INTERDIGESTIVE GASTRIC SECRETION IN DUODENAL ULCER

A STUDY OF THE COMPARATIVE INHIBITION BY HEXAMETHONIUM IODIDE AND L-HYOSCYAMINE

BY

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Since it was first demonstrated that patients subject to duodenal ulcer tend to have a higher interdigestive gastric secretion than normal subjects (Henning and Norpoth, 1933) its control has been attempted by various methods. The theories of its causation lie between continuous formation of histamine-like substances and constant excessive activity of the gastric secretory fibres of the vagus nerve (Dragstedt, 1942). Dragstedt and Owens (1943) demonstrated that bilateral vagotomy reduced the interdigestive secretion to normal levels, and postulated that the excessive secretion was of neurogenic origin.

Hence atropine, being a parasympathetic paralyrant, is the natural drug of choice to reduce vagal secretion. Mears (1943) demonstrated a reduction in volume and acidity in a proportion of cases given 1/75 gr. (0.8 mg.) three-hourly by proctoclysis. He noted a greater relative reduction in cases of duodenal ulcer than in normal subjects. Kirsner *et al.* (1948), however, reported a number of patients with grossly excessive interdigestive acid outputs who were entirely unaffected by doses up to 6 mg. (1/10 gr.) of atropine. Other workers noted variable effects (Avey *et al.*, 1950; Keefer and Bloomfield, 1926).

Various ganglionic paralytics have also been used for their vagal paralyrant effect. Tetraethylammonium chloride (Ferrer, 1948) and other tetra-ammonium compounds—dibutoline (Levin *et al.*, 1949; Lorber, 1950) and bantnine (Smith *et al.*, 1950)—have reduced secretion in a proportion of subjects, but when compared with atropine have not proved significantly more effective. Hexamethonium salts (Kay and Smith, 1950a) have been shown to reduce interdigestive secretion effectively.

Preliminary studies with large doses of belladonna were found to reduce interdigestive secretion substantially. It was therefore decided to compare the effects of intramuscular hexamethonium with those of oral L-hyoscyamine, the alkaloid of belladonna with the greatest peripheral paralyrant effect (Goodman and Gilman, 1941). Oral hexamethonium has not been used, although it is reported to reduce the volume and acidity of gastric secretion (Kay and Smith, 1950b).

Methods

Five male subjects with symptoms of peptic ulcer dyspepsia and radiologically demonstrable duodenal ulcer were studied. Their ages ranged from 30 to 53 years and their weights from 125 to 162 lb. (56.7 to 73.5 kg.). Symptoms had been present from seven to fifteen years.

At 3.30 p.m. the patient had a light meal of a cup of tea and two plain biscuits. Ryle's tube was passed, at 8 to 8.30 p.m., through the nose, after local analgesia. The position of the metallic tip of the tube was con-

firmed by x-ray fluoroscopic examination to overlie the left half of the vertebral column. The subject lay on the left side. No attempt was made to get him to spit out saliva. The stomach was emptied, and continuous suction then applied by means of an electrical pump, a valve being used to prevent a greater suction pressure than 4 cm. Hg. Even so, blood clots were found in some specimens.

At the end of each hour the receiver was emptied, the volume being measured. A syringe was used to aspirate any residual juice, and air was then squirted down the tube to ensure patency so far as was possible. Continuous suction was applied again, collection being continued for ten hours. These duties were performed by the nursing staff. We wished to assess that the majority of the collection was made by continuous, not intermittent, suction, for which purpose the hourly volume by pump suction was compared with the total hourly volume. Samples collected at the end of each hour were placed in a refrigerator until estimated.

The final dose of belladonna or L-hyoscyamine was determined by giving gradually increasing oral doses nightly at 8 p.m., until that dose was reached at which the subject complained of blurring of vision and dry tongue on waking the next morning—that is, at 7 to 8 a.m. On those evenings when collections were made after giving belladonna or its alkaloids no aspiration was made before an hour had elapsed. Hexamethonium iodide ("hexathide") was given intramuscularly in three doses of 100 mg., each at three-hourly intervals—at 9 p.m., midnight, and 3 a.m.

The next afternoon the following values were determined: volume, free and total acidity, and peptic activity of each hourly sample. Samples were studied irrespective of the presence of bile staining. The volume of each sample was measured to the nearest millilitre in a graduated cylinder. The acidity was determined by titration with N/10 NaOH on 2 ml. of gastric juice with Topfer's reagent and phenolphthalein as indicators. The pepsin content was estimated by Hunt's method, in which dried human plasma is the source of the substrate (Hunt, 1948).

Results

It so happened that the maximum tolerated dose of L-hyoscyamine was of the same order in all subjects—7/100 gr. (4.6 mg.)—and that the dose of tincture of belladonna was comparable—210 min. (12.6 ml.). (The B.P. lays down a standard strength of about 1/100 gr. (0.65 mg.) hyoscyamine in 30 min. (1.8 ml.) of tincture.) All subjects received the same dose of hexamethonium iodide, irrespective of body weight.

In the Table are given mean hourly values for each collection made. The percentage reduction of output, as a result of the drug given, is worked out from the mean of the control collections made before and after administration of the drugs. In two subjects a third collection was made between the exhibition of the two drugs, and in these cases this collection also is taken into consideration in calculating the mean of the control readings.

The Chart shows graphically the mean outputs relative to the initial control values, which feature as 100%. It will be seen that with tincture of belladonna, or L-hyoscyamine, and with hexamethonium iodide, it was possible to reduce secretion volume and acid and pepsin output. Comparison of the two drugs showed that the reduction of secretion volume and acid output were of

Subject	Age	Weight	Duration of Symptoms	Date	Drug Dosage	Mean Hourly Values				Output: % Reduction			
						Vol. (ml.)	Free Acid Output (mEq)	Total Acid Output (mEq)	Pepsin Output (Units)	Vol.	Free Acid	Total Acid	Pepsin
1	34	lb. kg. 162 73.5	10 yrs.	10-11/3/50	—	150.3	10.72	11.93	No readings	61.6	82.3	74.7	43.7
				21-22/3/50	Tr. bellad., 210 min.	51.9	1.48	2.46	9,300				
				24-25/3/50	—	127.4	6.86	8.77	20,500				
				28-29/3/50	Hexamethonium, 100 mg. 3-hrly	45.0	1.26	1.97	4,130				
				31-3/4/50	—	128.0	7.42	9.08	12,450				
2	39	145 65.8	15 yrs.	30-31/5/50	—	55.7	2.30	3.22	9,200	41.7	80.5	62.7	27.3
				7-8/6/50	L-hyoscyamine, 7/100gr.	42.9	0.88	1.88	8,800				
				13-14/6/50	Hexamethonium, 100 mg. 3-hrly	28.4	0.53	1.00	2,125				
				15-16/6/50	—	91.2	5.70	6.84	14,800				
3	30	132 59.9	10 yrs.	20-21/6/50	—	94.0	7.99	9.20	11,900	60.5	78.0	71.0	37.7
				27-28/6/50	L-hyoscyamine, 7/100 gr.	39.0	1.50	2.34	8,330				
				29-30/6/50	—	102.0	8.57	10.03	No readings				
				3-4/7/50	Hexamethonium, 100 mg. 3-hrly	43.4	3.57	4.13	6,100				
				6-7/7/50	—	99.0	3.94	5.08	14,860				
4	53	125 56.7	11 yrs.	21-22/7/50	—	148.0	10.2	11.9	22,110	63.0	83.3	82.0	78.2
				24-25/7/50	Hexamethonium, 100 mg. 3-hrly	49.0	1.6	2.0	3,880				
				25-26/7/50	L-hyoscyamine, 7/100 gr.	53.0	1.7	2.3	6,990				
				28-29/7/50	—	118.0	9.2	10.3	12,980				
5	41	132 59.9	7 yrs.	20-21/11/50	—	92.0	2.7	3.85	13,980	71.0	87.3	84.5	90.5
				21-22/11/50	Hexamethonium, 100 mg. 3-hrly	26.6	0.36	0.60	1,080				
				27-28/11/50	L-hyoscyamine, 7/100 gr.	28.0	—	0.26	570				
				30/11-	—								
				1/12/50	—	86.0	2.96	3.85	8,960				

about the same order, but the reduction of pepsin output was greater with intramuscular hexamethonium iodide than with L-hyoscyamine or tincture of belladonna (one subject included in L-hyoscyamine results). The difference, however, is not statistically significant in so small a series.

Another point of interest is the return of the control values, after exhibition and withdrawal of the inhibitory drugs, to their former levels, demonstrating a lack of residual effect from the drugs. The control values, when averaged for the series, are remarkably constant.

Effects on concentration are not shown, being unreliable, as no precautions could be taken to prevent swallowing of saliva, the subject usually sleeping for the greater part of the test; nor was biliary contamination a deterrent to examination of a sample. It was noticed, however, that the tendency was for higher individual hourly concentrations of pepsin to occur after L-hyoscyamine administration than after hexamethonium.

Bile tended to be present, as judged by a rough plussing assessment of degree of staining of samples, in greater quantity

after giving hyoscyamine than after hexamethonium, but similar quantities were sometimes present on nights when no drug was given.

Discussion

Collections of interdigestive secretions have been criticized (James and Pickering, 1949). Despite discrepancies in control readings on individual subjects, when readings made before administration of drugs, and afterwards, are averaged for the five subjects, there is good agreement (see Chart). The importance of screening the intragastric tube fluoroscopically cannot be too strongly stressed. The difficulty of manoeuvring the tube into position on occasions has to be experienced to be believed. In other secretion studies achlorhydria has resulted from imperfect placing of the tube, an acid juice being readily obtained when the tube was properly located. Since preliminary screening of the tube has been the rule, it has been found coiled in the fundus of the stomach on a number of occasions.

L-Hyoscyamine was studied mostly, as it is said to lack the central excitatory effects of atropine, the racemic mixture, but little difference in inhibitory effects has been noted between L-hyoscyamine and tincture of belladonna. Where one has been effective a comparable dose of the other has produced similar inhibition. Likewise, in one of two patients in whom belladonna lacked inhibitory effect on interdigestive secretion, L-hyoscyamine also was ineffective. During these studies the tube was not being screened, hence data are not given in this paper. It is possible, but unlikely, that the control collections were incomplete. Hexamethonium was not available for trial in these subjects.

There was little complaint of side-effects of either drug. One patient complained of headache, which disturbed sleep, after a maximal dose of L-hyoscyamine. As he had been investigated a year previously, and his limit of tolerance to belladonna was known, the dose was increased to maximum more rapidly than was

Chart showing mean outputs as percentages of initial control values in five subjects.

customary. He was the only patient, however, to feel the orthostatic hypotensive effect of hexamethonium, falling flat on his back on rising from bed, four hours after the last dose. All patients were warned not to leave their beds while receiving hexamethonium injections.

Belladonna, or its alkaloid, was given so early in the evening in order that there might be adequate opportunity for absorption of the drug before gastric suction was applied. The residue aspirated after an hour was not tested for unabsorbed belladonna alkaloids. Absorption of belladonna from the small bowel would continue after aspiration had been started. Therapeutically, smaller doses of belladonna should suffice to produce the symptoms of dryness of the mouth and mydriasis on waking, as the drug would be taken at a later hour. In most of the patients studied, data from all of whom are not given in this paper, the administration of belladonna, or its alkaloids, was not continued for any length of time, as it was necessary to withdraw the drug and demonstrate the return of the spontaneous secretion to former levels. However, the drug has been given for periods of many days to other patients to control interdigestive secretion, without ill effect. The use of intramuscular hexamethonium salts is limited to institutional treatment.

Conclusions

Adequate doses—larger than are normally used—of belladonna, or its alkaloids, orally, and intramuscular hexamethonium iodide produce substantial inhibition of interdigestive gastric secretion in patients with duodenal ulcer. The inhibition obtained compares favourably with a series studied by Clarke *et al.* (1947) before and after the operation of vagotomy. In 16 patients they found a reduction by a half of the average total acid output.

Summary

The effects of oral belladonna, or L-hyoscyamine, and hexamethonium iodide intramuscularly on interdigestive gastric secretion are compared.

Similar substantial reduction in secretion volume and acid and pepsin output is obtained by means of either drug. Results compare favourably with a reported series after vagotomy.

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MECHANISM OF THE RENAL EXCRETION OF METHONIUM COMPOUNDS

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It has been reported (Milne and Oleesky, 1951) that in normal man hexamethonium bromide given intramuscularly is almost completely excreted in the urine in the 24 hours following the injection. Zaimis (1950) has also shown that in rabbits 60 to 70% of an intravenous dose of hexamethonium iodide is excreted in the urine during the next 24 to 48 hours. The following observations were made to find out in what manner the kidneys excrete hexamethonium bromide (C6) and pentamethonium bromide (C5). The clearance of these substances has been compared with the simultaneous clearance of inulin in man and experimental animals.

Technique

Clearances were estimated in two unanaesthetized hypertensive patients and in three subjects during varicose-vein ligation or herniorrhaphy under light ether or cyclopropane anaesthesia; in three cats; and in four rabbits anaesthetized with pentobarbitone sodium 40 to 60 mg./kg., or chloralose 75 mg./kg.

Inulin clearance was taken to equal glomerular filtration rate. An intravenous priming injection of inulin was given, followed by an intravenous maintenance injection delivered by an electrically driven syringe. At least half an hour was allowed for stabilization before clearance periods were begun.

The administration of C5 and C6 was not uniform. The two hypertensive patients had been on methonium compounds for several weeks before the day of the experiments, and a plasma and urine blank was therefore not obtainable. In these two patients 50 mg. of methonium compound was given intramuscularly 15 minutes before the start of the first clearance period, followed by an intravenous maintenance of 0.5–1 mg. a minute. In the three anaesthetized subjects C5 was given intravenously in divided doses, and clearance periods were begun 5 to 10 minutes after the last injection; no C5 was given during the clearance periods. The cats and rabbits were given an intravenous priming injection of C6, 1 to 3 mg./kg., in divided doses, 5 to 20 minutes before the start of the first clearance period. Only three animals were given a C6 intravenous maintenance injection (16 µg. a minute) during the clearance periods.

A diuresis was promoted by a continuous intravenous injection of 8 to 12% mannitol in the anaesthetized subjects and experimental animals. In the two unanaesthetized subjects a brisk diuresis was induced by 1,000 ml. of water given by mouth an hour before the first clearance period. Urine was collected by urinary catheter in all instances, the bladder being washed out with saline at