Histaminase: An Experimental Study

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Histaminase has been recommended for the treatment of all disturbances in which histamine may play a rôle (1). Recently, Babkin pointed out that histamine may be a factor in the gastric secretion of hydrochloric acid, and possibly in the genesis of peptic ulcer (2), and histaminase has been reported as beneficial in the treatment of ulcer (3). Clinical and laboratory reports on the effects of histaminase have been controversial. Recently, Roth and Horton (4) showed that in man gastric acid secretion, provoked by cold or by histamine, could be suppressed by histaminase (Torantil) but Atkinson and Ivy (5), working on pouch dogs did not find any effects of histaminase on gastric secretion stimulated by histamine or food; they employed their own preparation of histaminase on gastric secretion in pouch dogs (5). (f) It is believed however, that large doses of histamine given by mouth destroying histamine, formed in the intestines. We know, however, that large doses of histamine given by mouth have no pharmacologic effects, and apparently are destroyed during their passage through the intestinal walls.

We were prompted to analyze the biologic effects of
H for two reasons: the recent experimental evidence by Roth and Horton (4) on inhibition of gastric secretion by histaminase (v.s.) and by the idea, which suggested itself naturally, that the preparation of histaminase on the market (Torantil) being an impure substance, might have other effects, hitherto unknown. For this reason all available preparations of histaminase which were obtainable, old ones and new ones, were employed and the substance was administered in a variety of ways: intravenous, subcutaneous, intramuscular, intragastric and intraduodenal.

1. Secretion of the Pavlov Pouch. The closest approach to a physiological test of histaminase seemed to be to give repeated injections of histamine to dogs with pouches and, after a constant secretion had been obtained, to administer histaminase. Healthy dogs were employed after their constant response to histamine hydrochloride had been established in control experiments. The pouch secretion was collected at ½ hour intervals and titrated in the usual way. Experiments on 4 dogs demonstrated that no decrease in volume or acid secretion occurred following histaminase. On the contrary, a slight increase in acidity was observed in experiment 1. This dog was not as good a secretor as the other dogs and therefore may have been more susceptible to an additive stimulus. In experiment 4 the injection of histaminase was followed by a considerable rise of rectal temperature (from 38.9 to 39.9° C.) not observed in the other dogs, and some blood appeared in the pouch secretion, lowering the free acidity of that sample.

Since it is believed that the secretory process in the stomach may be mediated by the liberation of histamine in the mucosa, and since histamine seems to be a constant constituent of gastric juice (2), six experiments were performed with healthy Pavlov pouch dogs who received histaminase with or following a meat meal. The normal response of the animals to the meal had been established in a number of control tests. After feeding, the pouch secretion of acid and fluid rose to a maximum within 60 to 90 minutes; after that, the volume of fluid usually dropped gradually along a curve more or less constant for each dog. Acid secretion, however, stayed maximal for three to four hours after the meal. For this reason histaminase was injected one hour after feeding. The values for acidity two hours after the meal, that is one hour after histaminase, were expected to indicate an effect of the drug. Except in experiment 2, the secretion of acid was not diminished following the intravenous, subcutaneous, or oral administration of histaminase in various dosages. In experiment 2, the intravenous injection of histaminase was followed by a rise of rectal temperature of 1.2° C. which explains the depression of volume and acidity. In experiment 6, in which 5 pills of histaminase was administered in the meal meat, a small rise of gastric acidity occurred. This dog like the one in experiment 1 with histamine stimulation (v.s.) was also a low secretor.

A boiled solution of histaminase had no effect on meal or histamine secretion.

2. Secretion of the Stomach, Liver and Pancreas in Acute Experiments. As mentioned above the pharmaceutical preparation of histaminase (Torantil), which we employed, is a rather impure substance, and we suspected therefore that it might contain other biologically active substances. We therefore treated the effects of histaminase on gall bladder motility, and on salivary, gastric, biliary and pancreatic secretions of anesthetized dogs. In various acute experiments a small balloon was introduced into the gall bladder with the cystic duct ligated; the maxillary, common bile, and main pancreatic ducts were cannulated and their secretions recorded by electric drop recorders; the cardia was ligated and a tube introduced into the stomach through the pylorus which was ligated around the cannula. Gastric juice was aspirated by constant suction and every 10 cc. registered on the record. Constant intravenous injection of histamine was administered in 2 experiments, of saline in one, and nothing in another. When the rate of secretion had become constant, various preparations of histaminase were administered intravenously, intramuscularly, subcutaneously or into the duodenum.

No effects of histaminase were obtained on the motility of the gall bladder or on salivary secretion. Seven experiments were performed on gastric, biliary and pancreatic secretion, in four of which certain changes in secretion were obtained following histaminase. In experiment 1, gastric secretion was considerably greater following various preparations of histaminase given intravenously, intramuscularly, or into the duodenum while biliary secretion was not affected. In experiment 2, the intravenous injection of two units of histaminase produced a slight increase of pancreatic and of biliary secretion. The intraduodenal administration of 50 units of histaminase was followed by a large increase in pancreatic secretion and no marked change in biliary secretion. In experiment 3, the intraduodenal administration of 10 and 60 units of histaminase respectively was followed by a slight increase of both pancreatic and biliary secretion. In experiment 4, histaminase was administered subcutaneously. A considerable and prolonged effect was noted on bile secretion following the injection of two preparations of histaminase.

3. Effect of Histaminase on Gastric Motility in Normal Unanesthetized Dogs. Although histamine does not seem to have any relation to gastric motility, the following experiments were performed in order to elucidate some unknown mechanism or constituent in the preparation of histaminase employed. Normal healthy dogs with gastrostomies received only water for 24 hours preceding the experiment. Gastric motility was stimulated by subcutaneous administration of small doses of insulin and prostigmin respectively, and recorded in the usual way. Such motility would persist continuously for 4 to 8 hours. Previous control experiments had established the usual variations for each dog. Histaminase was administered after a suitable control period and at a time when gastric motility was known to continue for two hours or more. Gastric motility was roughly graded as type 1, that is, tonus waves and very small contractions; type 2, medium size contractions; and, type 3, very large contractions. Ten such experiments were performed and in only one was inhibition observed following the intravenous injection of 1 unit of a preparation of histaminase which in another test on a smaller dog did not affect gastric motility (experiments 1 and 2). In experiment 3, a decrease of gastric motility oc-