Ionic Flux Across the Gastric Mucosa: Effects of Atropine on the Permeability of Fundus and Antrum[1] (35104)

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Under normal circumstances the surface epithelium of the gastric fundus is relatively impermeable to the movement across it of hydrogen ions, sodium, and potassium (1); the antrum on the basis of unit surface area is relatively more permeable (2). A variety of substances may alter the barrier function of the gastric mucosa. Since acetazolamide, a potent gastric secretory inhibitor, disrupts the mucosal barrier of the fundus (3), we studied the effects of atropine, the classical anticholinergic gastric secretory inhibitor, on the permeability of the fundic and antral mucosa.

Methods and Materials. Five mongrel dogs ranging in weight from 16 to 25 kg were utilized. Three were prepared with vagally denervated fundic and antral pouches, one with an antral pouch and one dog with only a fundic pouch. In order to obtain pure antral pouches, delineation of the antrum–corpus junction was obtained colorimetrically by the intravenous administration of 1% toluidine blue (4) during histamine stimulation. Each pouch was equipped with a nylon-coated stainless steel gastric cannula which was brought out through the abdominal wall through a point in the midline.

Experiments were commenced 4 weeks later, with the animals in good health and maintaining a stable weight. Animals were deprived of food but not water for 18 hr prior to each observation and were studied no more than twice a week and never on consecutive days. Pouch secretion was collected for at least 30 min before each experiment to ensure that no spontaneous basal secretion occurred. The volumes of test solutions instilled were determined individually for each pouch as previously described (2). Fundic pouch instillations (at a pressure of 6 cm water) ranged from 60 to 80 ml and antral pouch instillations (at a pressure of 15 cm water) ranged from 17 to 30 ml. The pouches were utilized only as long as it could be demonstrated that no leak was present.

The test solution consisted of HCl (160 m*N*) and phenol red (4 mg/100 ml) as a nonabsorbable dilution indicator. Each pouch was initially washed out with acid solution without phenol red indicator and the pouch was emptied as completely as possible. 0.16 *N* HCl with phenol red was then introduced into the pouch and, after mixing, a 3-ml aliquot was removed to determine the residual volume. The solution was allowed to remain in the pouch for 30 min, then emptied by gravity drainage and gentle massage over the pouch area; a fresh solution was then instilled and the procedure was repeated. During all fundic pouch experiments the antrum was acidified to prevent the release of endogenous gastrin. Residual volumes were determined for each 30-min instillation; they were 2.4 ± 0.26 (SE) ml for the fundic and 1.6 ± 0.16 (SE) ml for the antral pouches. Four or five control instillations were carried out, following which atropine sulfate 0.05 mg/kg was administered intravenously; a further 4–5 instillations were then repeated.

The volume of fluid recovered was determined to the nearest 0.1 ml. Specimens were analyzed individually for volume, acidity, sodium, potassium, chloride, phenol red, and osmolality; all chemical determinations were performed in duplicate. Acidity was measured by titration to end-point pH 7.0 with a

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TABLE I. Net Changes in Ions (μeq/30 min), Volume, and Osmolality in Fundic Pouches.[a]

Dog no.		N	(μeq/30 min) H+	Na+	K+	Cl−	Net vol gain (ml/30 min)	Δ Osmolality (mOsm/kg)
V-128	Control	15	−127 ± 125	468 ± 37	13 ± 2	84 ± 82	2.67 ± 0.64	−8.5 ± 1.3
	After atropine	15	−400 ± 109[b]	601 ± 39[b]	16 ± 2	61 ± 92	2.30 ± 0.33	−13.1 ± 1.5[b]
V-153	Control	20	−371 ± 82	455 ± 23	18 ± 2	−37 ± 72	1.85 ± 0.39	−9.7 ± 0.9
	After atropine	18	−636 ± 144[b]	620 ± 30[c]	22 ± 2[b]	4 ±130	2.66 ± 0.73	−10.4 ± 2.3
9711	Control	14	−795 ± 149	364 ± 27	16 ± 1	−161 ± 88	1.53 ± 0.43	−9.5 ± 1.2
	After atropine	13	−1528 ± 356[b]	530 ± 54[b]	18 ± 2	−56 ±182	2.63 ± 0.82	−8.7 ± 3.2
1206	Control	19	−494 ± 128	261 ± 15	17 ± 2	−137 ± 63	1.47 ± 0.29	−9.3 ± 0.8
	After atropine	16	−851 ± 349	291 ± 16	13 ± 1[b]	4 ±111	2.32 ± 0.44	−7.6 ± 1.7
Mean	Control	68	−440 ± 62	383 ± 17	16 ± 1	−56 ± 39	1.86 ± 0.22	−9.3 ± 0.5
	After atropine	62	−821 ± 133[c]	510 ± 24[d]	17 ± 1	5 ± 65	2.48 ± 0.30	−9.2 ± 1.2

[a] N = no. of observations. ± = mean ± SE.
[b] $p < 0.05$. [c] $p < 0.01$. [d] $p < 0.001$.

radiometer pH–stat titrator (Model 1 No. TTT 1c). Sodium, potassium, and chloride were determined by automated flame photometry (Technicon Autoanalyzer), and osmolality with an Advanced Osmometer. Phenol red determinations were performed according to the method of Hunt (5).

Results (Tables I and II). *Electrolytes.* Atropine increased the net loss of hydrogen ions in both pouches. In the control periods there was a greater loss of H^+ ions from the fundic pouches (−440 μeq/30 min) than in the antral pouches (−279 μeq/30 min); this is due to the larger size of the fundic pouches since we have demonstrated (2) that antral pouches lose 15 times as much H^+ on the basis of unit surface area. Following atropine administration, mean H^+ loss increased to −821 μeq/30 min in the fundus and −463 μeq/30 min in the antrum. Although there was individual variation in some animals, atropine increased the mean H^+ loss in the fundus by 86% and in the antrum by 66%.

Sodium gain increased from 383 to 510 μeq/30 min in the fundus, but was only minimally altered in the antrum. In the fundus, Na^+ gain paralleled H^+ loss in control periods, but was less than H^+ loss after atropine; Na^+ gain in the antrum considerably exceeded H^+ loss in control periods, but only slightly after atropine. K^+ gain, greater in the antrum than fundus, was not altered by atropine in either pouch. No clear pattern of net chloride flux emerged. Both increases and decreases were noted in individual animals and in the mean results.

Volume. Atropine increased the net volume gain from 1.86 ± 0.22 to 2.48 ± 0.30 ml/30 min in the fundic pouches, but decreased the gain from 3.30 ± 0.18 to 2.68 ± 0.21 ml/30 min in the antral pouches.

Osmolality. In the control periods, osmolality decreased by 9.3 ± 0.5 mOsm/kg in the fundic pouches, and by 20.4 ± 0.9 mOsm/kg in the antral pouches. Atropine did not alter the decrease in osmolality in either pouch.

Discussion. These results demonstrate that atropine increases the loss of hydrogen ions across antral and fundic mucosa. The loss of H^+ was equal in each of the four postatropine periods, in contrast to the effects of bile (6) where the most marked effect was evident in the first postbile period, after which spontaneous recovery occurred. The magni-

TABLE II. Net Changes in Ions, Volume, and Osmolality in Antral Pouches.[a]

Dog no.		N	(μeq/30 min) H^+	Na^+	K^+	Cl^-	Net vol gain (ml/30 min)	Δ Osmolality (mOsm/kg)
V-128	Control	15	−528 ± 70	820 ± 78	45 ± 2	437 ± 89	3.42 ± 0.55	−26.5 ± 0.6
	After atropine	13	−915 ±106[d]	847 ± 58	43 ± 3	−174 ±125[c]	1.46 ± 0.60[c]	−26.3 ± 0.7
V-153	Control	25	−144 ± 32	537 ± 29	33 ± 2	343 ± 77	3.68 ± 0.33	−22.4 ± 1.6
	After atropine	21	−221 ± 65	542 ± 25	35 ± 2	220 ±109	3.39 ± 0.34	−19.8 ± 2.3
9711	Control	20	−348 ± 45	435 ± 16	25 ± 1	−46 ± 70	2.41 ± 0.17	−15.1 ± 1.3
	After atropine	17	−488 ± 49[b]	516 ± 18[c]	30 ± 1	−35 ± 31	2.51 ± 0.19	−17.6 ± 1.1
V-145	Control	15	−162 ± 31	481 ± 24	33 ± 3	312 ± 51	3.38 ± 0.25	−18.4 ± 1.6
	After atropine	12	−359 ± 88[b]	477 ± 18	33 ± 2	104 ± 81[b]	2.67 ± 0.44[b]	−16.3 ± 2.1
Mean	Control	75	−279 ± 27	536 ± 22	33 ± 1	273 ± 42	3.30 ± 0.18	−20.4 ± 0.9
	After atropine	63	−463 ± 48[d]	588 ± 23	35 ± 1	50 ± 52[c]	2.68 ± 0.21	−19.9 ±10

[a] N = no. of observations. ± = mean ± SE.
[b] $p < 0.05$. [c] $p < 0.01$. [d] $p < 0.001$.

tude of the effect was much less than that produced by acetazolamide (3) or bile (6). It is unlikely that the increased H^+ loss following atropine is due to buffering of H^+ ions by HCO_3^- from nonparietal secretion. Since this would result in the evolution of free CO_2, a greater reduction in osmolality would be expected after atropine.

Atropine increased H^+ loss across fundic mucosa to a greater extent than across antral mucosa. While the effects of atropine on the antrum might be considered a direct effect on the mucosal barrier, the greater loss of H^+ from the fundus could conceivably be due to inhibition of basal acid secretion. However, a nonsecretory state was ensured by carrying out these experiments in vagally denervated fundic pouches in fasting animals, and acidifying the antrum during each experiment. Furthermore, since the entry of K^+ into the lumen of the fundus is linked with H^+ secretion, a diminished entry of K^+ would be expected if this were purely a secretory inhibitory effect.

The effects of atropine on gastric secretion is generally explicable in terms of its blocking effect on postganglionic cholinergic fibers. However, the secretory inhibition is not solely an anticholinergic effect since atropine also inhibits acid secretion in vagally denervated fundic pouches (7) and in isolated frog gastric mucosa (8), a completely denervated preparation. To this inhibitory effect must be added the effects of atropine on the ability of the gastric mucosa to maintain acid solutions within the gastric lumen. A transmucosal loss of H^+ ions would further decrease the output of H^+ ions recovered from the lumen during secretory stimulation.

These results are in accordance with the study of Ivey *et al.* (9) in the vagally innervated intact human stomach. They demonstrated that atropine, together with bile instillations, increased the loss of instilled acid from the stomach, which was only partially due to secretory inhibition. In contrast, Lick *et al.* (10) reported that atropine reduced the rate of insorption from fundic pouches, but they instilled acid solutions for 5-hr periods whereas we used repeated 30-min instillations.

The present data suggests a direct effect of atropine on the mucosa of the fundus and antrum, altering its ability to contain in-

traluminal acid solutions. Non-anticholinergic effects on water and ion movement have been demonstrated for atropine on other membranes. It prevents loss of water from erythrocytes in the rat (11) and reduces the capacity of human skin to absorb or secrete water vapor (12). Externally applied atropine increases the flux of Na^+ and the flow of electrical current across frog skin, neither of which action is antagonized by acetylcholine (13). Thus atropine may act on water transport and on sodium flux, the latter apparently independent of its anticholinergic activity.

A possible mechanism might be found in the reduction of gastric mucosal blood flow by atropine (14). This might alter transport across capillary walls by ultrafiltration and diffusion, and thus reduce the interstitial fluid pressure which affects the movement of fluid and ions through pores in tissue membranes.

Summary. The effects of atropine were evaluated on ionic movement across fundic and antral mucosa. 0.16 *N* HCl solutions were instilled into vagally denervated fundic and antral pouches. Atropine (0.05 mg/kg) increased the mean net loss of H^+ ions in both pouches, but to a slightly greater extent in the fundus (86%) than in the antrum (66%). Although the mechanism of action is speculative, it is suggested that the diminished acid output in gastric secretion following atropine may be due to secretory inhibition, and to a lesser extent, a transmucosal loss of hydrogen ions.

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