Effects of Nicotine on Gastric Secretion and Ulcer Formation in Cats[1] (35966)

STANISLAW J. KONTUREK, TADEUSZ RADECKI, PIOTR THOR, ARTHUR DEMBINSKI, AND EUGENE D. JACOBSON

Institute of Physiology, Medical Academy, Krakow, Poland; and Department of Physiology and Biophysics, University of Oklahoma Medical Center, Oklahoma City, Oklahoma 73104

Although an epidemiologic relationship has been established between cigarette smoking and duodenal ulcers, the mechanistic link between the habit and the disease is uncertain. In recent studies on dogs, we have shown that "smoking" doses of nicotine depress pancreatic and biliary secretion of bicarbonate and water. Furthermore, we have found an inhibitory effect of nicotine on both the pancreatic secretory mechanism and the duodenal mucosal release of secretin (1, 2). While decreased neutralization of gastric acid in the duodenum would create a milieu conducive of ulcer formation, these findings, of themselves, do not prove that nicotine is ulcerogenic.

The present study was designed to determine the effect of nicotine on the formation of experimental duodenal ulcers in animals. Increased gastric acid output and duodenal ulcer formation were produced by prolonged infusion of pentagastrin into conscious cats. In addition, we studied the action of nicotine on feline gastric acid secretion.

Methods. Secretory Studies. Ten cats, weighing 1.8–2.2 kg each, were anesthetized with pentobarbital and were provided with a small Thomas-type cannula inserted into the stomach to form a gastric fistula. About 3 weeks after the cats had recovered from this surgical procedure, the secretory tests were started.

Before each experiment, the animals were deprived of food, but not water, for at least 18 hr. Throughout the 3.5 hr study period, a 154 m*M* NaCl solution was infused intravenously at a rate of 20 ml/hr, via a peristaltic pump (Harvard Apparatus Co.). Two basal collections were obtained at the ends of the first two 15-min periods; then pentagastrin was added to the saline infusion at a constant rate (8 μg/kg-hr) for the next 3 hr. This dose of pentagastrin has been shown to elicit a near-maximal gastric acid output (3). One hour after the start of pentagastrin infusion, nicotine was added in one of the following doses: 100, 200, or 400 μg/kg, administered over a 1-hr period. Then pentagastrin alone was infused for the last hour. In control tests, only pentagastrin was infused for the 3-hr experimental period after basal collection. The order of nicotine doses or pentagastrin was randomized for cats and days. Only one dose of nicotine was used for any single test. Gastric juice was collected every 15 min. The acidity was measured with an autoburette and pH meter (Radiometer) titrated to a pH of 7.0.

Production of peptic ulcers. Peptic ulcers were induced in conscious animals (42 cats, weighing 1.5–2.5 kg each) according to a method described previously (4). By random assignment, 10 animals served as controls. In the control experiments, pentagastrin alone was infused intravenously for 36 hr (the time required to produce peptic ulcers) at a dose of 8 μg/kg-hr. In experiments on the other 32 cats, nicotine was added to the pentagastrin infusion throughout the experiment in one of these doses: 100 μg/kg-hr was infused in 11 cats, 200 μg/kg-hr in 15 others, and 400 μg/kg in the remaining 6 cats. At the end of the experiment, each animal was sacrificed with intravenous pentobarbital. Only one dose of nicotine was used throughout a single experiment. Next, the upper gastrointestinal mucosa was assessed

[1] This study was aided by a grant from the American Medical Association Education and Research Foundation.

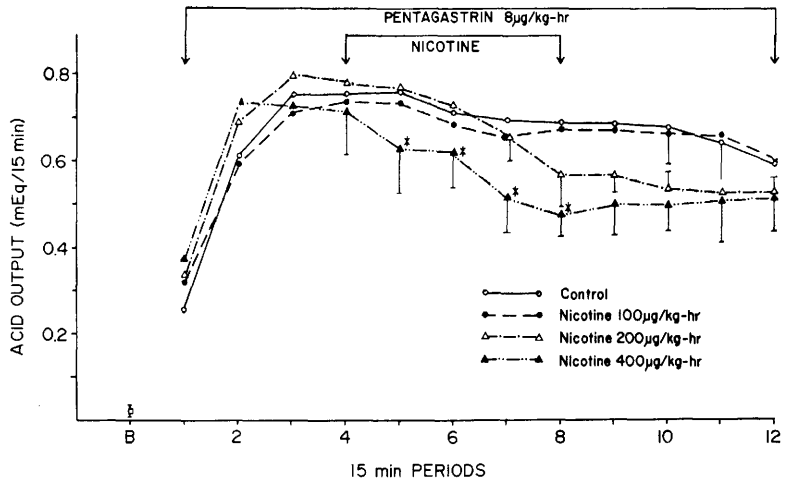

FIG. 1. Effect of intravenous infusion of nicotine in doses ranging from 100 to 400 µg/kg-hr on gastric acid output in response to pentagastrin infusion (8 µg/kg-hr) in 10 cats with gastric fistulas: (each point) a mean value based on data from 2 experiments on each of 10 cats. (vertical bars) standard errors of the means; (*) a significant difference from control values at $p<.05$.

for ulcers by a method previously described (4).

Results of all experiments were analyzed with a paired t test (5) comparing secretory data at times the cat received nicotine with secretory rates from control experiments at similar times when no nicotine was infused.

Results. Secretory studies. A near-maximal gastric acid output was produced in cats by intravenous infusion of pentagastrin in a dose of 8 µg/kg-hr (Fig. 1). In control experiments with pentagastrin alone, acid response reached the peak during the first 60 min of infusion, after which acid output steadily declined, falling to 80% of the initial peak level by the end of the experiment. Nicotine added to the intravenous infusion in doses of 100 and 200 µg/kg-hr had no effect on the acid response to pentagastrin. However, nicotine infused at the dose of 400 µg/kg-hr produced a significant decrease in response; this was accompanied by retching and restlessness in some animals. The depression of acid output was due to a decrease in both volume and acid concentration.

Gastric acid output under basal conditions was negligible. Nicotine alone, in doses ranging from 100 to 400 µg/kg-hr (added to the intravenous saline infusion for a 90-min period) failed to alter this basal gastric secretion; the results are not presented here.

Production of peptic ulcers. In the control experiments, intravenous infusion of pentagastrin alone for 36 hr resulted in the formation of duodenal ulcers and multiple erosions in 8 of the 10 cats studied. The mean ulcer area was about 80 mm^2. No ulcer complications, such as perforation or hemorrhage, occurred in this group of animals (Fig. 2).

When nicotine was added in a dose of 100 µg/kg-hr to the pentagastrin infusion throughout the experiments on 11 cats, the mean ulcer area did not differ significantly from that associated with pentagastrin administration alone. However, the duodenal ulcers and erosions appeared in all 11 animals.

Nicotine added in a dose of 200 µg/kg-hr to the pentagastrin infusion produced duodenal ulcer formation in all 15 animals tested. The mean ulcer area in these animals was about twice that found in the control group ($p<.05$). In 4 cats, perforations of the duodenal wall with subsequent peritonitis developed. In 3 others, hemorrhage occurred from the ulceration.

Peptic ulcers appeared in only 2 of the 6 cats in which nicotine was infused in a dose of 400 µg/kg-hr together with pentagastrin, and the mean ulcer area was reduced ($p<.05$) compared with control animals. In some of these cats, retching, vomiting, and restless-

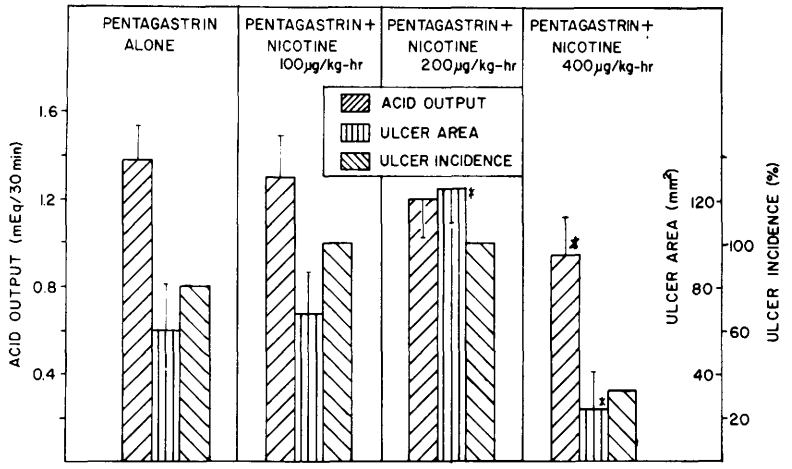

FIG. 2. Gastric acid output, incidence of peptic ulcers, and ulcer area in experiments with pentagastrin alone or with pentagastrin in combination with varying doses of nicotine: (each column for acid output) 30 min peak output in response to 8 μg/kg-hr of pentagastrin in cats with gastric fistulas; (*) a significant difference from pentagastrin alone at $p < .05$.

ness were observed throughout the period of peptic ulcer production.

Discussion. This study provides evidence that nicotine in "smoking" doses does not alter basal or pentagastrin-induced gastric acid secretion but does increase the area and the incidence of pentagastrin-evoked duodenal ulcerations in cats.

The failure of short-term nicotine administration to alter gastric acid secretion in humans, dogs, and rats was also reported previously (1, 7, 8). In this study, depression of the gastric secretory response to pentagastrin occurred only with the highest dose of nicotine (400 μg/kg-hr equivalent to smoking 16 cigarettes in 1 hr), when retching and restlessness were present; retching has been reported to reduce gastric secretion (6). The decrease of acid output with this dose (Fig. 1) probably explains the low incidence of peptic ulcer formation in cats infused with the highest dose of nicotine.

The maximal rate of ulcer formation with perforation or hemorrhage occurred when the nicotine dose was 200 μg/kg-hr, which corresponds to smoking 8 cigarettes/hr (9). This observation remains in agreement with a previous report concerning the effect of cigarette smoking on histamine-induced peptic ulcerations in dogs (10), in which the mechanism of the ulcerogenic action of nicotine was not elucidated.

The main cause of pentagastrin-induced duodenal ulcers in cats has been shown to be inadequate neutralization of highly acidic gastric juice in the duodenum (4), and nicotine has been demonstrated (1, 2) to strongly depress pancreatic and hepatic secretion of bicarbonate. Probably the additional ulcerogenic effect of nicotine in our preparation was due to a further decline in duodenal neutralization leading to an increase in the incidence and the area of peptic ulcerations.

Although only short-term administration of nicotine was used and only acute duodenal ulcerations were observed, this study suggests that the epidemiological association (11) between tobacco smoking and peptic ulcer formation in man can be considered causally related.

Summary. Nicotine infused intravenously in doses corresponding to the nicotine absorbed by smoking 4 to 8 cigarettes/hr failed to alter basal and pentagastrin-induced gastric acid secretion in conscious cats with gastric fistulas. In these doses, nicotine exhibited a potentiating effect on pentagastrin-induced peptic ulcer formation, probably due to its interference with the neutralization of acid in the duodenum.

1. Konturek, S. J., Solomon, T. E., McCreight, W. G., Johnson, L. R., and Jacobson, E. D., Gastroenterology **60**, 1098 (1971).

2. Jacobson, E. D., Konturek, S. J., and Johnson, L. R., Gastroenterology **60**, 780 (1971).

3. Konturek, S. J., Radecki, J., Biernat, J., and Thor, P., Scand. J. Gastroenterol. **5**, 613 (1970).

4. Konturek, S. J., and Dubiel, J., Scand. J. Gastroenterol. **4**, 59 (1963).

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

6. Gregory, R. A., "Secretory Mechanisms of the Gastrointestinal Tract," 117 pp. Arnold, London (1962).

7. Cooper, P., and Knight, J. B., J. Amer. Med. Ass. **217**, 255 (1956).

8. Thompson, J. H., Amer. J. Dig. Dis. **15**, 209 (1970).

9. Kuhn, H., Tob. Alkaloids Related Compounds, Proc. Int. Symp. **1964**, 42 (1965).

10. Toon, R. W., Cross, F. S., and Wangensteen, O. H., Proc. Soc. Exp. Biol. Med. **77**, 866 (1951).

11. Monson, R. R., Gastroenterology **58**, 337 (1970).

Received Feb. 25, 1971. P.S.E.B.M., 1971, Vol. 138.