Effect of secretin on histamine-induced duodenal ulceration in guinea-pigs

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Grossman (1966) proposed the use of secretin in the treatment of duodenal ulcer. Animal studies support this proposal; secretin prevents histamine (Konturek et al 1973) or pentagastrin-induced (Schleyerbach et al 1973; Konturek et al 1973) duodenal ulceration in cats. But studies in man (Höj et al 1973; Henn et al 1975; Demling et al 1975; Scholten et al 1977) have not so far established exogenous secretin as an effective antiduodenal ulcer agent. We present results of experiments to determine the effect of this hormone on histamine-induced duodenal damage in the guinea-pig. Both antiduodenal ulcer and gastric ulcerogenic activities were observed following multiple subcutaneous injections of this hormone.

Depot histamine injection (Hay et al 1942) was used to induce duodenal mucosal damage in fasted albino guinea-pigs of either sex, 380–740 g, housed five to a cage. Food, but not water, was withheld for 24 h before and during the experiments. Each animal received a subcutaneous injection of the antihistamine tripelennamine (5 mg kg^{-1}) 30 min before receiving a subcutaneous injection of histamine dihydrochloride (10 mg base kg^{-1}) suspended (6 mg ml^{-1}) in beeswax and peanut oil (5% w/v) in the morning on days 1 and 2 of an experiment. Additionally, each animal received either Boots secretin (10, 20, 30 or 40 Crick, Harper and Raper Units kg^{-1}; 20 Units ml^{-1}) or carrier (distilled water) subcutaneously immediately after receiving histamine and also at noon, 4.30 p.m., and midnight on days 1 and 2. The animals were killed and exsanguinated after noon on day 3 and examined for gastric and duodenal mucosal damage by a pathologist without knowledge of the treatment. The Fisher exact probability test was used to determine the significance of differences in lesion incidence in control and treated animals.

The results of experiments to determine the effect of secretin on histamine-induced duodenal damage are summarized in Table 1. Subcutaneously administered histamine dihydrochloride (10 mg base kg^{-1}) caused a high incidence of duodenal (67–90%) and a low incidence of gastric (11–22%) damage. Controls were routinely lesion free. Secretin, administered subcutaneously four times a day for two days, had no statistically significant effect against histamine-induced duodenal damage at 10, 20, and 30 U kg^{-1}, although the incidence of damage was reduced 34–40% at these doses. A significant ($P < 0.01$) decrease in the incidence of duodenal damage to 25% was observed with 40 U secretin kg^{-1}, while the incidence of gastric damage increased significantly ($P < 0.01$) to 75%. Secretin had no effect on the incidence of gastric damage at 10, 20 and 30 U kg^{-1}. Three of the guinea-pigs receiving 40 U kg^{-1} secretin were found dead after noon on the second day. Autopsy revealed each had an undamaged duodenum and a perforated gastric ulcer.

To our knowledge, secretin has not been reported to exhibit a protective effect against histamine-induced duodenal ulceration in the guinea-pig. Our results indicate the antiduodenal ulcer activity of subcutaneously administered secretin in this animal model. A significant reduction in the incidence of duodenal mucosal damage was observed with the highest dose of secretin (40 U kg^{-1}). Konturek et al (1973) have demonstrated that secretin will prevent duodenal damage induced by intravenously administered histamine in cats.

In addition to reducing duodenal ulcer incidence, an observation supporting Grossman's (1966) proposal, secretin, at 40 U kg^{-1}, also exhibited gastric ulcerogenic activity in this animal model. The incidence of gastric damage rose significantly from a control level of 10 to 75% in the secretin-treated group. Secretin has not been reported to cause gastric damage in histamine (Konturek et al 1973) or pentagastrin (Konturek 1968;

Table 1. Effect of subcutaneous secretin(S) in histamine (H)—treated guinea-pigs

Treatment	Dose of secretin U kg^{-1}	n	% Animals with lesions[1] in proximal duodenum	% Animals with lesions[1] in glandular stomach
H[2] + D.W.[3]		9[5]	67	22
H + S	10	9[5]	44	11
H + D.W.		10	90	10
H + S	20	9[5]	56	22
H + D.W.		9[5]	67	22
H + S	30	10	40	30
H + D.W.		10	90	10
H + S	40	8[6]	25[7]	75[7]

[1] Erosions or ulcers.
[2] Ten mg base kg^{-1} s.c. day^{-1} for two days.
[3] Distilled water.
[4] Secretin was administered 4 ×/day for two days.
[5] Ten animals were originally included in this group; one died shortly after the first histamine injection.
[6] Eleven animals were originally included in this group. Three animals were found dead after noon on the second day of the experiment; each had a perforated gastric ulcer and no duodenal damage.
[7] Significantly different from control; $P < 0.01$.

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Konturek et al 1973; Schleyerbach et al 1973) infused cats. Schleyerbach et al (1973) found isolated haemorrhagic inrosions in the antral mucosa of both secretin- and control injected pentagastrin-infused cats, suggesting that secretin neither prevents nor potentiates pentagastrin-induced gastric damage in this animal. The significance of our observation in the guinea-pig relative to the use of secretin as an antiduodenal ulcer agent remains to be determined.

The mechanisms by which secretin coincidently prevents histamine-induced duodenal damage and causes gastric ulceration in this guinea-pig duodenal ulcer model are at present unknown. Although much is known about this hormone (Rayford et al 1976), its gastrointestinal actions have not been defined in normal or histamine-treated guinea-pigs. It has been suggested that the antiduodenal ulcer activity of secretin in histamine-infused cats results primarily from its ability to increase output of neutralizing fluids in the duodenum (Konturek et al 1973). Our results with the lower doses of secretin, 10, 20 and 30 U kg^{-1}, suggest duodenal mechanisms alone are not particularly effective in blocking ulceration in this animal model. Similar (34–40%), but non-significant, reductions in duodenal ulcer incidence were observed with these doses which did not cause an increase in gastric damage. Significant antiduodenal ulcer activity was only observed coincident with a high incidence of gastric damage. This suggests activities of this hormone that lead to gastric damage contribute to its ability to prevent histamine-induced duodenal damage in the guinea-pig. Secretin can decrease gastric emptying (Chey et al 1970; Chvasta & Cooke 1973) and increase pepsin secretion (Stening et al 1969; Brooks et al 1969). Also, secretin is unable to antagonize the positive effect of histamine on gastric acid output in cat (Emas et al 1971; Konturek et al 1973) and dog (Gillespie & Grossman 1964; Johnson & Grossman 1969; Lucien et al 1970). Assuming secretin has this activity pattern in the guinea-pig, its administration could result in the accumulation of a large quantity of highly corrosive juice in the stomach, and consequently, a high incidence of gastric and low incidence of duodenal damage. This hypothesis, as well as the effect of antihistamine administration on the activity of secretin and the possibility that the natural secretin used in this study contains other active components, remain to be investigated.

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