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Effect of Glucagon on Gastric Secretion. (23525)

R. M. ROBINSON, KEITH HARRIS, C. J. HLAD AND B. EISEMAN

Department of Surgery and Radioisotopes, University of Colorado Medical School and Denver Veterans Admin. Hospital.

Zollinger and Ellison(1) recently have described a group of patients with progressive recurrent benign peptic ulcerations of the duodenum and upper jejunum associated with non-beta cell (presumably alpha cell) adenomas of the pancreas. These patients characteristically have a very high rate of gastric secretion and resistance to medical and surgical therapy. Although some of these patients have coexisting multiple adenomatosis of other endocrine glands(2) there is no clinical or laboratory evidence of hyperinsulinism. Since glucagon is secreted by pancreatic islet alpha cells which resemble the tumor cell type, Zollinger and Ellison suggested that glucagon might be the ulcerogenic factor. This study was designed to determine the effect of glucagon on gastric motility and secretion and thus to investigate(3) the likelihood of this substance being of pathogenic significance in the peptic ulceration associated with these bizarre pancreatic tumors.

Materials and methods. Gastric secretion: Nine adult males (age 29 to 59 years) were used; 4 of these patients had proven duodenal ulcer; 3 were diagnosed as psychophysiologic gastrointestinal reactions; and the remaining 2 patients were hospitalized for minor surgical problems unrelated to the gastrointestinal tract. Soon after awakening in the morning after a 12-hour fast, the patient was placed at bed rest for approximately 30 minutes before the experiment was begun. A No. 16 Levine tube was placed in the stomach and connected to a constant source of suction (100 mm Hg) with an intervening trap for collection of gastric secretions. The stomach was emptied and the initial specimen discarded. Gastric aspiration specimens were collected at 15-minute intervals during a one-hour control period, at the conclusion of which 1.5 mg of glucagon* in 10 cc of saline was rapidly injected by way of a previously established intravenous saline infusion in the forearm, and collections continued as before. The test period was continued for a maximum of 2 hours longer, or until the post glucagon infusion secretory rate approached the pre-infusion control. Venous blood samples were drawn without stasis from an indwelling needle in the antecubital vein and analyzed in duplicate. Capillary blood was drawn from a finger puncture. Glucose concentrations were determined by the Nelson-Somogyi method(4). The volume and free hydrochloric acid content was determined on each 15-minute sample(5). Gastric motility studies were performed on a series of 8 patients, 4 of whom had proven duodenal ulcers, the other 4 serving as normal controls. Motility was measured by an intragastric balloon attached to a recording device as designed by Hlad. As with the secretory studies, a one-hour pre-glucagon injection period was

* Kindly supplied by Eli Lilly Co., Indianapolis, Ind.

TABLE I. Effect of Glucagon on Gastric Secretion.

	Mean gastric secretory vol (ml/min.)		Mean HCl secretory rate (meq/min.)		Arterio-venous difference (mg %)	
	Control	Following glucagon	Control	Following glucagon	Control	Following glucagon
1*	26	8	.04	.02	4	13
2*	40	30	.5	.12	3	12
3*	29	18	.03	0	3.5	13.5
4	14	7	.02	0	4	9
5*	21	4	.03	.004	3	3
6	14	7	0	0	2.5	3
7	8	2.5	.02	.004	7	9
8	7	4	.01	.002	1	18
9	34	13	0	0	4	20

* Proven peptic ulcer.

used for the baseline control.

Results. The effect of intravenous administration of glucagon on the gastric secretory volume and its hydrochloric acid content is demonstrated in Table I and a typical experiment shown in Fig. 1. Following glucagon infusion there was a diminution in the total volume of gastric secretion; (mean 57%, range 25%-85%); and in the total and free hydrochloric acid fractions (mean 82%; range 50%-100%). In each instance gastric motility diminished following administration of intravenous glucagon. Both the diminution in gastric motility and the secretory changes occurred at the time of maximum arteriovenous blood glucose differences, but there was no definite correlation between the degree of peripheral glucose utilization and the degree of gastric response. The maximum response routinely occurred during the 30 minutes immediately following glucagon administration and in no instance did it persist for more than ninety minutes. There was no evidence of a later rebound response as described by Poth(6).

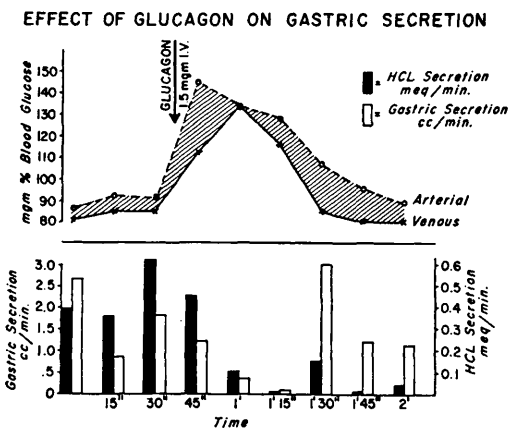

FIG. 1.

Discussion. The ulcerogenic properties of pancreatic secretion have been under investigation for many years. Complete diversion of pancreatic secretions by fistula from the gastrointestinal tract(7), and pancreatic duct ligation(8,9) both produce peptic ulceration, presumably by the removal of the alkaline pancreatic juice. Since total pancreatectomy does not result in ulceration, some pancreatic hormonal influence apparently is of importance in protecting against ulceration.

Hyperinsulinism, either from tumor or excessive administration, results in hypersecretion of HCl, and ulceration presumably due to the resultant hypoglycemia(10). Contrariwise, hyperglycemia in diabetes has been associated with a diminished incidence of peptic ulceration(11). Stunkard and Van Itallie(3) suggest that this effect is more intimately related to the glucose a-v difference (*i.e.*, utilization) than to the absolute blood glucose concentrations.

These previous studies(12) and the data presented in our experiments, suggest that the hyperglycemia and the increased glucose a-v difference(13) produced by glucagon results in diminished gastric motility, diminished total gastric secretory volume, and diminished hydrochloric acid secretion, activities that are associated with anti-ulcerogenic properties.

It seems unlikely, therefore, that the ulcerogenic factor in non-insulin producing adenomas of the pancreatic islet cells is glucagon. Such ulceration may result from an endocrine dysfunction related to the co-existing multiple adenomatosis, or to some as yet undiscovered pancreatic hormone.

Summary. 1. Diminution in gastric motility, gastric secretory rate, and hydrochloric acid production has resulted from glucagon administration in 17 patients. 2. These antiulcerogenic properties suggest that some factor other than glucagon is responsible for the severe peptic ulcerations commonly associated with non-insulin producing tumors of the pancreatic islets.

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Development of Tolerance to Depressant Effects of Atropine on Isolated Rabbit Ileum.* (23526)

H. E. D'AMATO, M. R. BLAIR AND B. B. CLARK

Department of Pharmacology, Tufts University School of Medicine, Boston, Mass.

The development of acquired resistance (tolerance) to the depressant action of atropine on gastrointestinal motility has been observed in man and in the dog(1,2). While suggestion of a related phenomenon in the isolated rabbit intestine can be found in the literature(3-5), a clear, controlled demonstration of the development of such tolerance *in vitro* has not been made. The work reported below is limited to studies of the depressant effects of atropine sulfate (atropine) and adiphenine hydrochloride† (adiphenine) on the amplitude of spontaneous contraction of the longitudinal muscle of isolated rabbit ileum. The results indicate that in this preparation tolerance to the effect of atropine is a reproducible and reversible phenomenon. Similar tolerance to adiphenine does not develop.

Methods. Sections of rabbit ileum were cut in lengths of 2 to 3 cm and mounted according to the classical method of Magnus in a bath containing 100 ml of oxygenated Tyrode's solution. Recordings of spontaneous contractions were effected electrically on a kymograph, the recording current being automatically shut off 10 sec of every minute. Contractions were recorded continuously for 5 min before and for 10 min after each addition of drug to the bath solution. At the end of these 10 min the bathing fluid was replaced with fresh Tyrode's solution. Second and third replacements followed at 2 min intervals. The ileum was then considered to be washed.

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† Adiphenine hydrochloride = diethylaminoethyl diphenylacetate hydrochloride (Trasentine hydrochloride: Ciba).