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# Suppression of Gastric Secretion by Furosemide in Dogs[1] (41176)

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*Abstract.* Furosemide (1 mg/kg bolus injection) caused a transient decrease of pentagastrin-stimulated gastric acid secretion of 29 ± 4% in six dogs with gastric fistulas, whereas the same injection, followed by a continuous infusion of 1 mg/kg-hr, caused a sustained mean reduction of 40 ± 4%. A bolus injection of 5 mg/kg caused no further reduction in acid secretion. The relative decreases in $Cl^-$ and volume outputs closely paralleled the reduction in acid secretion.

Furosemide is known to affect the permeability of chloride ions in various cell and epithelial membranes. Its diuretic effect is produced by a reduction of active chloride transport in the thick ascending limb of Henle's loop (2). In addition to its effect on the kidney, furosemide reduces chloride permeability in cell membranes of red blood cells (3) and Ehrlich's ascites tumor cells (4); and in epithelial membranes like the frog cornea (5), frog skin (6), and toad bladder (7). Furosemide has been reported to affect transport processes in various parts of the digestive system, but little is known about its effects on gastric secretion. In recent experiments, Ayalon and colleagues (8) showed that furosemide suppresses acid secretion of fundic mucosa of the guinea pig *in vitro*. In the present study, the effect of furosemide on gastric secretion was examined in dogs *in vivo*.

**Materials and Methods.** Six mongrel dogs (weight, 20–25 kg) were prepared with gastric and duodenal fistulas. The duodenal fistulas were left open during each experiment to minimize duodenogastric reflux. Four kinds of experiments were performed in each dog. In all experiments, dogs were given a continuous infusion of pentagastrin (2 μg/kg-hr) for 150 min.

In a control experiment, pentagastrin was given alone. In the following three experiments, furosemide was administered intravenously after 75 min of pentagastrin infusion. Furosemide was first given as a bolus injection of 1 mg/kg; in the next study, it was given as a bolus injection of 1 mg/kg, followed by a continuous infusion of 1 mg/kg-hr for 75 min, and in the final study, as a bolus injection of 5 mg/kg.

Gastric secretion was collected at 15-min intervals after furosemide injection and was compared to the mean secretion during the 45-min period immediately prior to the administration of furosemide, which was arbitrarily set as 100%. To facilitate evaluation, percentage changes in gastric secretion induced by furosemide were compared with the percentage changes seen at the same time intervals in the control experiment in the same dog. The experiments with furosemide injection were performed twice with each dose, and the control experiment once.

During all the experiments, fluid losses due to induced diuresis were replaced with Ringer's solution. Blood pressure and pulse rate were monitored throughout the study.

Acid output was determined by titration with NaOH and specimens of gastric secretion were analyzed for $Cl^-$ by autoanalyzer (Technicon AA-1).

Results are expressed as the mean ± 1 SE. Student's *t* test was used to analyze the data for statistical significance of differ-

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ences between means. Differences with a $P$ value of less than 0.05 were considered significant.

**Results.** Mean values of pentagastrin (2 μg/kg-hr)-induced gastric secretion, during the 45-min period prior to furosemide injection, are given in Table I.

A bolus injection of furosemide of 1 mg/kg suppressed acid secretion to 71 ± 4% of initial secretion (Fig. 1, Table II). This maximal effect was observed at 45 min after the furosemide bolus. Acid secretion recovered to its initial value after 60 min. A bolus injection of 1 mg/kg, followed by continuous infusions of 1 mg/kg-hr of furosemide, produced a decrease in acid secretion to about 60% of initial secretion, which was sustained during the 75-min study (Fig. 1, Table II). A higher dose of furosemide (5 mg/kg bolus injection) caused no further decrease in acid secretion (Table II).

The relative decreases in $H^+$, $Cl^-$, and volume outputs did not differ statistically one from the other at 45 min after a bolus of 1 mg/kg and at 60 min after 5 mg/kg (Table III).

**Discussion.** Furosemide has been reported to affect transport processes in various parts of the gastrointestinal tract. It has been shown to reduce the salivary flow rate and $Cl^-$ secretion of the rat parotid gland (9). A decrease in volume flow and $HCO_3^-$ concentration, with a concomitant increase in $Cl^-$ concentration of the dog's pancreatic secretion (10), suggests interference with $Cl^-/HCO_3^-$ exchange in the gland's ductal system. An increase in bile flow in dogs has also been reported (11).

An increase in the fecal excretion of electrolytes and water in horses (12) and in man (13) represents gross summation effects of the drug on the intestine. This loss of fluid and electrolytes has been applied to the treatment of patients with severe chronic renal failure, with resultant loss of edema fluid (13).

TABLE I. MEAN VALUES OF PENTAGASTRIN (2 μg/kg-hr)-STIMULATED GASTRIC SECRETION DURING THE 45-min PERIOD PRIOR TO FUROSEMIDE ADMINISTRATION

| | Initial concentration (meq/liter) | Initial secretion |
|---|---|---|
| Volume | | 46 ± 4 ml/15 min |
| $H^+$ | 125 ± 7 | 6.28 ± 0.22 meq/15 min |
| $Cl^-$ | 158 ± 2 | 7.11 ± 0.69 meq/15 min |

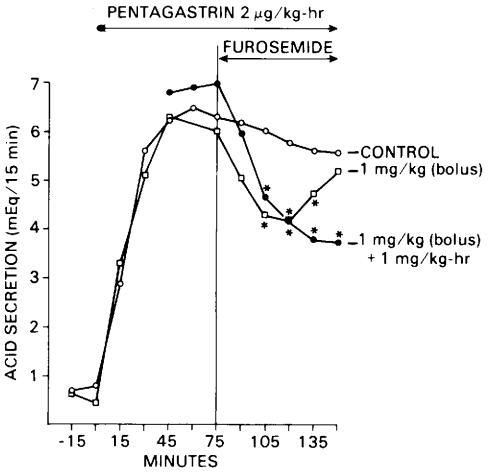


FIG. 1. Pentagastrin-stimulated acid secretion in the control experiment, and after injection of furosemide. (*) Significantly different from values before furosemide administration.

In the small intestine, electroneutral NaCl absorption is inhibited by furosemide by means of blockage of the $Cl^-$ pathway (14–17).

Little is known about the effects of furosemide on gastric ion transport. Two previous reports provide contradictory results. In one study, no effect on volume or ion concentration of gastric secretion in man was found (18); in the other, a decrease of acid secretion of 18.8% was reported (19).

In studies on isolated guinea pig gastric mucosa, furosemide decreased acid secretion by 40%. The short circuit current, which represents the "nonacidic" electrogenic $Cl^-$ transport, dropped by 47%, and net flux of $^{36}Cl$ from serosal to mucosal side decreased by 42%. It has been suggested that furosemide blocks the entrance of $Cl^-$ by the $Na^+-Cl^-$ cotransport mechanism, through the basolateral membrane of the secreting cell, causing the observed decrease in acid secretion and in electrogenic, "nonacidic," $Cl^-$ transport (8).

The rapidity of onset and the relative ease of reversing the inhibition in the *in vitro* preparation, as well as in other

TABLE II. ACID SECRETION AFTER FUROSEMIDE ADMINISTRATION EXPRESSED AS PERCENTAGE OF THE MEAN, PENTAGASTRIN-STIMULATED SECRETION DURING THE 45-min PERIOD PRIOR TO FUROSEMIDE ADMINISTRATION, WHICH WAS ARBITRARILY SET AS 100%

| | 15 min | 30 min | 45 min | 60 min | 75 min |
|---|---|---|---|---|---|
| 1 mg/kg (bolus) | 83 ± 5 | 79 ± 4″ | 71 ± 4″ | 94 ± 6 | 97 ± 8 |
| 1 mg/kg (bolus + continuous 1 mg/kg-hr) | 84 ± 4″ | 69 ± 3″ | 61 ± 7″ | 60 ± 4″ | 61 ± 7″ |
| 5 mg/kg (bolus) | 92 ± 3 | 72 ± 3″ | 64 ± 5″ | 60 ± 4″ | 56 ± 5″ |

″ Significantly different from 100%; $n = 6$.

TABLE III. GASTRIC OUTPUT AFTER FUROSEMIDE ADMINISTRATION, EXPRESSED AS PERCENTAGE OF THE MEAN, PENTAGASTRIN-STIMULATED OUTPUT DURING THE 45-min PERIOD PRIOR TO FUROSEMIDE ADMINISTRATION, WHICH WAS ARBITRARILY SET AS 100%

| | 15 min | 30 min | 45 min | 60 min | 75 min |
|---|---|---|---|---|---|
| | | | After 1 mg/kg (bolus) | | |
| Volume | 85 ± 1 | 78 ± 2″ | 73 ± 3″ | 86 ± 7 | 96 ± 6 |
| $H^+$ | 83 ± 5 | 79 ± 4″ | 71 ± 4″ | 94 ± 6 | 97 ± 8 |
| $Cl^-$ | 87 | 88 ± 5 | 75 ± 2″ | 82 ± 4″ | 96 ± 4 |
| | | | After 5 mg/kg (bolus) | | |
| Volume | 99 | 75 ± 2″ | 69 ± 4″ | 65 ± 5″ | 63 ± 7″ |
| $H^+$ | 92 ± 3 | 72 ± 3″ | 64 ± 5″ | 60 ± 4″ | 56 ± 5″ |
| $Cl^-$ | 92 | 74 ± 4″ | 66 ± 5″ | 66 ± 6″ | 61 ± 7″ |

″ Significantly different from 100%; $n = 6$.

biologic membranes (2–4), are consistent with the findings in the present *in vivo* experiments, which show recovery of acid secretion after the lower dose of 1 mg/kg. After the higher dose of 5 mg/kg, recovery was not observed, as the drug probably was not yet sufficiently eliminated from the circulation by excretion or metabolism, during the limited duration of the experiment. This suggests that furosemide acts by reversible binding to a superficial site on the cell membrane.

The 40% reduction in acid and $Cl^-$ secretion, induced by furosemide at clinically used doses, in the present *in vivo* experiment, fully corresponds to the effects of furosemide on acid secretion and $Cl^-$ transport in the *in vitro* experiments.

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