EFFECT OF ORAL HEXAMETHONIUM SALTS ON GASTRIC SECRETION

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Hexamethylene-*bis*trimethyl-ammonium (hexamethonium) iodide (C6) has been shown by Paton and Zaimis (1949) to exert a blocking effect at the synapses of autonomic ganglia. In a previous paper (Kay and Smith, 1950) we have shown that this compound, when given intramuscularly, inhibits the gastric secretion and motility. In the present paper we give the results obtained with the same drug administered by mouth, and also compare the effects of the other halides.

In the first series of experiments we have observed the effect of a single dose of the iodide salt on the gastric secretion; in the second, the effect of repeated administration; and in the third, the comparative effects of equivalent doses of the iodide, bromide, and chloride.

Effect on Spontaneous Gastric Secretion

Ten male patients with duodenal ulceration were selected for study. Cases of peptic ulcer complicated by organic stenosis were excluded, since it was felt that the use of hexamethonium iodide would exaggerate gastric retention. Secretion tests were begun at 9 a.m., after a 12-hour fasting period. In the control test, specimens were aspirated every 30 minutes for a period of three hours. On the following day 500 mg. of the drug was given by stomach tube immediately on removal of the fasting juice. After one hour specimens were aspirated at 30-minute intervals. This method was used for six patients. In the other four, to avoid aspiration of unabsorbed drug retained in the stomach, the first aspiration was delayed until two hours after giving the drug.

At each aspiration the stomach was emptied, and the volume, bile staining, and titratable free hydrochloric acid were noted. All saliva was expectorated. It will be seen from Figs. 1 and 2 that achlorhydria was reached in five patients, being of short duration in three and lasting four hours in the other two. Of the remainder, three patients showed an appreciable fall in the level of acidity. Two, however, showed no significant change. That the reduction of acidity was due to diminished secretion and not to regurgitation of duodenal juice was indicated by the small volume of the fluid withdrawn and the absence of bile.

Effect of a Repeated Dose on Spontaneous Gastric Secretion

In view of the variable results noted above, it seemed desirable to determine if consistent results were obtained in individual patients. With this in view 500 mg. of hexamethonium iodide was administered to four patients on two successive occasions and the results compared with preliminary and final controls. As in the first group, the drug was given after aspiration of the fasting juice. Beginning one hour later, specimens were removed at half-hourly intervals. The results are shown in Fig. 3. It will be

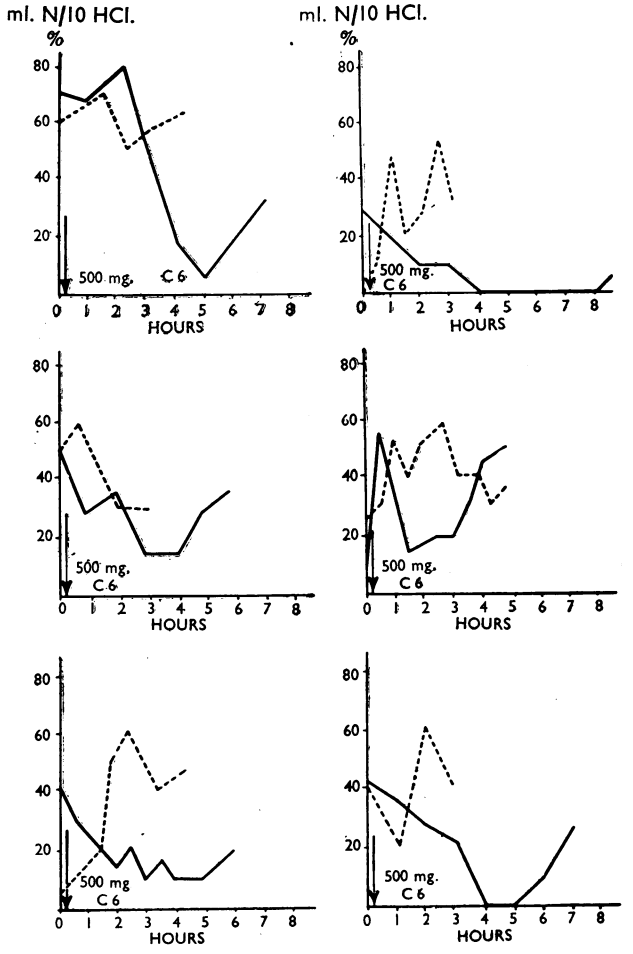

FIG. 1.—Spontaneous gastric secretion. Effect of oral C6, dosage 500 mg. (six cases). Broken line shows control readings.

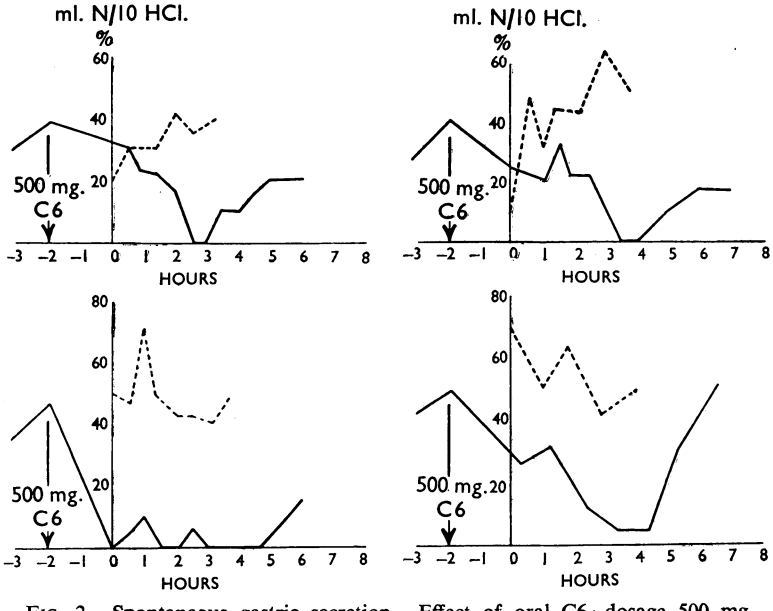

FIG. 2.—Spontaneous gastric secretion. Effect of oral C6, dosage 500 mg. (four cases).

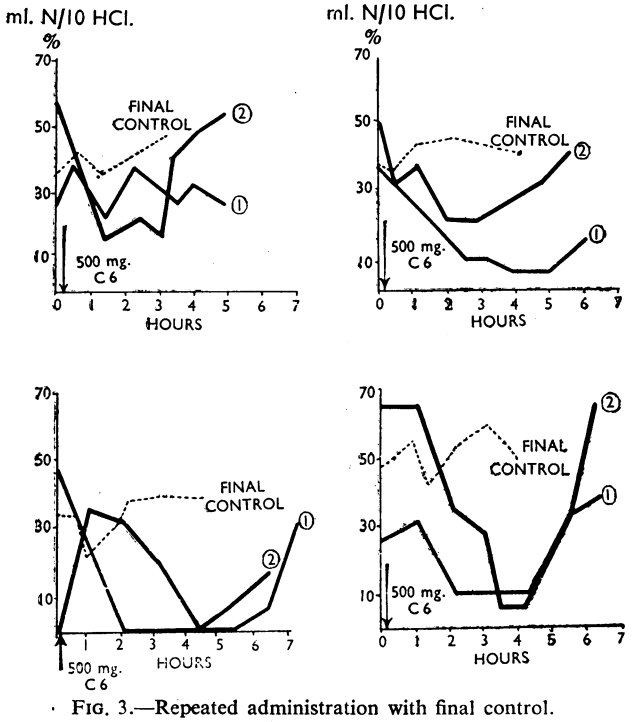

FIG. 3.—Repeated administration with final control.

seen that, while the effects differed in the four individuals, in each of them the successive results were consistent. It will be noted also that there was no evidence of prolonged action of the drug from one day to the next.

Comparison of Hexamethonium Halides

In a further series of six patients the action of equivalent amounts of hexamethonium iodide (500 mg.), hexamethonium bromide (440 mg.), and hexamethonium chloride (340 mg.) was tested on spontaneous gastric secretion. Control tests were performed before and after the test experiments. To avoid fallacies due to possible summation effects, the methonium salts were given in varying order, using all combinations. The tests were made on consecutive days, and in each case the fasting juice was removed, followed by a further specimen one hour later. The drug was then given and repeated aspiration delayed for two hours.

The average figures of the six cases are shown in Fig. 4, from which it will be seen that the iodide appears to give the most effective control of spontaneous secretion, the chloride being the least effective. Results obtained with individual patients agreed with the above finding in four cases; in one case the bromide gave a more satisfactory result, while another was inconclusive.

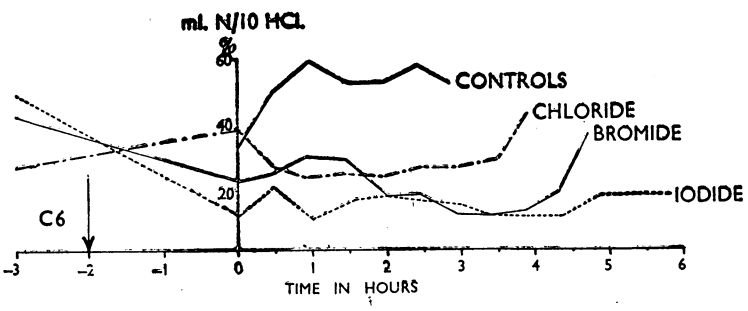

FIG 4.—Comparison of hexamethonium halides: oral administration. Average of six cases.

Observations on Side-effects.—During this investigation hexamethonium was administered on 36 occasions. Observations were made throughout on the frequency and severity of the known side-effects. After 12 of the administrations there was definite impairment of accommodation with resultant blurring of vision, though this was severe in only two cases. There was no visual upset in the remaining 24, but 8 patients complained of heaviness about the eyes; dryness of the mouth was mentioned by three patients; there was a tendency to constipation in several patients, especially in the group receiving hexamethonium on successive days. The sensation of warmth noted after intramuscular injections was not evident after oral administration.

Hypotension

It was found that with the patient supine there was an average drop of 5–10 mm. Hg in systolic and diastolic blood pressure. On standing motionless the fall in blood pressure was increased by 15 mm. Hg. This hypotension, elicited in the above manner, was present from one hour after administration, reached a maximum at two to two and a half hours, and lasted three to four hours. In these circumstances several patients complained of faintness, which was relieved by recumbency. It should be noted, however, that the subjects of this investigation had been fasting for more than 12 hours. It was noted that by taking active exercise faintness was prevented or overcome.

As an experiment under more rigorous conditions in which postural hypotension would be seen at the maximum, the action of hexamethonium was studied in four post-operative cases. They were males, aged 14, 21, 23, and 62 years, and were examined within one week of operation (ruptured appendix, perforated ulcer, inguinal hernia, and appendicitis). The patient aged 21 was ambulant for the first time. In this series particular note was taken of the effect on the blood pressure of standing motionless and of active movements.

Before giving hexamethonium, blood-pressure readings were obtained with the patient at rest in bed, immediately on standing, after standing motionless for five minutes, after walking for five minutes, and, finally, after recumbency for five minutes. Similar observations were made one, two, three, and four hours after 500 mg. of hexamethonium orally. On successive days the drug was given (*a*) after 12 hours' fast, the patient fasting throughout; (*b*) after 12 hours' fast, the administration being followed immediately by a meal; and (*c*) after a meal.

In control observations (without hexamethonium) immediately on standing there was a slight fall of blood pressure (5–10 mm. Hg), which was rapidly compensated by vasoconstriction. After hexamethonium, in two cases a similar fall of pressure occurred, but persisted while the patient remained motionless. In the third (Fig. 5) the fall was considerable (from 100/60 to 65/45). In the fourth there was a transitory severe hypotension with a feeling of faintness. In all cases the pressure rose towards the normal level when purposeful activity was begun. The findings in the man aged 62 are shown in Fig. 5.

When the drug was given on an empty stomach the blood-pressure changes were of the same order, whether the patient was subsequently given a meal or kept fasting, though in the latter state the subjective sensations were severe. When the drug was given after a meal, however, the hypotension on standing was slightly less. This

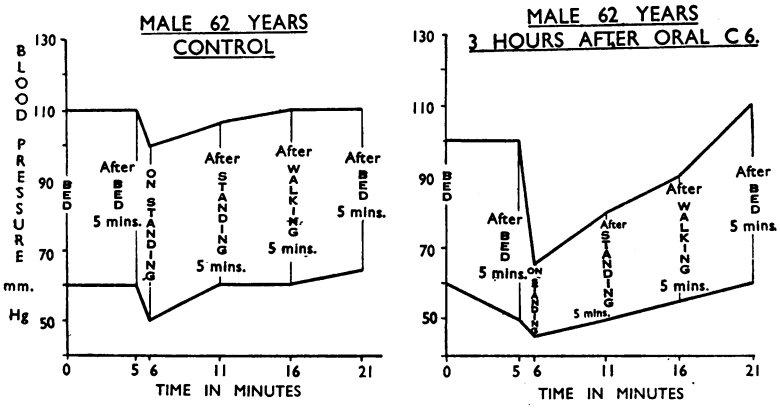

FIG. 5.—Effect of posture and activity on blood pressure before and after C6.

may have been due to delayed absorption, a point which requires further study.

Discussion

Our observations show that hexamethonium iodide given by mouth may depress the acid secretion, but does so less consistently than when administered intramuscularly. In about one-third of our cases the secretion was depressed to the point of achlorhydria, in one-third there was an appreciable lowering, while in the remainder there was no demonstrable effect. Since in this refractory group there were side-effects, including hypotension, the failure cannot be attributed entirely to faulty absorption. The observation that in four cases consecutive experiments gave closely similar results suggests that the failures may be due to individual variations in susceptibility to the drug.

Experimental work has shown that hexamethonium appears to be more effective in blocking the cat's superior cervical ganglion when this ganglion is excited frequently and for a long period than when it is excited briefly and with less frequent stimuli (Paton ; personal communication). It seems possible, therefore, that hexamethonium may in some cases depress abnormal ganglionic activity before it interferes with normal function. Thus the gastric effects would be most marked in cases with excessive vagal tone. Indeed, we gained the impression that side-effects such as hypotension were least marked in these cases in which acid secretion was most affected. Thus the drug may act at different sites in different individuals, according to the nature of the predominant autonomic tone.

The three halide salts of hexamethonium have been compared as regards their action on spontaneous gastric secretion. In this small series we gained the impression that the iodide and bromide gave better control of secretion than the chloride. This slight difference in potency may depend on a variation in the absorption of these compounds, though further investigation will be required on this point.

The beneficial effects of parasympathetic blockade are partly offset by the undesirable side-effects resulting from blockade of the sympathetic ganglia, the most notable of which is postural hypotension. The normal drop in blood pressure which occurs on standing is rapidly compensated by vasoconstriction. After oral administration of hexamethonium this mechanism is more or less depressed and postural hypotension is therefore apt to occur, but this can be controlled by muscular activity or recumbency. A feeling of faintness is rare except when standing motionless. The possibility of these symptoms arising is greater in the fasting patients. In general, however, faintness has been an uncommon experience in our series, presumably because standing motionless for several minutes on end is a rare event in everyday life. It is possible that the small risk of faintness could be removed by the use of a long-acting sympathomimetic drug.

Summary

Hexamethonium iodide was given orally to 10 patients with duodenal ulcer—five were rendered achlorhydric, three had a substantial fall in gastric acidity, and in two there was no significant difference between control and test observations.

Comparable results were obtained for each individual when the drug was given on repeated occasions. The effect was not prolonged from one day to the next.

All hexamethonium halides were found to be active in controlling spontaneous gastric secretion. In a small series of cases the iodide and bromide were found to produce a greater fall in gastric acidity than the chloride.

Side-effects, notably postural hypotension, may be present during routine administration of the drug.

Rigorous conditions for an experiment with four patients produced marked hypotension reduced by activity and by the taking of food.

Throughout the investigation a variability of the action of the drug characteristic to the individual was noted.

We are indebted to Professor C. F. W. Illingworth for his advice and helpful criticism throughout this investigation. We wish to acknowledge the interest taken by Dr. W. D. M. Paton, of the National Institute for Medical Research, in this work, and to record our thanks to Dr. N. S. Conway for kind assistance. Our thanks are also due to Mr. Gabriel Donald and the technical staff of the Surgery Department, University of Glasgow, and to May and Baker Ltd. for supplies of hexamethonium salts.

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On September 9 President Truman signed a Bill making lawful the call-up of all United States doctors, dentists, and "allied specialists" (including pharmacists, veterinary surgeons, and osteopaths), who are less than 50 years old, for a period of thirty-two months' military service. At the same time the Defence Department has issued a statement to explain in what order doctors will be called. It is intended that the first group will be those who received all or part of their professional training under wartime special training schemes but who had no military service owing to the ending of the 1939–45 war before they qualified. Next come those trained under these schemes but having military experience, those with least service being called first. Finally, all medical officers on the Reserve will be recalled in an order of priority, men trained at Government expense first, those with less than ninety days' active service, then those with less than twenty-one months, then those who had never previously served ; and finally doctors who trained at their own expense and have a military record. The officers' Reserve is voluntary, and every medical volunteer gets a pay bonus of $100 (£35) per month, to which the conscript will not be entitled. It is hoped that this, taken with the new call-up, will encourage volunteering to such an extent that it will in fact be unnecessary to apply conscription. The American Services say they need an additional 5,000 doctors and 2,000 dentists this year, and, if all the men trained at least partly with Government aid during World War II but who saw no service can be induced to volunteer, this need will be met. If conscription should prove necessary, it will be administered with the help of a national medical committee which will consider civilian needs in each district ; and interns in civilian hospitals will be reserved for a period of twelve months.