Brit. J. Pharmacol. (1956), **11**, 231.

THE ACTION OF ATROPINE AND HEXAMETHONIUM IN COMBINATION ON GASTRIC SECRETION AND MOTILITY

BY

A. W. KAY AND A. N. SMITH

From the University Department of Surgery, Western Infirmary, Glasgow

(RECEIVED DECEMBER 19, 1955)

The action of atropine is known to vary with the dose, probably owing to a dual action; large doses block the effects of acetylcholine at the periphery, whereas small doses stimulate the medullary centres (Bastedo, 1936; Clark, 1940). We have sought to use the blocking effect of hexamethonium at autonomic ganglia in order to analyse this biphasic response. This study has been made on human subjects using alterations in gastric motility as an index. The second objective was to see if atropine and hexamethonium were additive or potentiating in their acetylcholine-blocking effect, using gastric secretion and motility as indices.

METHODS

In a first series of experiments, five male patients with uncomplicated duodenal ulcer were selected for study of gastric motility, which was recorded by a modification of Carlson's balloon method (Kay, 1947). In each subject, tests were made on each of three consecutive days. The balloon was introduced at 9 a.m. after a 12-hour fast. Control observations were made for 20–40 min. before injecting the test substance. On the first day 0.1 mg. atropine sulphate was given intravenously; on the second day 0.65 mg. atropine sulphate was given intravenously; on the third day 50 mg. hexamethonium iodide was given by intramuscular injection 30 min. before an intravenous injection of 0.1 mg. atropine sulphate.

In a second series of experiments, the effects of atropine and hexamethonium, independently and in combination, were examined on acid secretion and on gastric motility. An object of the experiments was to determine whether the known blocking effects of atropine and hexamethonium are additive or potentiating. A simple way of determining how the interaction of the drugs can be classified (Gaddum, 1953) is to administer half the dose of one necessary for a given effect, with half the corresponding dose of the other. If the combination then causes the effect, the two drugs are additive; if more than the effect there is potentiation. We have modified this method to study the combined action of hexamethonium and atropine on gastric secretion and motility. The effects measured were the development of achlorhydria and inhibition of gastric motility. A combination of the two substances was made: with hexamethonium the effective dosage producing inhibition of acid gastric secretory activity was halved, but with atropine, with which effective dosage is limited by side effects, the standard therapeutic dose was halved. The drugs were given by intramuscular injection, hexamethonium iodide in a dose of 100 mg., atropine sulphate in a dose of 0.65 mg., and for the combined injection 50 mg. hexamethonium iodide with 0.325 mg. atropine sulphate. As there is no chemical incompatibility, the atropine was dissolved in the solution of hexamethonium iodide and the mixture given as a single injection.

Spontaneous secretion of hydrochloric acid, spontaneous night secretion and gastric motility were in turn examined after injection of the drugs alone and in combination.

Spontaneous Secretion of Hydrochloric Acid.—Tests were made on ten patients. A secretion test was given on each of five consecutive days. Control observations were made on the first and last day; the effects of hexamethonium, atropine, and the combined drugs were studied on the intervening days.

Each secretion test was begun at 9 a.m. after a 12-hour fast. The fasting juice was aspirated and the specimens removed every 15 min. thereafter until the end of the series of observations. The control observations were continued for 3 hr. On each of the test days the selected injection was given immediately after the aspiration of the second 15-minute specimen. Special precautions were taken to empty the stomach at each aspiration and all saliva was expectorated. The volume and bile staining of each specimen was noted and the titratable free acid estimated in ml. 0.1N-HCl. Acid output was calculated in milliequivalents.

Spontaneous Night Secretion.—A comparative study was made of the action of hexamethonium, atropine, and hexamethonium with atropine upon the nocturnal secretion of five subjects. The patients fasted from 5 p.m., and a wide bore stomach tube, with multiple perforations at its tip, was passed at 8 p.m. Continuous gastric aspiration was performed using the constant suction provided by an electric pump until 8 a.m. Sedatives were not given. Tests were made on four successive nights. The first night provided control observations and no injections were given. On subsequent nights the drug or combination of drugs to be

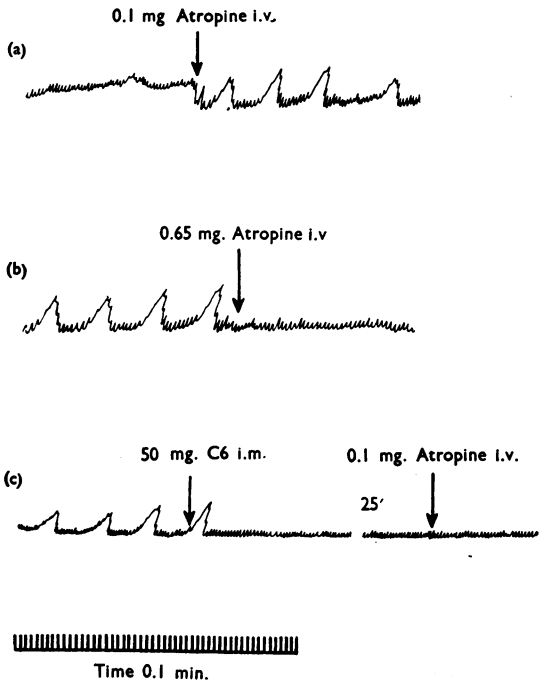


FIG. 1.—Tracings of gastric motility showing (a) the *stimulant* action of 0.1 mg. atropine sulphate i.v., (b) the *inhibitory* action of 0.65 mg. atropine sulphate i.v., and (c) prevention of the stimulant effect of atropine (2nd arrow) by previous administration of 50 mg. hexamethonium i.m. (1st arrow).

tested was given intramuscularly at 8 p.m., midnight, and 4 a.m.

Gastric Motility.—Motility recordings were taken from the ten patients on whom the studies on spontaneous secretion had been made. On each of three successive days each patient was given hexamethonium, atropine, or the combined injection in the doses already described. The injections were made following control periods of observation varying from 35 to 40 min. during which pronounced gastric contractions were observed. The order in which the three drugs were given was varied in each patient.

RESULTS

In the first series of five male patients with uncomplicated duodenal ulcer it was confirmed that the effect of atropine varies with the dose. The intravenous injection of 0.1 mg. atropine, purposely given during a phase of relative quiescence, produced an increase in gastric contractions for 5 to 10 min. in four patients and no change in the existing high amplitude contractions in the remaining patient. On the contrary, the intravenous injection of 0.65 mg. atropine, purposely given during a phase of activity, produced immediate and complete inhibition of the gastric movements in all patients. The intramuscular administration of 50 mg. hexamethonium, as has been reported previously (Kay and Smith, 1950), resulted in complete inhibition of gastric motility after a brief latent period. This inhibitory phase was well established when 0.1 mg. atropine was given intravenously. In each of the five tests atropine failed to stimulate gastric movements (Fig. 1).

In view of this result—namely, that atropine has both central-stimulant and peripheral-inhibitory effects—it was thought that hexamethonium combined with atropine might reduce the acidity of the gastric juice and the motor activity of the stomach. The effects of atropine at the parasympathetic nerve endings might be expected to enhance the block produced by hexamethonium at the ganglia.

The results are now recorded of injecting these substances alone or in combination, on spontaneous gastric secretion of hydrochloric acid, spontaneous night secretion, and gastric motility. Side effects have been noted throughout.

The effect of the combined injection was firstly assessed on the spontaneous secretion of hydrochloric acid.

In 9 of the 10 subjects, the combined injection produced a dramatic fall in the level of free acid with a period of complete achlorhydria of from 1 to 5 hr. The achlorhydric phase was the more prolonged in 8 cases after the combined injection (Table I). The specimens with no free acid were further characterized by low volume and absence of bile. In the remaining patient the titratable acid was reduced from 105 to below 30 ml. 0.1N-HCl. Achlorhydria followed the single injection of atropine in three subjects, but it was not maintained for more than 1 hr.; the volume of the

TABLE I

COMPARISON OF HEXAMETHONIUM, ATROPINE, AND HEXAMETHONIUM+ATROPINE ON INHIBITION OF SPONTANEOUS SECRETION OF HYDROCHLORIC ACID

Patient No.	Hexamethonium (100 mg.)		Atropine Sulphate (0·65 mg.)		Hexamethonium (50 mg.)+ Atropine (0·325 mg.)	
	Control Acid Output (mEq./hr.)	Duration of Anacidity (hr.)	Control Acid Output (mEq./hr.)	Duration of Anacidity (hr.)	Control Acid Output (mEq./hr.)	Duration of Anacidity (hr.)
1	3·64	4	3·60	0	4·80	4¾
2	7·28	4	4·56	1	7·84	4¾
3	6·48	1¾	6·24	0	6·52	4
4	3·44	3	3·00	0	3·76	3
5	5·12	1	4·16	1	4·32	4½
6	3·80	2	3·68	0	3·60	5¼
7	3·52	1¾	2·48	0	2·32	3¼
8	7·20	3¼	8·48	¼	8·80	5
9	16·38	0	16·08	0	16·84	0
10	3·68	1½	4·56	0	5·24	2

TABLE II

COMPARISON OF HEXAMETHONIUM, ATROPINE, AND HEXAMETHONIUM+ATROPINE ON NIGHT SECRETION

Drugs given at 8 p.m., midnight, and 4 a.m.

Patient No.	Control			Hexamethonium (100 mg.)			Atropine (0·65 mg.)			Hexamethonium (50 mg.) +Atropine (0·325 mg.)		
	Volume (ml.)	Free HCl (Clinical Units)	mEq./ hr.	Volume (ml.)	Free HCl (Clinical Units)	mEq./ hr.	Volume (ml.)	Free HCl (Clinical Units)	mEq./ hr.	Volume (ml.)	Free HCl (Clinical Units)	mEq./ hr.
1	556	87	4·03	150	36	0·45	134	56	0·63	70	33	0·19
2	1,460	72	8·76	715	22	1·31	600	55	2·75	450	20	0·75
3	850	60	4·25	325	14	0·39	350	48	1·40	300	10	0·25
4	1,015	64	5·41	370	12	0·37	320	50	1·33	210	12	0·21
5	520	25	1·08	180	5	0·08	210	18	0·32	165	5	0·07

specimens was diminished in a further four cases.

Secondly, the effect of the combined injection was assessed on the spontaneous night secretion.

All three drugs reduced the volume of the night secretion by more than half. The acidity of the gastric juice was markedly reduced by hexamethonium and by the combined injections, but reduced to a slight extent only by atropine alone. In these five experiments, the combined injection was at least as active, and sometimes more active, than the effect of hexamethonium alone (Table II).

Motility recordings were taken from the 10 patients on whom the studies on spontaneous secretion had been made. They again showed the enhanced action of the combined injection. In each case, after a brief latent period, gastric motility was completely inhibited by 100 mg. hexamethonium and by 50 mg. hexamethonium plus 0.325 mg. atropine. It will be seen that the combined injection was at least as effective on 8 subjects in diminishing gastric contractions as hexamethonium alone (Table III). The duration of inhibition after the combined injection varied from 2½ to 4 hr. It is of interest that 0.65 mg. atropine failed to inhibit motility in 5 subjects although this dose, when given intravenously, is invariably effective.

TABLE III

COMPARISON OF HEXAMETHONIUM, ATROPINE, AND HEXAMETHONIUM+ATROPINE ON INHIBITION OF GASTRIC MOTILITY

Patient No.	Duration of Inhibition of Gastric Motility (min.)		
	After Hexamethonium (100 mg.)	After Atropine (0·65 mg.)	After Hexamethonium (50 mg.)+ Atropine (0·325 mg.)
1	170	90	180
2	80	0	180
3	150	120	190
4	180	0	150
5	105	0	160
6	195	0	240
7	125	70	185
8	110	50	175
9	150	0	150
10	180	80	220

Side Effects.—In the foregoing studies on spontaneous secretion and gastric motility, 100 mg. hexamethonium, 0.65 mg. atropine, and the combination of drugs, 50 mg. hexamethonium plus 0.325 mg. atropine, have each been administered on two occasions to each of 10 subjects. The frequency and severity of the known side-effects of the drugs have been noted.

Impairment of accommodation with resultant blurring of vision was experienced by 9 patients after hexamethonium, by 5 after atropine, and by 4 after the combined injection. Dryness of the mouth was volunteered by 2 patients after hexamethonium, by 8 after atropine, and by 1 after the combined injection.

As these injections were given to recumbent subjects it is not surprising that none complained of faintness or lightheadedness.

The hypotensive effect of the drugs under investigation has been studied in greater detail in five males aged 22, 28, 30, 45 and 52 years. Before giving the drug to be tested, blood-pressure readings were made with the subject at rest in bed, immediately on standing, after standing erect for 5 min., after walking for 5 min., and finally, after being recumbent for 5 min. Similar observations were made 1 hr. after an intramuscular injection of 100 mg. hexamethonium, after 0.65 mg. atropine, and after 50 mg. hexamethonium plus 0.325 mg. atropine. The three tests were made on separate days.

In the control observations, and after atropine, a slight fall of blood pressure occurred immediately on standing (5–10 mm. Hg). This fall was transient and was quickly overcome by compensatory vasoconstriction. After hexamethonium the resting blood pressure was reduced and the fall of pressure on standing was considerable and persisted while the subject was erect (45, 20, 15, and 30 mm. Hg). The fifth patient had a syncopal

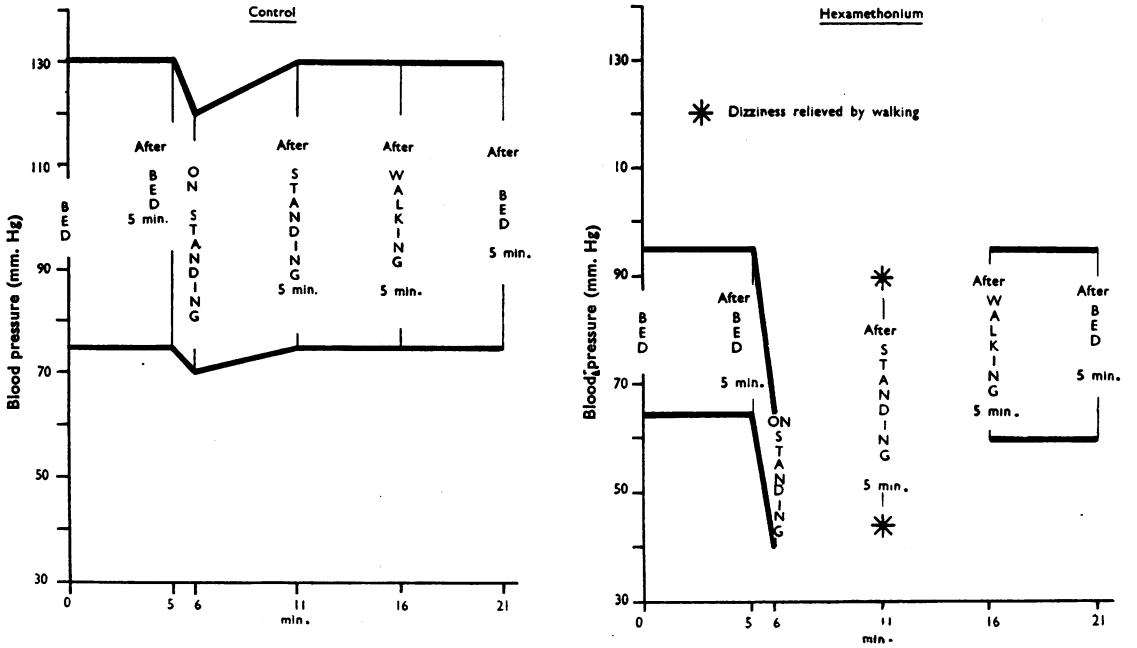
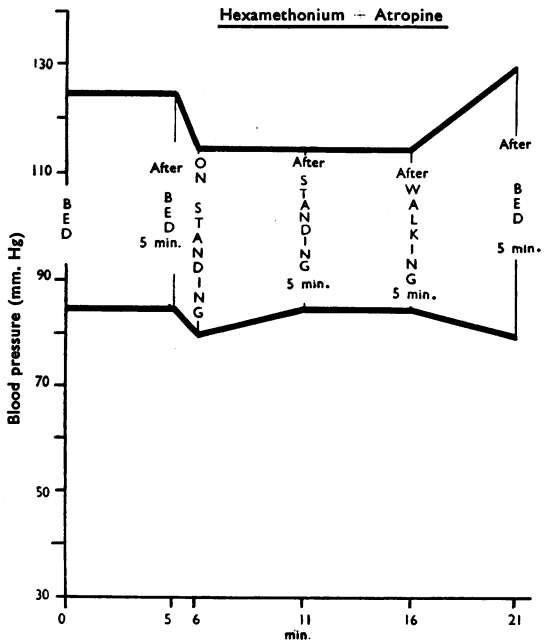


FIG. 2.—Blood pressure changes in a man aged 52 years, (a) at rest in bed; (b) immediately on standing; (c) after standing erect for 5 min.; (d) after walking for 5 min.; (e) after being recumbent for 5 min.



attack and a blood pressure reading was not obtained for the standing position. After hexamethonium plus atropine, the resting blood pressure was only slightly lower than the control reading and the fall of pressure on standing, though persisting while the subject was erect, was less than after hexamethonium alone. The findings in the man aged 52 are shown in Fig. 2.

It will be noted that bodily activity causes a compensatory rise in blood pressure when it has fallen after hexamethonium. The severity of blood-pressure changes are in general more marked with hexamethonium alone than when the smaller dose is given in combination with atropine.

DISCUSSION

The most important action of atropine is on the effector cells in the distribution of the cholinergic fibres of the autonomic system, rendering them insensitive to acetylcholine. Meyers and Abreu (1952), however, found that the effects of atropine vary with the dose; either lethargy or excitement, for instance, may occur under special conditions in the human subject. They observed temporary

bradycardia which they attributed to preliminary medullary stimulation, but this feature was later obscured by the more usual tachycardia associated with the predominant action of the drug. The biphasic response has been further examined by Anderson (1952), who found initial slowing of the pulse followed by an increase, and, in studies on gastric tone, an increase followed by a decrease.

This two-fold action of atropine has been analysed by using the specific ganglion-blocking effect of hexamethonium. The stimulant effect of atropine is not seen when the parasympathetic ganglia have been paralysed, but the possibility exists that this action is exerted at the ganglia. This is, however, unlikely, for pulse rate and mental function are also influenced by particular doses of atropine. Thus the stimulation is probably central.

Hexamethonium, atropine and hexamethonium combined, and atropine alone, have been compared for their actions on gastric secretion and motility. We have confirmed that atropine in a dose of 0.65 mg. intramuscularly is not a reliable inhibitor of gastric secretion and motility. Its main effect on secretion is to diminish the volume of the gastric juice without altering appreciably the acid concentration. In this group of subjects hexamethonium combined with atropine had a marked effect on gastric secretion—usually greater than the effect of hexamethonium alone. Furthermore, the combination of the two drugs, each in half the dose given alone, was relatively free from side effects; in particular the postural hypotension of hexamethonium was greatly reduced. The effectiveness of the two drugs in combination may be due to a complex of actions. Ganglion blockade by hexamethonium blocks the transmission of central stimuli due to atropine. The preganglionic stimulation produced by atropine may sensitize the ganglion to hexamethonium and so augment its effect (Paton, 1951). Ganglion blockade may depress the peripheral production of acetylcholine and enhance the inhibitory action of atropine on the tissues (Grossman and Robertson, 1952).

We have confirmed that, whereas large doses of atropine inhibit gastric motility, small doses stimulate it; preliminary blockade of the parasympathetic ganglia by means of hexamethonium prevents this stimulant action of atropine. While it can thus be shown that both drugs have properties which lead us to expect that they will reduce the motor and secretory activity of the stomach, it is unlikely that this combination of the two will have general clinical value. Though the use of halved doses has at least an additive, and even a potentiating effect, and reduces the side effects, it is unlikely to have a practical application, for the combination of drugs must be given by injection and such a method is inapplicable for the treatment of peptic ulcer, where a large number of patients require treatment over long periods.

SUMMARY

1. It is confirmed that, in human subjects, atropine has both central stimulant and peripheral inhibitory effects, and that hexamethonium is capable of blocking its central action.

2. The effect of hexamethonium alone and of atropine alone on gastric secretion is shown, in general, to be less than the effect of the drugs given in combination in half the dose.

3. Similar results were obtained in studies of gastric motility.

4. The drugs in combination in half-doses produce fewer side effects than do hexamethonium alone or atropine alone.

REFERENCES

Anderson, W. F. (1952). *Lancet*, **2**, 255.
Bastedo, W. A. (1936). *J. Amer. med. Ass.*, **106**, 85.
Clark, A. J. (1940). *Applied Pharmacology*. London: Churchill.
Gaddum, J. H. (1953). *Pharmacology*, p. 479. London: Oxford Univ. Press.
Grossman, M. I., and Robertson, C. R. (1952). *Proc. Soc. exp. Biol., N.Y.*, **79**, 226.
Kay, A. W. (1947). *Lancet*, **1**, 448.
—— and Smith, A. N. (1950). *Brit. med. J.*, **1**, 460.
Meyers, F. H., and Abreu, B. E. (1952). *J. Pharmacol.*, **104**, 387.
Paton, W. D. M. (1951). *Brit. med. J.*, **1**, 776.