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Comparison of Intravenous and Intragastric Aspirin in Production of Antral Gastric Ulcers in Cats (40921)

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Abstract. In cats receiving continuous intravenous infusion of histamine dihydrochloride (160 μg kg^{-1} hr^{-1}; 40 mg kg^{-1} of aspirin was given as a bolus injection either intravenously or intragastrically. When the animals were killed either 1 or 4 hr later, all cats in both groups had ulcers of the antral part of the stomach extending through the mucosa. The mean area occupied by the ulcers was not significantly different in the two groups. Plasma and mucosal salicylate concentrations at the end of the study were not significantly different in the two groups. We conclude that, in cats receiving an intravenous infusion of histamine, intravenous and intragastric aspirin are equally effective in producing antral gastric ulcers.

In an earlier study (1), we found that aspirin given to cats by continuous intravenous infusion for 7 days produced gastric ulcers without the occurrence of the conventional indices of a "broken barrier," namely, increased loss of hydrogen ions from the lumen, increased gain of sodium ions to the lumen, and decreased electrical potential difference. We (2) recently reported that giving histamine intravenously hastened the appearance and increased the severity of the gastric ulcers produced by an intravenous infusion of aspirin in cats.

The present study was done to compare intravenous and intragastric administration of aspirin, both given with intravenous histamine, in regard to the incidence and severity of antral gastric ulcers in conscious cats. We found no significant difference between intravenous and intragastric administration of aspirin in regard to incidence or severity of antral ulcers.

Methods and materials. General plan. Aspirin was given as a single rapid bolus injection either intragastrically or intravenously. With both routes of delivery of aspirin, histamine was given by continuous intravenous infusion. The cats were killed 1 or 4 hr after administration of aspirin.

Cats. Mongrel cats of both sexes weighing 1.5 to 6.0 kg were used.

Test procedures. After withholding food but not water for 24 hr, the cats were lightly restrained in a comfortable position using canvas slings. A foreleg vein was cannulated with a polyethylene catheter (1-mm o.d.) which was connected to a syringe pump (Harvard Apparatus, Millis, Mass.) which delivered 7 ml hr^{-1} of 0.15 *M* NaCl. Histamine dihydrochloride (Vega–Fox, Inc., Tucson, Ariz.) was added to the intravenous infusion in the amounts required to give 160 μg kg^{-1} hr^{-1}, a dose which produces near maximal rates of acid secretion in cats (3). This histamine dose was infused intravenously for 1 hr prior to the introduction of aspirin and during the remainder of the test period. Bolus doses of aspirin were given either through the intravenous catheter or orally through a feeding tube (size 8 French, Pharmaseal, Inc., Glendale, Calif.) to the conscious cat. The volume of the oral bolus injection was 4 ml and an additional 2 ml of saline was given to wash out the tube. Solutions of aspirin were freshly prepared at the start of each test by dissolving 3 g of $NaHCO_3$ and 3 g of acetylsalicylic acid (J.T. Baker Chemical Co., Phillipsburg, N.J.) in 100 ml of distilled water, giving a solution containing 30 mg ml^{-1} of aspirin at pH 7.1. This solution was further diluted with 0.15 *M* NaCl to give the desired dose for intravenous or intragastric administration.

Blood samples. A blood sample for determination of plasma salicylate concentration by the method of Saltzman (4) was taken 10 min after the bolus injection of aspirin from a vein other than the one used for injection of aspirin. At the end of the test,

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the cats were killed by injecting Repose (1 g secobarbital and 125 mg mephenesin per cat, Diamond Laboratories, Des Moines, Iowa) intravenously. Another sample of blood was taken from the heart.

Tissue samples. The stomach and duodenum were opened along the greater curvature. The lesions were counted and the length and width of each lesion was measured to the nearest millimeter. The area of each lesion and the sum of the areas of all lesions in each cat was calculated. Full thickness biopsies were removed with a dermal punch (6 mm) from fundal and antral sites. The samples were taken from areas which did not show evidence of gross lesions. Antral and oxyntic mucosa were dissected off of these biopsies and stored frozen for later salicylate determination (4).

Statistical analyses. The significance of differences in mean values for ulcer area and salicylate concentrations between cats given intravenous and intragastric aspirin were tested by Student's t test for unpaired values.

Results (Table I). Controls. Intravenous histamine alone or aspirin alone, either intravenous or intragastric, produced no antral ulcers and almost no fundic ulcers.

Bolus injection of aspirin plus histamine infusion. All cats which received 40 mg kg^{-1} of aspirin as a bolus either intravenously or intragastrically had antral ulcers both at 1 and 4 hr. The ulcers were much more extensive at 4 than at 1 hr. At 4 hr, in some instances the ulcers involved more than 50% of the area of the antrum (Fig. 1). The measured mean total ulcerated area per stomach was not significantly different ($P > 0.05$) with the two routes of administration (Table I). The character of the ulcers by gross inspection did not differ with the two routes of administration.

Plasma and tissue salicylate. Plasma levels of salicylate were significantly ($P < 0.05$) higher at 10 min in the intravenous than in the intragastric group, but at the end of the study there were no significant differences between the intragastric and intravenous routes of infusion. Plasma salicylate level never exceeded 120 μg ml^{-1}, well below the upper limit of the therapeutic dose level, 300 μg ml^{-1} plasma (5).

TABLE I. PLASMA AND TISSUE SALICYLATE CONCENTRATION AND INCIDENCE AND SIZE OF ANTRAL AND FUNDIC GASTRIC ULCERS IN CATS GIVEN ASPIRIN INTRAVENOUSLY OR INTRAGASTRICALLY DURING A CONTINUOUS INTRAVENOUS INFUSION OF HISTAMINE (VALUES ARE MEAN ± SE)

Aspirin[a]	Histamine[b]	Duration (hr)	n	Plasma salicylate (μg ml^{-1})		Tissue salicylate (μg g^{-1})		Antral ulcers		Fundic ulcers	
				10 min	At death	Antral	Fundic	% of cats w/ulcer	Total area ulcerated (mm^2)	% of cats w/ulcer	Total area ulcerated (mm^2)
0	+	4	4	—	0	0	0	0		0	
iv	0	4	4	117 ± 13	109 ± 11	48 ± 3	41 ± 2	0		25	0.2 ± 0.2
ig	0	4	4	55 ± 13	136 ± 23	52 ± 2	41 ± 3	0		0	
iv	+	1	4	80 ± 4	94 ± 7	85 ± 15	69 ± 12	100	16 ± 14	25	4 ± 2
ig	+	1	4	59 ± 17	80 ± 14	146 ± 80	67 ± 19	100	16 ± 10	50	3.8 ± 3.4
iv	+	4	8	92 ± 7	86 ± 5	55 ± 6	42 ± 5	100	289 ± 114	50	15 ± 12
ig	+	4	8	42 ± 12	84 ± 12	75 ± 8	61 ± 8	100	229 ± 97	38	0.9 ± 0.8

[a] Bolus dose of aspirin, 40 mg kg^{-1}. iv, intravenous; ig, intragastric.
[b] Continuous intravenous infusion of histamine—di-HCl (160 μg kg^{-1} hr^{-1}).

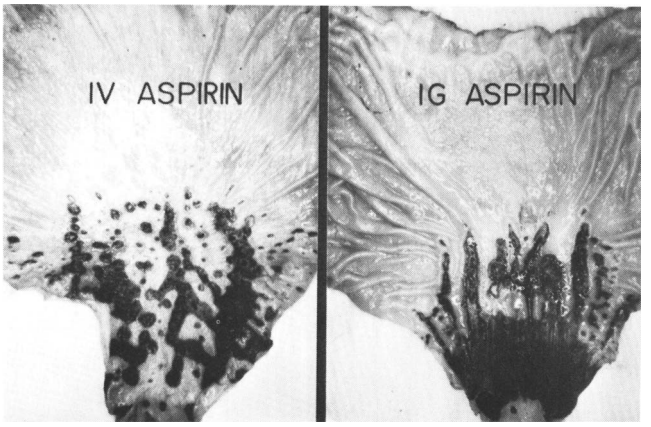

FIG. 1. Equal extent of antral ulcers in stomachs of cats killed 4 hr after being given a bolus dose of aspirin (40 mg kg^{-1}) intravenously (left) or intragastrically (right). Both cats were given histamine dihydrochloride (160 μg kg^{-1} hr^{-1}) intravenously for 1 hr prior to and 4 hr after the aspirin bolus.

Discussion. Under the conditions of the present study, intragastric aspirin alone, that is without histamine, failed to produce gastric mucosal lesions. However, previous studies clearly show that under other conditions of study in rats intragastric or intraperitoneal aspirin alone does cause gastric mucosal lesions (6). The lesions seen with aspirin alone are superficial erosions of the fundic or antral mucosa in contrast with the deep ulcers of the antral mucosa seen in the present study with intragastric or intravenous aspirin plus histamine. Histamine is not essential for the production of deep antral ulcers but giving histamine greatly speeds up their formation (2). The present study was directed toward a comparison of intravenous and intragastric aspirin in the production of these deep antral ulcers.

This study showed that intragastric or intravenous aspirin, both given with intravenous histamine, produced antral gastric ulcers in cats and that there was no significant difference between the two routes of administration of aspirin in regard to ulcer incidence or severity. If different mechanisms are involved, it is not reflected in the character or severity of the lesions. This suggests that the mechanism of production of these ulcers may be the same for the two routes of administration of aspirin. Since previous studies have shown that intragastric aspirin is a "barrier breaker" and intravenous aspirin is not (1), barrier breaking is apparently not the common mechanism by which both intravenous and intragastric aspirin produce ulcers. These studies (1) were done without infusion of histamine. We have not studied the effect of intravenous aspirin with histamine on the barrier.

Aspirin and other aspirin-like drugs inhibit the synthesis of prostaglandins (7, 8), and giving exogenous prostaglandins to rats markedly inhibits the ulcerogenic action of aspirin (9) and of a wide variety of other experimental ulcerogenic agents (10). Inhibition of prostaglandin synthesis may be the common mechanism by which intravenous and intragastric aspirin produce ulcers, but this speculation awaits confirmation by further studies.

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