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Mecamylamine, a New, Orally Effective, Hypotensive Agent

Experimental and Clinical Evaluation

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Stone and his co-workers * have reported recently on certain unusual pharmacological properties of mecamylamine (3-methylaminoisocamphane) hydrochloride. This compound, a secondary amine, produces a marked and prolonged degree of blood pressure reduction and ganglionic blockade in animals. Mecamylamine also is well absorbed from the gastrointestinal tract, the L. $D._{50}$ being approximately the same whether the drug is adminished subcutaneously or orally. By contrast, previously successful ganglion-blocking agents, which are tertiary amines, are poorly absorbed from the gastrointestinal tract. The ratio of oral to subcutaneous hypotensive dosages of the latter drugs in man is approximately 15 : 1.†

In patients under treatment with ganglion-blocking agents it is possible that some of the difficulties of clinical management, such as irregular fluctuations of blood pressure and gastrointestinal atony, may be due to the poor absorption and, hence, large local accumulations of the previously available compounds in the gastrointestinal tract. It seemed worth while, therefore, to evaluate the use of mecamylamine, a readily absorbed blocking agent, in hypertensive patients.

MATERIALS AND METHODS

The subjects for the experimental studies were patients from the wards of the Georgetown University and the Veterans Administration Hospitals, Washington, D. C. The methods of investigation used were similar to those published in a previous communication.[3] Mecamylamine was administered in sterile water containing 1.0 mg. of active substance per milliliter.

In the clinical studies the patients were chosen from the wards and hypertensive clinics of the above hospitals. They represented a mixed group of severe hypertensives, white and Negro, representing all varieties of social and economic classes.

EXPERIMENTAL RESULTS

Comparison of Intravenous and Oral Dosages

The blood pressure response in both the supine and erect positions was followed in nine patients given single intravenous doses of 15 to 20 mg. of mecamylamine. The next day the same patients were given an oral dose which was 5 to 10 mg. less than the previous intravenous dose. Following all doses there was a significant reduction of supine blood pressure and a marked postural hypotension, which was as great after oral as after intravenous administration (Table 1). These results, in marked contrast to the relatively large oral dosages required with other

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Mecamylamine was supplied under the trade name of Inversine by John R. Beem, M.D., Sharp & Dohme.

From the Cardiovascular Research Laboratory, Georgetown University Hospital, the Department of Medicine, Georgetown University School of Medicine, and the Veterans Administration Hospital.

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* Stone, C. A.; Torchiana, M. L.; O'Neill, G. P., and Beyer, K. H.: Ganglionic Blocking Properties of 3-Methylaminoiso-Camphane Hydrochloride (Mecamylamine), a Secondary Amine, read before the American Society for Pharmacology and Therapy, Iowa City, Sept. 7, 1955.

† References 1 and 2.

TABLE 1.—*Comparative Hypotensive Effects of Single Intravenous and Single Oral Doses of Mecamylamine*

Intravenous						Oral				
		Arterial Pressure, Mm. Hg					Arterial Pressure, Mm. Hg			
		Before		After			Before		After	
Case	Dose, Mg.	Supine	Erect	Supine	Erect	Dose, Mg.	Supine	Erect	Supine	Erect
1	20	190/120	180/125	130/90	90/80	10	170/115	160/115	135/90	100/75
2	15	180/110	190/110	130/85	110/70	10	150/92	146/92	120/85	98/70
3	15	190/120	180/130	140/105	120/98	10	190/130	190/130	170/110	150/112
4	20	190/115	190/120	140/95	115/90	10	170/122	168/124	146/102	148/102
5	20	240/160	230/160	180/140	150/120	10	190/140	186/130	160/118	156/110
6	20	200/130	198/135	150/100	130/90	10	205/125	200/135	160/110	150/100
7	20	200/115	190/120	160/98	140/90	10	170/110	160/115	140/90	110/70
8	20	220/115	200/120	160/100	102/75	15	210/120	160/100	145/80	80/60
9	20	230/120	200/120	160/100	100/60	10	220/120	160/110	160/90	115/80
						15	210/100	150/100	100/70	80/60
						10	200/110	170/110	150/90	90/70
						5	200/110	160/110	155/100	120/80

ganglion-blocking agents, provided clear evidence that mecamylamine is well absorbed from the human gastrointestinal tract.

Following intravenous administration, the blood pressure began to fall gradually several minutes after injection, reaching minimum values in one-half to one hour. It remained at the lowest level for several hours or, in others, began to rise after one hour reaching control values in all cases by 6 to 12 hours.

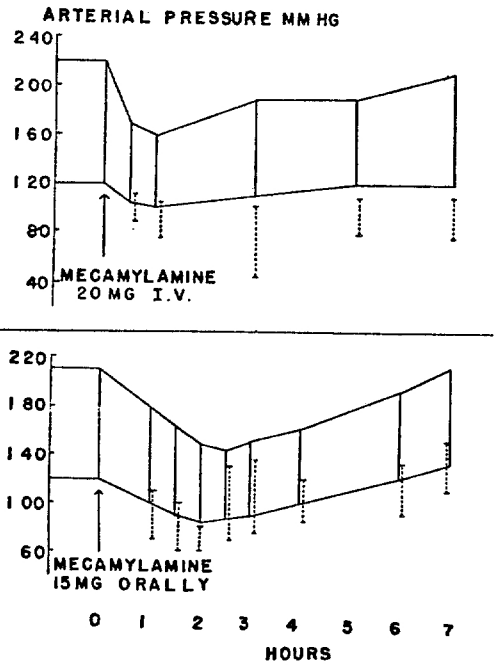

Fig. 1.—Charts showing characteristic blood pressure response to 20 mg. of mecamylamine intravenously (above) and 15 mg. orally (below) in a 62-year-old man with essential hypertension. The tests were carried out on successive days. The broken vertical columns indicate the blood pressure in the erect position. See text for further details.

The postural hypotension usually followed a similar time pattern (Fig. 1).

Following oral dosage, the blood pressure began to fall after 1 hour, reached minimum values at approximately 2 hours, and returned gradually to control values in 4 to 12 hours. The more profound the reduction of blood pressure the longer the duration of the response. Postural hypotension sometimes persisted for several hours after the blood pressure in the supine position had returned to control levels.

Effect of Mecamylamine on Sympathetic Vasoconstrictor Reflexes

Previous studies with the ganglion-blocking agent hexamethonium demonstrated a marked inhibition or abolition of homeostatic vasoconstrictor reflexes.[3] Postural hypotension alone does not indicate such inhibition, since peripheral vasodilators acting directly on blood vessels, such as sodium nitrite, may induce a postural fall of blood pressure.

Four criteria were used to measure the reactivity of the sympathetic vasoconstrictor responses and the effect of mecamylamine thereon. These were the hypertensive overshoot following the Valsalva maneuver,[4] the cold pressor test,[5] the skin temperature gradient between the digits and the umbilicus in patients exposed in a cold constant-temperature room,[6] and reflex vasoconstrictor responses as revealed by digital plethysmography.[7]

(*a*) *The Valsalva Maneuver.*—If a patient blows out forcibly into a closed tube for 10

TABLE 2.—*Vasopressor Responses to the Valsalva Maneuver Before and After the Intravenous Administration of Mecamylamine*

Case	Dose, Mg.	Control: Arterial Pressure, Mm. Hg: Basal	Control: Arterial Pressure, Mm. Hg: After Valvalsa	Control: Overshoot,* %	Time After Drug, Min.	After Mecamylamine: Arterial Pressure, Mm. Hg: Basal	After Mecamylamine: Arterial Pressure, Mm. Hg: After Valsalva	After Mecamylamine: Overshoot,* %
1	20	263/142	288/142	20	10	228/128	253/160	15
					40	240/150	260/162	9
4	20	201/98	240/125	18	10	160/88	174/95	8
					40	162/90	173/98	7
7	20	225/111	253/160	20	2	210/98	232/110	12
					30	190/84	204/88	6
3	15	194/110	290/160	47	10	180/114	225/136	22
					40	174/114	218/135	22
2	15	168/90	190/98	11	10	142/82	133/76	0
					40	140/80	134/74	0
5	20	262/160	310/188	18	10	225/145	274/172	34
					30	218/150	268/180	29
					50	222/160	270/178	17
					120	210/150	232/156	7

* Calculated from the mean (one-half the sum of the systolic and diastolic) pressure.

seconds, intrathoracic pressure is markedly increased and the blood pressure will fall. When the expiratory effort suddenly is released there is a transient overshoot of blood pressure above the basal level. Wilkins has presented evidence that the pressor overshoot is due primarily to reflex vasoconstriction mediated over sympathetic pathways.[4] After lumbodorsal splanchnicectomy [4] or certain "sympatholytic" agents ‡ the overshoot is abolished.

The Valsalva overshoot was determined in six patients before and periodically for one hour after intravenous mecamylamine, with use of direct continuous recording of arterial pressure [3] (Table 2). The overshoot was abolished in one of the six cases and reduced by 50% to 70% in the remaining subjects.

(*b*) *The Cold Pressor Test.*—The blood pressure response during one minute of immersion of the patient's hand in ice water was determined before and one-half hour after intravenous mecamylamine. After the drug the cold pressor response was significantly reduced in only two of the six patients (Table 3).

(*c*) *The Skin Temperature Gradient.*—Nine hypertensive patients, who had no evidence of peripheral vascular disease, were exposed to room temperatures of 63 to 71 C. In any one experiment the room temperature was kept constant within a range of 3 C. The skin temperature of the digits and umbilicus was recorded every three minutes. After one hour mecamylamine was given intravenously and the skin temperature and blood pressure values were recorded for an additional hour.

The results followed no consistent pattern (Table 4). In three patients there was a significant elevation of toe temperature; in four, a partial rise, and in two there was no significant change. There was a significant rise

‡ References 3 and 5.

TABLE 3.—*Effect of Intravenous Mecamylamine on the Responses to the Cold Pressor Test*

Case	Arterial Pressure, Control: Basal, Mm. Hg	Arterial Pressure, Control: Peak Response to Ice, Mm. Hg	Arterial Pressure, Control: Increase,† %	Arterial Pressure After Mecamylamine*: Basal, Mm. Hg	Arterial Pressure After Mecamylamine*: Peak Response to Ice, Mm. Hg	Arterial Pressure After Mecamylamine*: Increase,† %
1	262/142	300/164	15	232/142	264/166	12
4	194/98	218/112	13	166/95	188/110	14
7	232/100	240/108	5	210/94	218/98	3
3	154/98	188/108	17	174/110	190/120	9
2	198/100	256/138	32	166/98	214/120	28
5	274/156	280/166	3	222/160	225/156	0

* The post-treatment tests were carried out approximately one-half hour after administration of mecamylamine. For dosages see Table 1.
† See footnote, Table 1.

TABLE 4.—*Changes in Skin Temperatures After the Intravenous Administration of Mecamylamine*

Case	Dose, Mg.	Control: Blood Pressure, Mm. Hg Supine	Control: Blood Pressure, Mm. Hg Erect	Control: Skin Temp., F* R	Control: Skin Temp., F* U	Control: Skin Temp., F* T	Control: Skin Temp., F* F	After Mecamylamine: Blood Pressure, Mm. Hg Supine	After Mecamylamine: Blood Pressure, Mm. Hg Erect	After Mecamylamine: Skin Temp., F* R	After Mecamylamine: Skin Temp., F* U	After Mecamylamine: Skin Temp., F* T	After Mecamylamine: Skin Temp., F* F
10	15	195/115	190/115	68	94	69	72	166/100	140/95	68	91	71	87
11	10	190/110	190/110	69	94	69	74	150/95	120/90	70	94	76	88
9	20	230/120	200/115	63	90	77	66	160/108	110/80	65	87	87	66
12	20	190/135	188/120	68	88	66	70	166/120	150/115	68	82	82	69
13	18	190/125	190/120	70	95	77	77	158/108	140/100	70	94	86	83
14	28	240/135	230/120	70	91	76	79	170/110	130/120	70	92	80	87
15	16	180/110	180/108	71	86	73	84	130/105	130/100	71	88	79	85
16	12	130/90	130/88	67	93	68	74	115/90	100/80	67	94	78	91
17	15	120/75	120/75	71	88	73	85	105/72	90/80	71	86	86	95

* R, room temperature; U, umbilicus temperature; T, toe temperature; F, finger temperature.

in finger temperature in five cases and an insignificant change in four.

(*d*) *Digital Plethysmography.*—Following a deep inspiration there is normally a sharp decrease in the volume of the digit and the digital pulse, indicating vasoconstriction. This reflex vasoconstriction, which can be detected readily in the digital plethysmograph, is abolished after sympathetic denervation [7] and after hexamethonium.[8]

During the period of observation, which lasted 30 to 60 minutes following intravenous mecamylamine, there was a partial inhibition of the vasoconstrictor response to a deep inspiration in two cases and no change in four (Table 5). To one of these patients hexamethonium, 50 mg., was given intravenously, with an immediate abolition of the vasoconstrictor reflex (Fig. 2). Because of the possibility that insufficient time was allowed to permit the development of sympathetic blockage, three patients under continous oral administration of mecamylamine were studied. These showed a persistence of digital reflex vasoconstriction despite significant reductions of blood pressure and marked postural hypotension.

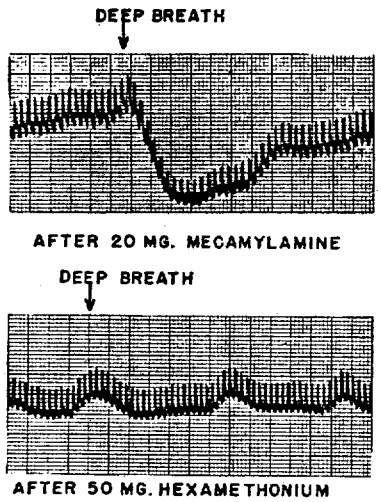

Fig. 2.—Tracings of the digital plethysmograph in a 39-year-old man with essential hypertension. The upper tracing shows an active vasoconstrictor response following deep inspiration 40 minutes after 20 mg. of mecamylamine. The lower tracing was taken 10 minutes after 50 mg. of hexamethonium in the same patient. The vasoconstrictor response is completely blocked, the fluctuations in base line being due to respiratory movement.

CLINICAL RESULTS

EFFECT OF CONTINUOUS ORAL ADMINISTRATION ON BLOOD PRESSURE

Thirty-six patients with "fixed" moderately severe to severe hypertension were

TABLE 5.—*Effect of Mecamylamine on Digital Vasoconstrictor Reflexes*

Case	Dose, Mg.	Control: Blood Pressure, Mm. Hg Supine	Control: Blood Pressure, Mm. Hg Erect	Control: Vasoconstrictor Reflexes	After Mecamylamine: Blood Pressure, Mm. Hg Supine	After Mecamylamine: Blood Pressure, Mm. Hg Erect	After Mecamylamine: Vasoconstrictor Reflexes, Time After Drug, Min. 2	10	30	60
10*	20	200/130	170/130	++++	180/130	Not taken	++++	++++	+++	.....
18	10	160/110	160/110	+++	130/98	100/80	+++	+++	+++	+++
19	20	190/120	190/125	+++	160/110	140/100	+++	+++	+++	.....
20	18	190/125	190/120	++	150/115	130/100	++	++	++	.....
21	20	120/75	120/75	++++	95/70	95/70	++	++	++	+++
22	5	100/65	100/65	+++	90/50	95/50	++	+++	++	+++

* Hexamethonium, 50 mg. intravenously, while producing no further reduction of supine blood pressure, completely abolished the vasoconstrictor response in this patient.

treated continuously with oral mecamylamine for periods varying from one to four months (average, 2.8 months). The Keith, Wagener, and Barker classification of the optic fundi [8] in these patients prior to any treatment was as follows: Grade IV, 8 patients; Grade III, 15 patients; Grade II, 13 patients, and Grade I, no patients (Table 6).

For the group as a whole the mean pretreatment blood pressure was 217/129 mm. Hg. After treatment the mean blood pressure was 167/108 in the supine position and 153/101 in the erect position. This represented a reduction of 21% systolic and 16% diastolic in the supine position and of 27% systolic and 20% diastolic in the erect position. In every case the control and posttreatment blood pressure values were the average of many obtained in the hospital, by the patient's families in the home, and in the clinic.

Dosage

The average total daily dose was 29 mg. (range, 3 to 90 mg.). In general, this was divided into three doses per day, generally at 8 a. m., 2 p. m., and 10 p. m. However, some patients exhibited such a prolonged effect from the drug and were so sensitive to it in the morning hours that the dose taken the night previously controlled their blood pressure until the early afternoon. In such cases, only two doses per day were required, at noon and at bedtime. Other patients exhibited resistance to the drug during the evening hours and so required an extra dose at 5 or 6 p. m.

Table 6.—*Average Blood Pressure Before and After Treatment with Mecamylamine in Thirty-Six Hypertensive Patients*

Case	Age, Yr.	Sex	Optic Fundi, Grade	Control B. P., Mm. Hg	Daily Dose, Mg.	Duration, Mo.	Post-Treatment Blood Pressure, Mm. Hg		Per Cent Decrease			
									Supine		Erect	
							Supine	Erect	Systolic	Diastolic	Systolic	Diastolic
1	57	M	III	200/135	3	3	160/105	150/102	20	22	25	24
2	41	M	III	200/130	32.5	3.5	150/110	130/100	24	15	35	23
3	42	M	II	180/120	5	2.5	168/110	154/100	6	8	14	16
4	39	M	III	220/130	3	3.5	145/110	125/105	34	15	43	19
5	59	M	II	180/120	32.5	3	140/95	120/90	22	20	33	25
6	43	M	III	240/135	25	2.5	172/116	152/106	28	14	36	21
7	39	M	III	200/130	25	2.5	180/108	170/100	10	17	15	23
8	39	M	III	200/135	20	3.5	170/120	140/115	15	11	30	15
9	45	M	II	190/120	25	3	160/105	150/100	16	13	21	17
10	61	M	III	198/125	40	3.5	150/100	120/90	24	20	39	28
11	47	M	II	220/135	27.5	4	180/115	170/110	18	15	22	19
12	38	M	II	185/130	30	3.5	170/120	160/115	8	7	14	19
13	59	M	IV	220/140	55	4	200/115	170/110	9	18	23	21
14	62	M	III	200/115	32.5	3	180/110	170/105	10	4	15	9
15	43	M	III	200/135	10	3.5	170/120	150/110	15	11	25	19
16	37	M	II	190/135	27.5	3	140/102	135/100	26	23	28	26
17	45	M	III	210/120	27.5	2.5	170/112	170/115	19	6	19	4
18	65	M	III	200/140	25	2.5	150/110	150/110	25	21	26	21
19	54	M	II	210/115	3	1	150/98	135/90	28	15	35	22
20	62	M	IV	220/130	40	1.5	205/105	197/105	6	19	10	19
21	29	M	IV	200/150	32.5	2	180/115	170/110	10	23	15	27
22	49	F	II	230/130	40	3	170/100	160/100	26	23	30	23
23	53	M	II	200/120	50	3.5	168/110	160/108	16	8	20	10
24	45	F	IV	230/130	15	3.5	170/105	160/100	26	19	31	23
25	31	F	III	250/140	25	3.5	155/100	150/98	38	28	40	30
26	58	M	IV	230/130	50	2	180/110	160/105	21	15	30	19
27	55	M	II	230/120	35	2	175/110	168/105	24	8	27	13
28	40	F	II	220/120	30	4	158/108	150/110	28	10	31	8
29	48	M	IV	210/120	10	3.5	155/100	150/95	26	17	28	20
30	39	F	II	260/150	40	3	160/105	155/100	38	30	40	33
31	59	M	II	220/140	22	3.5	190/115	180/110	14	17	18	21
32	45	M	III	220/150	90	2	182/112	170/108	17	25	23	28
33	59	M	III	235/135	47.5	1	200/110	210/112	14	19	11	17
34	55	M	IV	230/130	15	1	170/110	130/95	26	15	43	27
35	55	F	III	230/120	80	3	165/98	120/80	28	18	47	33
36	58	M	IV	240/130	40	1	150/100	130/95	37	23	45	27
Mean				217/129	29	2.8	167/108	153/101	21	16	27	20

There also was evidence for some cumulative effects of mecamylamine. It was not uncommon on discontinuing the drug to observe a gradual disappearance of the hypotensive effects over a period of 24 to 72 hours. When dosages were being adjusted it often was found that the maximum effect from an elevation of dosage would appear on the second day of treatment at the new level, suggesting that some cumulation had occurred from the previous day.

On the basis of these experiences we are at present beginning therapy with a dose of 2 mg. after breakfast, at 2 p. m., and at bedtime and then increasing the dosage by 2 mg. every 48 hours, until a hypotensive effect is obtained. At this point the three doses during the day are individually raised or lowered, as the occasion demands so as to obtain the least diurnal fluctuation of blood pressure within the limits of tolerable side-effects. An additional dose may be given at 5 or 6 p. m. if the evening pressures are high, or the morning dose may be sharply reduced or omitted if the blood pressure is extremely low at that time. A running record of the supine and erect blood pressure values in the hospital and later at home was found to be essential in determining the need and extent of such modifications.[9]

Other Clinical Effects

(*a*) *Optic Fundi.*—Of the eight patients who exhibited Grade IV changes in the optic fundi prior to treatment, two reverted to Grade III and six to Grade II. In the group of 15 patients with Grade III fundi, 1 remained Grade III, 13 reverted to Grade II, and 1 reverted to Grade I. In the Grade II cases seven remained Grade II and six reverted to Grade I.

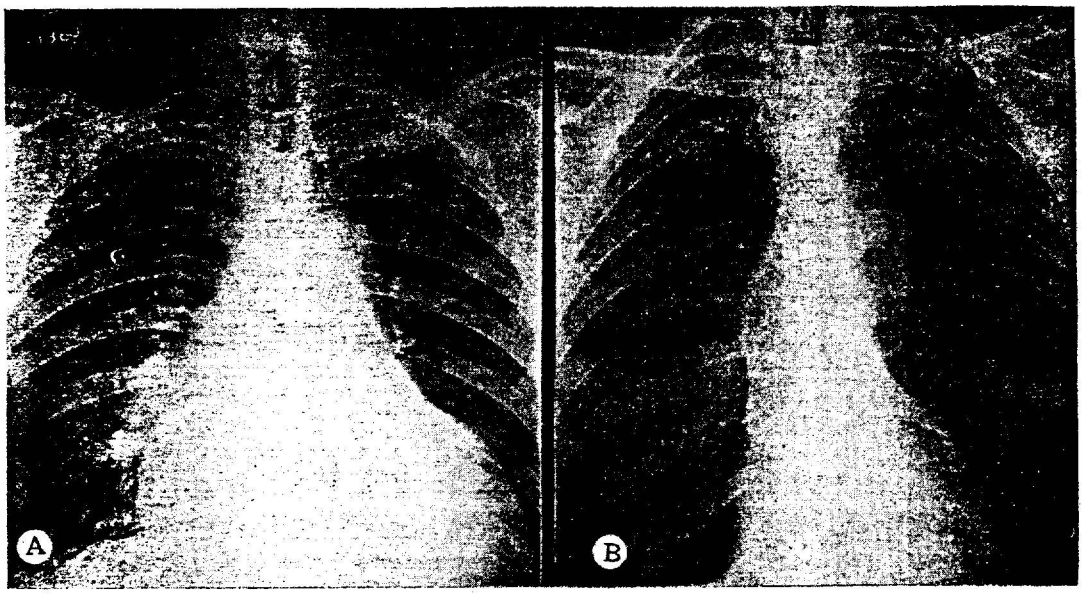

Fig. 3.—Roentgenograms of the chest taken before and three months after treatment with mecamylamine in a 57-year-old Negro man with malignant hypertension. Digitalis and mercurial diuretics were not used in treating this patient.

(*b*) *Cardiac Status.*—Cardiac size was measured roentgenographically before and after treatment in 31 cases. Only changes of 1 cm. or more in the transverse diameter of the heart were considered significant, since the depth of inspiration and other factors may influence the apparent size. Three cases showed an increase in transverse diameter ranging between 1.5 and 2.0 cm. (mean, 1.8 cm.). Twenty-one exhibited no change, while seven showed a decrease varying between 1 and 3 cm. (mean, 1.7 cm.) (Fig. 3).

Electrocardiographic changes were followed in 30 cases. Left ventricular hypertrophy was indicated in the electrocardio-

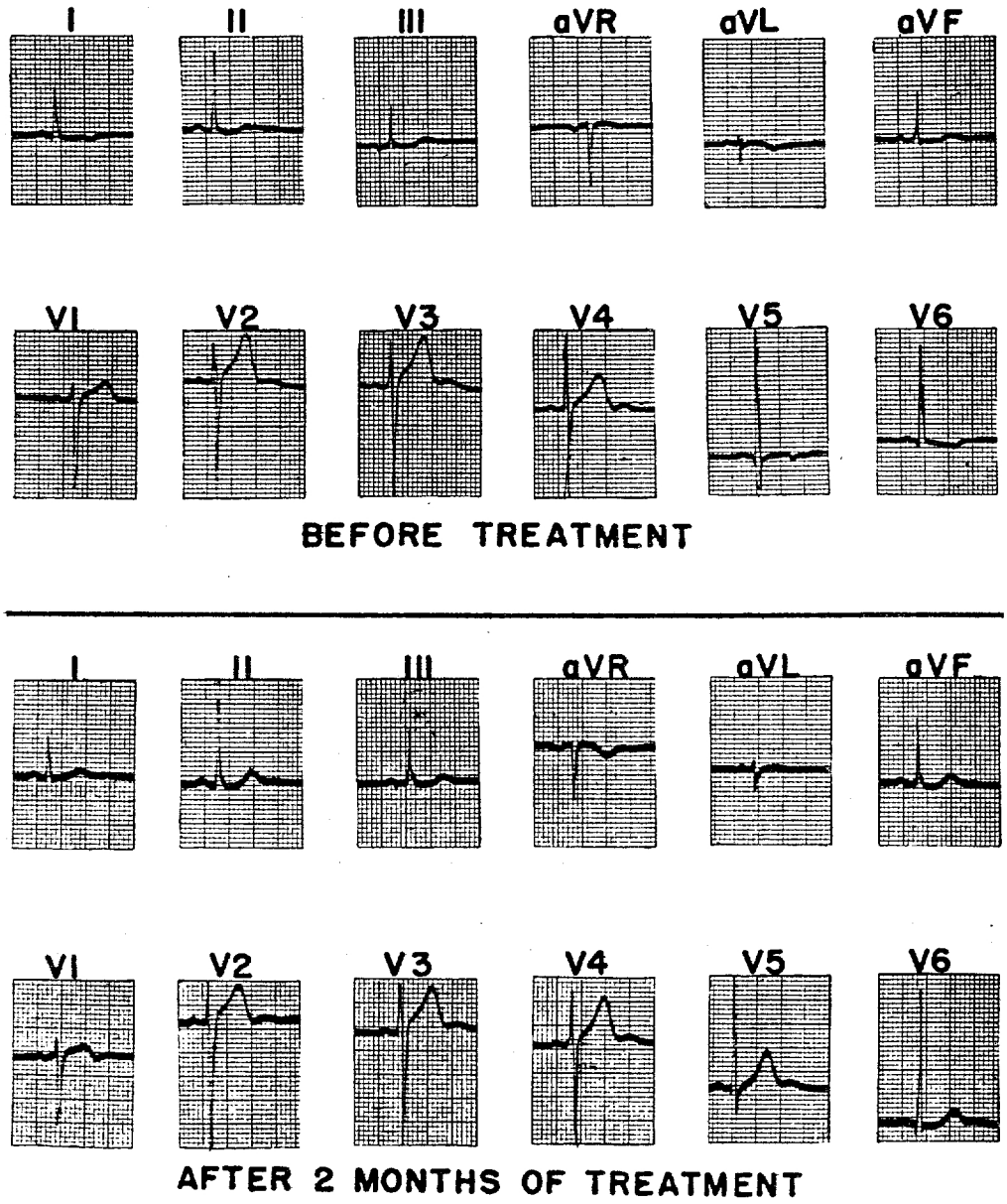

Fig. 4.—Cuttings taken from electrocardiograms of a 45-year-old man with essential hypertension. After two months of treatment with mecamylamine the pattern of left ventricular hypertrophy disappeared.

grams of 28 patients. Of this number, 23 were unchanged, 4 reverted to normal (Fig. 4), and 1 exhibited changes toward normal. Two patients with normal electrocardiograms before treatment showed no change after therapy.

(c) Renal Function.—Albuminuria tended to lessen after treatment in the patients who showed the greatest amounts of albumin before therapy (Table 7). In the patients with lesser degrees of albuminuria the changes were variable. In the 28 cases in which albuminuria was measured, 11 exhibited improvement, 11 were unchanged, and 6 showed a greater degree of albuminuria than before treatment. There were no significant changes in specific gravity or in the urinary sediments.

In 22 cases the excretion of phenolsulfonphthalein (PSP) dye was measured in a sample collected 15 minutes after the dye was injected. A change of 5% excretion or more was considered significant. Ten patients showed a mean decrease of 11% of dye excretion following treatment; seven exhibited no change, while in five patients there was a mean increase of 12% of dye excreted.

The blood urea nitrogen level was measured in 28 cases before and after therapy. Nine exhibited elevations of blood urea nitrogen concentration before treatment, the levels varying between 26 and 51 mg. per 100 cc. In five of these patients the BUN decreased to the normal range after therapy, and in one it changed toward but not to normal. In two cases there was no significant change, while in one, who had the highest level before treatment, there was an increase from 51 to 76 mg. per 100 cc.

TABLE 7.—*Changes in Degree of Albuminuria After Mecamylamine in Twenty-Eight Cases*

Degree of Albuminuria Before Treatment	Patients, No.	Degree of Albuminuria After Treatment					
		++++	+++	++	+	Tr.	Neg.
++++	2	..	..	1	..	1	..
+++	1	..	..	..	1	..	..
++	4	1	..	1	1	..	1
+	7	..	..	..	4	2	1
Tr.	8	..	1	1	1	2	3
Neg.	6	..	..	..	..	2	4

SIDE-EFFECTS

The commonest side-effect encountered was constipation, which occurred in 32, or 88%, of the patients (Table 8). In all except three of these the constipation could be controlled by giving neostigmine, 15 to 45 mg. orally, before breakfast and/or laxatives such as cascara sagrada or magnesium hydroxide. Impaired visual accommodation and postural faintness each occurred in 10, or 27%, of the cases. Impotence was complained of in 10 patients; it was partial in 4 and complete in 6. Difficulty in emptying the urinary bladder and dry mouth were common, each occurring at some time during treatment in nearly 30%. The urinary difficulty usually was mild, consisting only of diminution of the urinary stream. In two cases there was inability to empty the bladder completely, characterized by repeated small frequent voidings. This cleared later in both patients. Dryness of the mouth due to inhibition of salivary gland secretion occurred in 7 of the patients early in treatment and in 11, or 30%, of the cases at some time later in the course of treatment. In general, the side-effects did not tend to disappear over the relatively short period of this study.

TABLE 8.—*Incidence of Side-Effects Occurring in Thirty-Six Hypertensive Patients Under Continuous Treatment with Oral Mecamylamine*

Side-Effect	Early in Treatment		After 1 to 4 Mo.	
	No. of Patients	Per Cent	No. of Patients	Per Cent
Constipation	32	88	3	8
Mild	11	..	..	..
Moderate	15	..	..	..
Severe	6	..	..	..
Constipation controlled with laxatives and/or neostigmine	..	..	28	77
Impaired visual accommodation	10	27	8	22
Dry mouth	7	19	11	30
Impotence	..	..	10	27
Incomplete	..	..	4	..
Complete	..	..	6	..
Postural faintness	10	27	9	25
Postural syncope	1	3	4	11
Difficulty in emptying urinary bladder	7	19	11	30
Mild	5	..	7	..
Moderate	1	..	4	..
Severe	1	..	0	..

"TOLERANCE"

The extent of "tolerance" was estimated by comparing the dosage requirement early and late in treatment. Over the period of therapy with mecamylamine, varying from one to four months, there was no increase in

dosage in 19, or 53%; in 10 of these the dosage requirement actually lessened (Table 9). In 12, or 33%, an increase of 5 to 20 mg. in the total daily dosage was required. In five patients the dosage increase was greater than 20 mg. per day. During the period of this study, therefore, in the majority of cases the development of tolerance was slight or nonexistent.

TABLE 9.—*Extent of "Tolerance" to Oral Mecamylamine: Change in Daily Dosage Requirement After One to Four Months of Treatment*

Change in Daily Dosage Requirement	No. Patients	Per Cent of Total
More than 5 mg. decrease	10	28
No essential change	9	25
Between 5 and 20 mg. increase	12	33
More than 20 mg. increase	5	14
Total	36	100

Treatment Failure and Complications

Three patients died either while under treatment or shortly thereafter. Two of these had malignant hypertension with uremia. Both exhibited significant but not excessive reduction of blood pressure and a decreased urinary output. The blood urea nitrogen rose in one case and decreased slightly in the other. Autopsy revealed advanced malignant nephrosclerosis in both instances.

The third patient was a 55-year-old man with long-standing hypertensive heart disease. The blood pressure had been reduced from 230/120 to approximately 170/110 mm. Hg, with apparent improvement in cardiac decompensation. After six weeks of treatment, while at home, he suddenly was seized with severe substernal pain and died two hours later. The clinical impression was myocardial infarction; autopsy was not obtained.

Treatment was discontinued in four patients because of abdominal distention and vomiting, either with obstipation or with small frequent liquid stools diagnosed as a low-grade paralytic ileus. These symptoms cleared promptly on discontinuation of therapy. In one case it was possible to resume treatment in reduced dosage without recurrence. In another patient two later attempts at therapy were followed again by symptoms of ileus.

Treatment was discontinued in another uremic patient with malignant hypertension because of severe postural hypotension with syncope, decreased urinary output, and increasing uremia. This patient improved when veratrum was substituted for mecamylamine, although the blood pressure level rose. Treatment was discontinued in a 57-year-old-man because of severe postural hypotension with increased angina and in a 59-year-old man because of difficulty in emptying the urinary bladder and severe dryness of the mouth not relieved by oral pilocarpine nitrate.

One patient developed acute appendicitis after one month of therapy. He was operated upon, and recovery was uneventful. Another patient with congestive heart failure and massive ascites failed to respond to mecamylamine, even in large doses, until paracentesis was performed. After removal of the ascitic fluid the blood pressure fell from 220/120 mm. Hg to nearly normotensive levels on a total daily dose of 20 mg. of mecamylamine. He has remained clear of congestive heart failure and ascites over a three-month period. It is suggested that the tight ascites produced sufficient abdominal compression to overcome the vasodilator effects of the mecamylamine in the splanchnic area.

Addition of Other Hypotensive Agents

In assessing the effect of the addition of other agents the blood pressures were determined three to five times per day either in the hospital or at home. The average of the blood pressure values for the week immediately preceding and immediately following the change in medication were averaged and compared.

(a) Addition of Hydralazine.—The hypotensive effect of hydralazine when added to mecamylamine was tested in 13 patients. The daily dosage of hydralazine varied between 75 and 200 mg. per day, the average dose being 100 mg. per day. In three of these cases an additional hypotensive effect was observed. The reduction was not great, vary-

ing between 10% and 14% below the values obtained with mecamylamine alone. In the remaining 10 patients no additional hypotensive effects were observed following hydralazine. Two patients developed mild headaches; one, mild palpitation, and one, severe palpitation. These side-effects were transient. It is possible that the addition of hydralazine might have produced additional hypotensive effects in a greater number of patients if it had been given in larger doses. Such increases in dosage were not attempted, however, because of the possibility of developing collagen vascular syndromes.[10]

(b) Addition of Reserpine.—Reserpine was added to the regimen of 11 patients in dosages of 0.25 to 1.0 mg. (mean, 0.5 mg.) per day. In 5 of the 11 cases additional reductions of blood pressure occurred, varying between 9% and 25% below the values obtained with mecamylamine alone. Among these five patients, one experienced nasal stuffiness while the remaider had no side-effects attributable to reserpine.

Comparison of Mecamylamine and Pentolinium Tartrate

In 19 patients who had been under treatment with pentolinium tartrate for six months or longer the drug was discontinued and mecamylamine was substituted. The daily dosages of pentolinium tartrate had varied between 60 and 1150 mg. (average, 580 mg.). This had resulted in reductions of "mean" $\left(\frac{\text{systolic} + \text{diastolic}}{2}\right)$ blood pressure averaging 16% in the supine and 20% in the erect position.

The daily dosages of mecamylamine in the same group of patients varied between 3 and 90 mg. (average, 35 mg.). In general, the patients who required the higher dosages of pentolinium tartrate also needed the largest daily requirement of mecamylamine. The reductions of mean blood pressure averaged 21% in the supine and 25% in the erect position.

When asked which medication they preferred, 14 favored mecamylamine. The chief reason given was that the blood pressure reduction was more uniform from morning to night and from day to day with mecamylamine (all of these patients recorded their blood pressure levels at home). However, five patients preferred pentolinium tartrate, since they obtained a more uniform reduction with the latter drug and also experienced fewer or less severe side-effects.

Comment

Clinically, mecamylamine behaved as a typical ganglion-blocking agent. Experimentally, the inhibition of sympathetic vasoconstrictor reflexes was less than had been observed previously with hexamethonium.[3] The reason for this discrepancy is not evident at present. The dosages of mecamylamine were smaller than those given in the hexamethonium studies. However, the doses of the two agents were approximately equipotent so far as hypotensive effects were concerned. It is possible that if the patients had been studied for longer intervals than from 30 to 60 minutes after mecamylamine a more complete inhibition of sympathetic vasoconstrictor reflexes would have been observed. Still, the reflexes remained active in three patients who were restudied during continuous oral administration of the drug. Finally, there is the possibility that mecamylamine in man has peripheral or central vasodilator effects in addition to its ganglion-blocking action. However, this supposition gains no support from the animal data § or from our own clinical observations.

Because of its potency, relatively long duration of action, and complete absorbability, the daily dose requirement of mecamylamine was far less than that of other ganglion-blocking drugs. It was hoped that the complete oral absorption of mecamylamine would obviate some of the difficulties entailed in the use of ganglionic blocking agents clinically. In the majority of the pa-

§ Stone, C. A.; Torchiana, M. L.; O'Neill, G. P., and Beyer, K. H.: Ganglionic Blocking Properties of 3-Methylaminoiso-Camphane Hydrochloride (Mecamylamine), a Secondary Amine, read before the American Society for Pharmacology and Experimental Therapy, Iowa City, Sept. 7, 1955.

tients the blood pressure response was more uniform from day to day than with pentolinium tartrate, but this was not always the case. In addition, such side-effects as constipation were just as prominent with the small completely absorbed doses of mecamylamine as with the relatively large poorly absorbed doses of other ganglion-blocking agents.

SUMMARY AND CONCLUSIONS

Mecamylamine seems to be completely absorbed from the intestinal tract of man. The hypotensive effect began after 1 hour, reached the lowest values at 2 hours and disappeared in 6 to 12 hours.

In equipotent hypotensive doses mecamylamine did not produce as marked an inhibition of sympathetic vasoconstrictor reflexes as had been observed previously with hexamethonium.

In 36 patients with severe hypertension treatment with mecamylamine in an average dose of 29 mg. per day was followed by a mean reduction in blood pressure of 21% systolic and 16% diastolic in the supine position and 27% systolic and 20% diastolic in the erect position.

Continuous treatment for one to four months frequently resulted in improvement in the optic fundi and occasionally in the electrocardiographic patterns. A decrease in blood urea nitrogen levels also was noted in most patients exhibiting slight elevations but not in those with marked nitrogen retention.

The side-effects were typical of those experienced with other ganglion-blocking agents.

In the majority of patients the development of "tolerance" was slight or nonexistent.

The addition of small doses of hydralazine appeared to produce a slight additional hypotensive effect in 3 of 13 patients. Reserpine seemed to produce an additional hypotensive effect in 5 of 11 patients.

Mecamylamine appears to offer a slight advantage over other ganglion-blocking agents in that the effective dose is much smaller, and with careful dosage regulation the blood pressure usually fluctuates less than with other blocking agents.

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