Inhibition of Gastric Secretion in Dogs by Hexamethonium. (19331)

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Hexamethylene bis - trimethylammonium chloride (hexamethonium, C6) is a ganglionic blocking agent of high potency and moderately long duration of action(1). All of its pharmacological actions have thus far been explicable on the basis of its ability to block the action of acetylcholine on sympathetic and parasympathetic ganglia(1,2). Kay and Smith(3) found that intramuscular injection of 100 mg of the iodide salt in human subjects abolished basal gastric secretion for several hours. The gastric secretory response to insulin was delayed and depressed by this dose of hexamethonium. They found that the secretory response to histamine, alcohol or meat extract was not inhibited by hexamethonium, however they measured only acid concentration in the juice and did not give values for the volume of juice secreted.

The present report presents the results of a study of the effect of hexamethonium on gastric secretion in dogs.

Methods. Four dogs with vagotomized pouches of the entire stomach and four dogs with simple gastric fistulas were used. The animals were fasted for at least 12 hours before each test and 8 experiments were made in each phase of the study. Acid secretion was stimulated by subcutaneous injection every 10 minutes of either 0.04 mg histamine diphosphate or 0.05 mg Urecholine (carbamyl β-methyl choline chloride, Merck).† The gastric juice was collected every 20 minutes, the volume was measured and the acid concentration determined by titration with 0.03 N NaOH using p-dimethylaminoazobenzene and phenolphthalein as indicators. When the rate of acid secretion had reached a stable plateau (about 2 hours after beginning injections of the stimulatory drug) hexamethonium (Bistrium, Squibb)‡ was injected intravenously in a dose of 4 mg/kg. The details of this method for studying gastric secretory inhibitors have been presented elsewhere(4).

Results. The results are presented in Table I. Hexamethonium inhibited both Urecholine and histamine-stimulated acid secretion in both vagotomized total pouch dogs and vagally innervated gastric fistula dogs. The degree of inhibition of both drugs was greater in the dogs with vagally innervated stomachs than in those with vagally denervated stomachs, although the former secreted acid at a more rapid rate. In both types of dogs the inhibition of Urecholine induced secretion was greater than for histamine. This may be related to the fact that the dose of Urecholine used evoked a lower secretory rate than the histamine.

In all instances the inhibition persisted throughout the 3hr period after injection of hexamethonium during which observations were made.

Discussion. The inhibition of secretion in the vagally innervated stomach preparations can be explained on the basis of vagal blockade, because it has been shown that vagotomy reduces the response to histamine and other stimuli(5). However, the inhibition observed in the vagally denervated preparations cannot be attributed to vagal blockade. Hexamethonium has been shown to be devoid of antihistamine and anti-acetylcholine action when tested on isolated smooth muscle(2). A theoretically possible explanation of the mechanism of inhibition by hexamethonium in the vagally denervated stomach preparation is as follows: The vagally denervated stomach is known to be capable of synthesizing acetylcholine(6). This production of acetylcholine may be, in part at least, due to the activity of post-ganglionic vagal nerves. That is, we may postulate that the post-ganglionic vagal fibers continue to form some acetylcholine after the preganglionic fibers have been severed. We may further postulate that hexamethonium would depress the formation of acetylcholine

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† Kindly supplied by Merck & Co.

‡ Kindly supplied by E. R. Squibb and Sons.

TABLE I. The Effect of Hexamethonium (C6) on Histamine and Urecholine Stimulated Secretion in Dogs with Vagotomized Total Pouches and in Dogs with Gastric Fistulas (Vagally Innervated). Four dogs in each experiment; 2 tests on each dog.

Type of dog	Stimulant	Control secretory rate free HCl, mM/hr	% inhibition Hr after C6 1	2	3
Gastric fistula	H*	5.70 ± 1.1	47 ± 11.5	63 ± 6.3	68 ± 10.3
	U	2.70 ± .9	70 ± 7.6	97 ± 1.4	96 ± 1.8
Total pouch	H	2.50 ± .6	41 ± 1.3	31 ± 11	37 ± 5.5
	U	1.81 ± .6	44 ± 13.9	73 ± 19.9	68 ± 12.8

* H = Histamine, U = Urecholine.

by the preganglionically denervated ganglion cells. Since cholinergic stimuli potentiate the response of the parietal cell to other direct acting stimuli(7,8), a decrease in response would result. The ability of hexamethonium to suppress the spontaneous activity of preganglionically denervated ganglion cells is attested by the fact that it inhibits certain of the spontaneous movements of the isolated ileum(2).

Hexamethonium resembles atropine(9) in that both have a greater inhibitory activity in the vagally innervated than in the vagally denervated stomach. Atropine acts by blocking the effect of acetylcholine, hexamethonium, according to the present hypothesis, by depressing acetylcholine synthesis. If it is assumed that the basal rate of acetylcholine synthesis is greater in the vagally innervated than in the vagally denervated stomach then this difference in effectiveness of hexamethonium and atropine in these two types of stomach preparations would be explicable.

Summary. In dogs with gastric fistulas (vagally innervated) and in dogs with pouches of the entire stomach (vagally denervated), the secretion of acid in response to Urecholine or histamine is depressed for at least 3 hours following intravenous administration of 4 mg/kg of hexamethonium bis-trimethylammonium chloride. The inhibition is greater in the vagally innervated than in the vagally denervated stomach preparations.

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Effect of Antibacterial Substances on Fecal Clostridia Populations.* (19332)

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The reports of marked increase in the rate of gain of chicks, turkey poults and weaned pigs fed diets supplemented with antibiotics have aroused interest in the possible role of intestinal microflora on growth. In an effort to obtain information on the action of antibiotics, McGinnis and coworkers(1) have observed that the growth of *C. perfringens* is inhibited in the ceca of turkey poults fed

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