, J. E., and Phillips, J. P., Amer. J. Dig. Dis. **12**, 1073 (1967).

5. Brodie, B. B., and Axelrod, J. J., Pharmacol. Exp. Ther. **99**, 171 (1950).

6. Steel, R. G. D. and Torrie, J. H., "Principles and Procedures of Statistics" p. 107. McGraw-Hill, New York (1960).

7. Wilson, D. E., and Levine, R. A., Gastroenterology **56**, 1286 (1969).

8. Shehadeh, Z., Price, W. E., and Jacobson, E. D., Amer. J. Physiol. **216**, 386 (1969).

9. Bergström, S., Carlson, L. A., and Weeks, J. R., Pharmacol. Rev. **20**, 1 (1968).

10. Way, L. and Durbin, R. P., Nature **221**, 874 (1969).

11. Jacobson, E. D., Gastroenterology **48**, 85 (1965).

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