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# Mecamylamine (inversive) in severe hypertension : a review

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# MECAMYLAMINE (INVERSIVE)
# IN
# SEVERE HYPERTENSION
# A REVIEW

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# I. INTRODUCTION

Mecamylamine (Inversive), a potent ganglionic blocking agent has been proposed as the most effective agent for the treatment of severe, progressive essential hypertension.

The unique property claimed for the drug is that it is the first ganglionic blocking agent completely absorbed from the gastro-intestinal tract, thereby simplifying the problem of control and overdosage. It is also the first drug to show ganglionic blocking properties which is classified a secondary amine.

This paper is essentially a review of recent literature covering the physiology and pharmacology of Mecamylamine and the experimental and clinical investigations evaluating the drug in the treatment of severe, progressive hypertension.

## II. THE PROBLEM OF SEVERE HYPERTENSION

Severe, essential hypertension is a progressive elevation of the blood pressure associated with progressive retinal changes, cardiac and renal damage and in the malignant cases, ultimate death.

It is classified as essential hypertension because no definite etiology can be established to explain the sustained elevation of blood pressure, such as unilateral renal disease, pheochromocytoma, coarctation of the aorta and primary renal disease.

In Table I is presented a classification of essential hypertension based on the original classification by Keith, Wagner, and Barker.[4] This classification is basic because treatment hinges on severity of the disease.

Grade I

(a) Persistent diastolic blood pressure over 100 mm Hg

(b) Arteriolar narrowing but no other funduscopic findings.

(c) Female sex

Grade I A

Same as Grade I except for (c) male or female with evidence of recent rise in diastolic blood pressure.

Grade II

(a) Either sex

(b) Evidence of involvement of one or two of the following systems: Cardiac, renal or cerebrovascular (cardiac enlargement, ECG abnormalities, PSP excretion less than 25% in 15 minutes, less than 60% in 2 hours; previous history of cerebral thrombosis or hemorrhage.

(c) Either arteriolar narrowing or narrowing plus nicking on funduscopic examinations.

(d) Diastolic blood pressure persistently over 100 mm Hg

Grade II A

Same as Grade II, except for

(a) Evidence of recently rising blood pressure levels, angina or congestive failure.

Grade III

(a) Evidence of involvement of one or two of the following: cardiac, renal or cerebrovascular systems (cardiac abnormalities, ECG abnormalities; PSP less than 25% in 15 minutes and less than 60% in 2 hours; previous history of cerebral thrombosis or hemorrhage.

(b) Diastolic blood pressure 120 mm Hg or more.

(c) Arteriolar narrowing with nicking and/or

hemorrhages or exudates on funduscopic examination.

Grade III A

Same as Grade III and

(d) Evidence of rapidly rising diastolic blood pressure (over 130 mm Hg) and/or PSP of less than 20% in 15 minutes.

Grade IV

Same as Grade III A and

(a) Papilledema with hemorrhages and/or exudates with or without

(b) PSP excretion under 15% in 15 minutes and/or nitrogen retention.

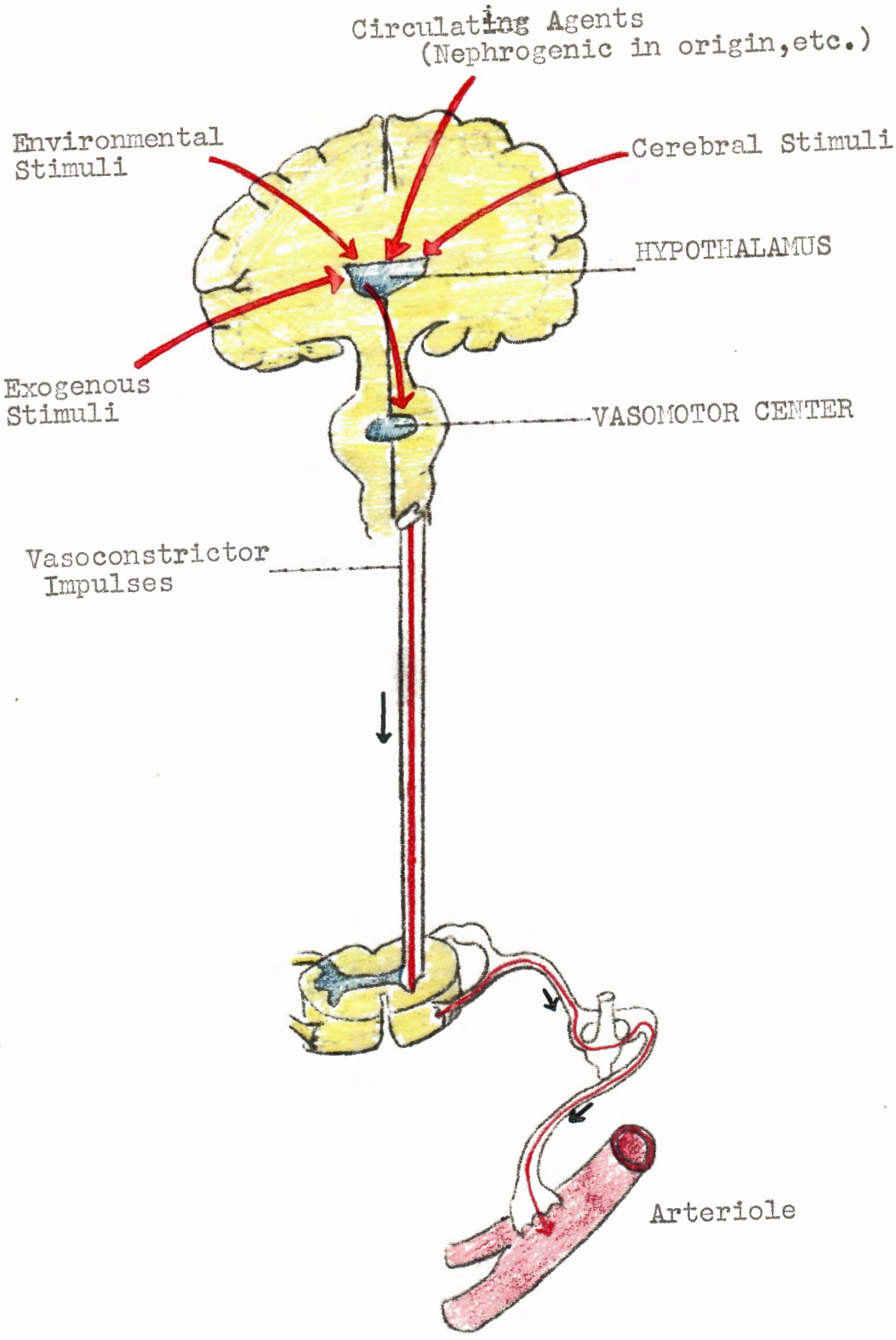



**Figure 1**
THE CONTROL OF BLOOD PRESSURE IN MAN

## Control of Blood Pressure in Man

In Figure 1[2] (on preceding page) is a diagram to illustrate the normal stimuli operating in control of blood pressure causing ultimately an outflow of impulses from the vasomotor centers, down the cord and out over the autonomics.

When this is in perfect balance, blood pressure is held within rather close limits. In the hypertensive patient, the outflow over the autonomic tracts of the cord and autonomic nerves is greatly increased causing vaso-constriction and elevated blood pressure.

In essential hypertension, the cause of this increased outflow is not known; whether it is from an increase in certain circulating agents of renal origin, increased endogenous stimuli, psychogenic factors or a host of other possibilities.

Hence present day therapy is not getting at the basic cause of essential hypertension and is only an attempt to lower the blood pressure by decreasing cerebral outflow with drugs or blocking autonomic impulses with drugs or surgery.

## The Value of Treatment of Hypertension

In cases of severe, progressive hypertension the value of lowering the blood pressure has been

found to be of life-prolonging value without any doubt. To allow hypertension to progress unchecked leads to many irreversible changes and if the disease becomes malignant, progression leads to eventual death from cardiac and renal disease.

Table 2 below illustrates the results obtained by Moyer, Ford, Kinard and Dennis in treating advanced hypertension.

TABLE 2

| | Number of Patients | Survival 1-2 yrs |
|---|---|---|
| Untreated 1949-1952 | 22 | 6 (27%) |
| Treated | | |
| Normal BUN | 11 | 10 (91%) |
| Elevated Bun | 5 | 3 (60%) |

In Table 3 below are the results obtained by Schroeder and Perry[5] in treatment of hypertension

TABLE 3

| | Number of Patients | Survival 1 yr |
|---|---|---|
| Untreated | | Less than 10% |
| Treated | | |
| Normal BUN | 47 | 37 (79%)* |
| Elevated Bun | 40 | 40 (50%) |

*8 of these stopped treatment voluntarily - died. If disregarded, survival becomes 92%.

It has been found that increased blood pressure over long periods causes damage to the vascular beds of the brain, heart and kidney. This damage can be prevented often by decreasing the blood pressure. Hence it is of definite value to treat those with mild to moderate disease to prevent damage and treat those with severe disease to prevent further damage. The treatment of malignant disease has been valuable in evaluation because without treatment the majority will be dead in one year.

In Table 4,[5] two patients are illustrated, one before 1950 (a), untreated, and the second (b) during treatment. The progressive downhill course of #1 is well illustrated.

TABLE 4 (a)

| Time | Blood Pressure | Glomerular Filtration Rate | Renal Blood Flow |
|---|---|---|---|
| Control | 270/150 | 90 | 990 |
| 2 mos. | 248/156 | 70 | 720 |
| 4 mos. | 260/160 | 55 | 600 |
| 8 mos. | 250/160 | 40 | 200 |
| 10 mos. | 270/165* | 28* | 120* |
| 11 mots. | Death | | |

*Uremia

TABLE 4 (b)

| | Mean Blood Pressure | Glomerular Filtration Rate cc/min. | Renal Blood Flow cc/min. |
|---|---|---|---|
| **No Treatment** | | | |
| Control | 160 | 90 | 940 |
| 6 months with no treatment | 175 | 55 | 365 |
| **After treatment** | | | |
| 3 months | 105 | 52 | 410 |
| 1 year | 98 | 56 | 458 |
| 2 years | 110 | 60 | 520 |

## III. ANTI-HYPERTENSIVE AGENTS

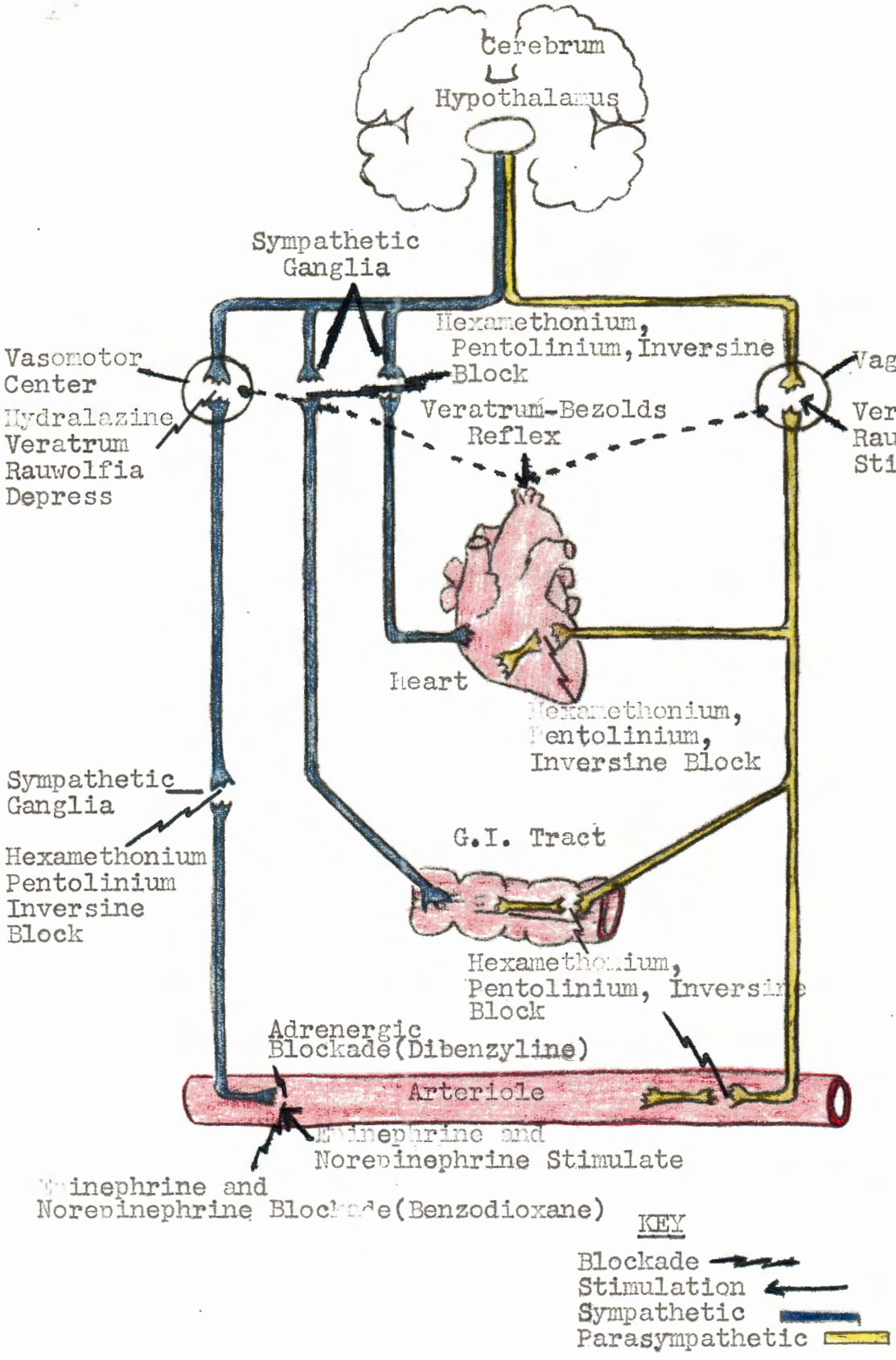
Today there are three major types of anti-hypertensive agents in use.

The first group are those which are chiefly centrally acting. Veratrum, Hydralazine and Rauwolfia are examples. They have their chief value in the treatment of mild hypertension and as adjuncts to more potent agents.

The second group is exemplified by Dibenzyline and blocks peripheral nerve ending by means of adrenergic blockade.

The third group is the ganglionic blocking agents, of which Hexamethonium, Pentolinium and Mecamylamine are examples.

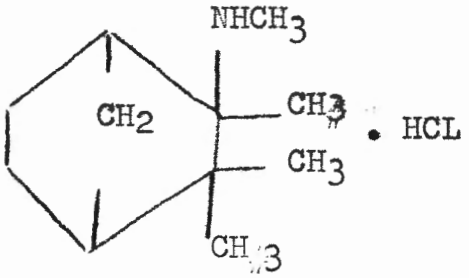
Figure 2 is a diagram of the sites of action of the various anti-hypertensive agents.




SITE OF ACTION
OF
HYPOTENSIVE AGENTS
FIGURE 2

## IV. PHARMACOLOGY OF MECAMYLAMINE

Mecamylamine is a crystalline, synthetic compound known chemically as 3-methylaminoisocamphane hydrochloride and has the following structural formula:




It is a stable compound and is soluble in water. The base is soluble in common organic solvents such as alcohol, tetrachlorethane, petroleum ether and chloroform. The drug was found to decompose at 246°C.

Mecamylamine is rather unique as an anti-hypertensive agent in that it is the first to show ganglionic blocking preoperties which is not a quaternary amine such as Hexamethonium, but is rather a secondary amine.

Mecamylamine was found to be a rather potent ganglionic blocking agent by Stone, Torchiana, Navarro, and Beyers[16, 17].

This was determined experimentally by the following tests:

1) Inhibition of the contraction of the

nictitating membrane in cats induced by pre-ganglionic stimulation but not by injection of epinephrine.

2) Blockade of nicotine vascular and respiratory response in cats and dogs and vascular response to carotid occlusion and peripheral vagal stimulation.

3) Prolonged vaso-depressor effect and a changed heart rate were not likely due to ganglionic blockade, though central nervous system action could not be excluded.

There was found no qualitative difference in Mecamylamine as compared to Hexamethonium and Pentolinium in inhibiting preganglionic induced contractions of the nictitating membrane in cats. Mecamylamine and Pentolinium were found about equal with respect to inhibition of nicotine pressor response. Mecamylamine was found two to four times as active as Hexamethonium.

The duration of ganglionic blockade caused by Mecamylamine was also found to be three to five times the duration of Hexamethonium and Pentolinium[16,17].

Mecamylamine was also found to have no anti-histaminic, surface local anesthetic, atropine-like or adrenergic blocking properties. A slight curare-like effect was noted.[17]

The above findings all seemed to indicate that Mecamylamine has a rather specific site of action at

the autonomic ganglion, both sympathetic and parasympathetic.

Another rather unique property of Mecamylamine is its apparently complete absorption from the gastrointestinal tract.

Fries and Wilson[3] found almost equal response to intravenous and oral administration of the drug.

Mecamylamine was given in sterile water to patients in intravenous doses of 15-20 mgm. The next day the same patients were given oral doses of 5-10 mgm. In both groups of patients the resultant decrease of supine blood pressure and marked postural hypotension were equally as great in the ones given oral as the ones given intravenous doses.

Zawoiski and others[18] also found Mecamylamine to be efficiently absorbed and excreted by the gastrointestinal mucosa of Heindenhain pouch dogs.

3.05 mgm/Kg of Mecamylamine were given to two dogs intravenously and in one hour without stimulation they secreted an average of 3.7 γ/ml of drug. Two dogs were given sodium acetate and secreted 72.3 γ/ml. Two secreted 25.6 γ/ml following intravenous histamine.

Following the above experiment, 24.4 to 24.4 mgm of Mecamylamine were instilled into pouches of four

dogs. Recovery at fifteen minutes averaged 78.1% and none of the compound was found in the plasma.

Intestinal absorption was studied in four phenobarbital anesthetized dogs. Eight loops of intestine were tied off in each dog and aliquots of Mecamylamine injected into each. Two loops were excised immediately, two in fifteen minutes and two in thirty minutes. The average residual drug remaining in the loops was 87% immediately, 47.9% after 15 minutes, and 32.6% after 30 minutes.

Drug plasma levels averaged 2.8 mg/liter after fifteen minutes and 2.7 mg/liter after 30 minutes.

In experiments by Baer, Paulson, Russo, and Beyer[1], Mecamylamine was found to be a strong base. Induced acidosis in dogs increased the excretion of Mecamylamine and increased the urinary concentration of the drug. Contrariwise, alkalosis caused a decrease of excretion and filtration of Mecamylamine. Large doses of p-amino hippurate were also found to have no decreasing effect on tubular excretion of Mecamylamine.

The following mechanisms were postulated to account for a shift in the direction of renal tubular transport of the drug:

1. Diffusion of a base in response to a pH gradient.
2. Active cation exchange.

3. pH induced gradient of an intracellular enzyme - Mecamylamine complex.

Also in studies of the renal hemodynamic effect of Mecamylamine in dogs, Moyer, Ford, Dennis and Handley[10] found that doses of 0.2-0.5 mg had no effect on blood pressure, renal hemodynamics or water and electrolyte excretion.

Doses of 0.5-2.0 mg/Kg caused a significant decrease in blood pressure but the initial blood pressure fall caused no decrease of glomerular filtration rate or renal blood flow. After 30 minutes a significant decrease in renal blood flow was noted but no alteration in water and electrolyte excretion.

Thus experimental observations show Mecamylamine to be a rather potent and specific ganglionic blocking agent, which is absorbed almost completely from the gastro-intestinal tract and finally selectively excreted by the kidney tubules.

## V. EXPERIMENTAL HYPOTENSION AND ANTI-HYPERTENSION

Moyer, Ford, Dennis and Handley[10] in 12 dogs anesthetized with Phenobarbital, demonstrated autonomic blockade and decreased blood pressure by the use of Mecamylamine.

The dosages used were .05-0.5-1.0 and 2.0 mg/Kg given intravenously over a 5 minute period. The blood pressure was followed for 5 hours.

The vagi were severed and the cut ends were stimulated every hour. Carotid occlusion tests were done every hour. Nonepinephrine was given in sufficient quantities to raise the blood pressure 20 mm in a control animal.

No consistent decrease in blood pressure was found with doses less than 0.1 mg/Kg. There was also no greater decrease in blood pressure with doses over 0.5 mg/Kg than with 0.5 mg/Kg. A more rapid onset of action and longer duration was found with larger doses of the drug. 0.5 mg/Kg or more of drug had a 5-10 minute delay of onset of action and a duration of 30-45 minutes. Vagal blockade occurred with 1.0 mg/Kg of Mecamylamine and carotid sinus reflex blockade with 0.5 mg/Kg.

The amount of Nonepinephrine necessary to

increase blood pressure 20 mm was only slightly increased by the ganglionic blockade and there was no adrenergic block present.

Fries, Wilson and Ilse[3], made clinical and experimental studies of hypotensive and ganglionic blocking properties of Mecamylamine by noting the effect of the drug on the sympathetic vaso-constrictor reflexes. The following tests were employed and results obtained:

1. Valsalva maneuver

If a normal person blows into a closed tube for 10 seconds, the blood pressure falls. When they cease this forced expiration, there is a blood pressure over-shoot from reflex vaso-constriction mediated over sympathetic pathways. This over-shoot is abolished by lumbo-dorsal splanchniectomy.

This test was done on six patients before and one hour after intravenous Mecamylamine. The reflex over-shoot of the blood pressure was abolished in one and reduced 50-70% in five patients.

2. 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. This reflex blood pressure elevation was abolished in only two out of six patients.

3. Skin Temperature Gradient

Nine patients were selected with hypertension and without peripheral vascular disease. These were placed in a temperature of 63-71°C. The skin temperature of the digits and the umbilicus was recorded every 3 minutes for one hour, then intravenous Mecamylamine was given. Recordings were made for one more hour. Three patients had increased toe temperatures, two had a partial rise and two no significant rise. There was a significant rise in five patients' finger temperatures and an insignificant rise in finger temperatures of four others.

4. Digital plethysmography

Normally, following deep inspiration there is a sharp decrease in the volume of the digital pulse, which is abolished after sympathetic denervation. Out of six patients given intravenous Mecamylamine, this reflex was partially abolished in two. There was no change in four. Of the four, 50 mgm of intravenous Hexamethonium abolished the reflex in one patient.

Moyer and others[7] also demonstrated blood pressure decrease with Mecamylamine and compared its duration and necessary concentration with Hexamethonium A group of dogs were used and the amount of Mecamylamine

to cause a maximum blood pressure response was found to be one mg/Kg. The amount of Hexamethonium necessary for a similar response was 5 mgm/Kg.

The same group also found the blood pressure to still be low 5 hours after Mecamylamine but rising 40 minutes after Hexamethonium was administered. Eight minutes after Hexamethonium administration, blood pressure had returned to control levels.

Moyer and others[6] also found the duration of action of Mecamylamine to be 10-20 times that of Hexamethonium and 3-4 times that of Pentolinium.

## VI. CLINICAL TRIALS OF MECAMYLAMINE

Numerous studies have been made to evaluate the clinical results of Mecamylamine in severe hypertension.

Schneckloth, Corcoran, Dunston and Page[14] studied 12 women and 23 men ages 28-62 years. These were all treated with Mecamylamine at least one month. Blood pressure readings were recorded four times daily, upright and supine. Of these patients, 13 had no previous treatment. 10 had severe essential hypertension, 10 malignant hypertension, and 11 had residual essential hypertension with degrees of vascular damage and in remission from previous treatment. Four had severe malignant hypertension secondary to renal disease.

The severity was graded from 0-4 on the basis of (1) Heart, (2) Kidney, (3) Brain, and (4) Diastolic blood pressure. The severity index was 3.0-14.0 with a mean index of 8.4.

A significant response was considered an average supine diastolic blood pressure of 110 mm or less.

The initial dose was 2.5 mg in the a.m. or twice daily in the a.m. and early p.m. The dose was

increased 2.5 mg every other day according to the standing systolic blood pressure. The average dose taken was 39 mg daily.

Of the 13 previously untreated patients, all 13 showed an initially significant response. One developed severe postural hypotension and one developed renal failure, necessitating discontinuation of the drug.

Eight of the 13 had an average supine diastolic blood pressure of 110 mm or less for 1-6 months (Average 3.8 months). The severity index decreased from 9.3 to 5.6. The average dose was 27 mg daily.

Out of the total 35 patients, 20 (57%) responded for one month and 15 (43%) did not respond. Twenty-three continued treatment for 2-12 months and 14 (61%) responded.

Thirteen of the 22 previously treated patients found Mecamylamine more effective than the drug previously used.

Moyer and others[7] treated 24 patients with Mecamylamine, all of which had diagnosed severe, progressive hypertension. 13% had hemorrhages and papilledema. The dose was 2.5 mg twice daily with step-wise increase weekly. A significant response was a decrease of 20 mm in the mean blood pressure.

Of those with a diastolic pressure of 100-120 mm, 60% were responsive when erect and only 10% when supine. 40% became normotensive (B.P. less than 150/100) when upright and none when supine. Out of a group of patients with pressure over 120 mm diastolic, 71% were responsive in upright position and 29% became normotensive.

Fries, Wilson and Ilse[3] studied 36 patients with malignant hypertension having a mean pre-treatment blood pressure of 217/129. After an average of 2.8 months of treatment with Mecamylamine, a mean of 167/108 supine pressure and 153/101 upright pressure was achieved.

Finally Moyer, Ford, Dennis and Handley found the average single dose necessary to lower the blood pressure to normotensive levels was 19 mg with a range of 5-40 mg. The duration of action was 12-48 hours with a latent period of 20-70 minutes parenterally and 30 minutes to two hours orally.

Combination of Mecamylamine and Reserpine

The main advantage obtained by combining Mecamylamine with Reserpine is to reduce the dose of Mecamylamine needed for a response, thus reducing the incidence of untoward effects caused by Mecamylamine. Eighty cases studied by Moyer and others[7] combining

Mecamylamine and Reserpine are reviewed in Table 5.

TABLE 5

| Side-Effects | Mecamylamine | Mecamylamine Plus Reserpine |
|---|---|---|
| Palpitation | 13% | 6% |
| Blurred vision | 54% | 43% |
| Sedation | 38% | 56% |
| Dry Mouth | More severe | Less severe |

Continued long term therapy with Mecamylamine and Reserpine also seemed to decrease side-effects, as illustrated in Table 6.

TABLE 6

| | Mecamylamine Plus Rauwolfia | |
|---|---|---|
| | 3 months | 6 months |
| Constipation | Increased | Decreased |
| Nasal congestion | | Improved |
| Weakness | | Improved |
| Blurred Vision | 29% | 46% |

Sedation Table 7, another study is presented to illustrate decrease of complications secondary to Mecamylamine therapy by use of Reserpine concurrently.

TABLE 7

| | Mecamylamine | Mecamylamine Plus Reserpine |
|---|---|---|
| Anorexia | 29% | 5% |
| Increased appetite | 0 | 23% |
| Nausea | Increased | Decreased |
| Constipation | 79% | 69% |
| Nasal stuffiness | 66% | 66% and more severe |
| Angina | 4-8% | 4-8% |
| Weakness | Under 46% | 46% |

Overall results of treatment with combinations of Mecamylamine and Reserpine were also somewhat better with responses of 80% in those with blood pressure 110-120 mm and 97% response in those with diastolic over 120 mm.

It was also found by Moyer[6] that Rauwolfia tends to lessen the reflex tachycardia common with Mecamylamine therapy and in one series, 25 patients got a bradycrotic response in erect position.

Moyer[11] also found a stablizing effect on blood pressure with combined use of Mecamylamine and Rauwolfia. A patient treated for 14 weeks was taking 30 mg of Mecamylamine daily and having considerable fluctuation in blood pressure and severe

symptoms of weakness and dizziness. Rauwolfia was added and by 36 weeks the pressure was stable. At 50 weeks the dose of Mecamylamine was reduced to 10 mgm daily and the patient was much more comfortable.

Mecamylamine with Hydralazine

In a series of Fries, Wilson, Ilse[3], Hydralazine was added to the regimen of 13 patients taking Mecamylamine. It was added in doses of 75-200 mgm (average 100 mgm). Of these, only three had further decrease in blood pressure of 10-14%. Ten patients had no further decrease in blood pressure. Of these, two experienced headaches, one palpitation, and one severe palpitation. It was felt that an increased dosage might be helpful but side-effects would probably be intolerable.

Perry & Schroeder[12] cite one patient treated at Barnes Hospital who had severe, advanced disease with blood pressure of 240/150 and renal azotemia with a non-protein nitrogen of 125 mg% initially. From November 21, 1955 to December 20, 1955 he was given step-wise increases in dosage of Mecamylamine and Hydralazine;. His final dosage was 1000 mg Hydralazine daily and 55 mg Mecamylamine daily. He was discharged, relatively symptom free and returned

to work. His blood pressure was 140/90 and his non-protein nitrogen was 40 mg%. This may illustrate a use of Hydralazine and Mecamylamine in large doses in patients with renal azotemia.

Schroeder and Perry[15] found Hydralazine to be a true renal vaso-dilator and to actually increase renal blood flow even in the face of decreasing blood pressure. This may explain beneficial effect of high doses in severe hypertension with renal azotemia.

Combination of Mecamylamine, Rauwolfia and Dibenzyline

Moyer[5] recommended a combination for use in extremely refractory cases experiencing intolerable side-effects from Mecamylamine. He recommended reduction of the dose of Mecamylamine to tolerable levels and when stable to give an adrenergic blocking agent and Rauwolfia. Dibenzyline in doses of 5 mgm with breakfast and supper was usually given. After a week the dosage was increased by 5 mg increments until response was obtained. Moyer felt this to be the most potent anti-hypertensive combination available today.

Results of Mecamylamine Therapy

TABLE 8

Result of Blood Pressure Response
Mecamylamine, Hexamethonium and Pentolinium[9]

| | Mecamylamine | | Rauwolfia | | | |
|---|---|---|---|---|---|---|
| | | | Hexamethonium | | Pentolinium | |
| | No. | % | No. | % | No. | % |
| Patients treated | 50 | 100 | 25 | 100 | 75 | 100 |
| Responsive | 46 | 92 | 57 | 76 | 59 | 79 |
| Normotensive | 12 | 24 | 28 | 37 | 25 | 33 |
| Unresponsive | 4 | 8 | 18 | 24 | 16 | 21 |
| Average dose of Responders | 17 mg | | 2307 mg | | 341 mg | |

The overall results of Mecamylamine therapy varied, with the severity of the hypertension. While up to 92% responded adequately if they had moderate disease, only 50% responded well with severe disease and few became normotensive.

It was interesting to note that Moyer reported much more even results and control with the use of Mecamylamine. In contradistinction, Schneckloth, Corcoran, Dunston and Page[14] found that only three out of ten patients had any significant difference in control with Mecamylamine than with other ganglionic blocking agents. The ten cases were, however, severe, long standing cases, all of which had been on therapy

for some time. Schneckloth felt better control was attributable to a more regular vascular response than to absorption.

Fewer side effects were noted when Mecamylamine was combined with Rauwolfia. Dibenzyline should be tried in refractory cases.

Problems of Mecamylamine Therapy

Mecamylamine has numerous side effects, most of which are secondary to ganglionic blockage. In Table 9 the various side effects of Mecamylamine are compared with those of Hexamethonium and Pentolinium.

TABLE 9

Side Effects of Mecamylamine, Hexamethonium and Pentolinium Plus Rauwolfia

| | Mecamylamine % | Hexamethonium % | Pentolinium % |
|---|---|---|---|
| Bradycardia | 50 | 68 | 67 |
| Nasal Congestion | 35 | 61 | 51 |
| Constipation | 64 | 52 | 49 |
| Weakness | 48 | ? | ? |
| Increased Appetite | 27 | 21 | 32 |
| Weight gain | 14 | 20 | 35 |
| Dizziness | 41 | 35 | 40 |
| Syncope | 1 | 5 | 1 |
| Nausea | 11 | ? | ? |
| Vomiting | 1 | 26 | ? |
| Blurred Vision | 35 | 65* | ? |
| Impotence | 57 | 50* | ? |
| Anxiety-Depression | 0 | 3 | 4 |
| Sedation | 46 | 27 | 39 |

*Initially only

Ecolid was studied by Moser, Macauley, Grangen and Trout[4] who felt its use would be limited by severe blurring of vision which occurs with its use.

Many of these untoward effects may be effectively controlled. The major ones are reviewed below.

1. Excessive reduction of blood pressure in patients with serious renal impairment. An excessive fall

in blood pressure will cause a decrease of glomerular filtration rate up to 65% which is not tolerated in hypertensive individuals with renal disease. In case of excessive reduction of blood pressure, the patient should be kept supine because renal function is increased in the supine position. If a severe drop in pressure occurs in event of overdosage, vasopressor agents such as Nonepinephrine may be used to increase the blood pressure. Judicious lowering of the blood pressure according to the table postulated by Moyer, Ford, Kinard, and Dennis[11] will aid in therapy. See Table 10.

TABLE 10

| BUN (mg%) | Maximum Decrease Possible in Upright Blood Pressure |
|---|---|
| Normal | 130-150/80-100 |
| 30-60 | 150-170/100-110 |
| 60-100 | 180-190/110-120 |
| 100 | No reduction |

Therapy should be stopped if BUN rises. It may be noted that as a general rule, those with advanced renal disease do poorly on any regimen to achieve hypotension.

2. Constipation and ileus

This is probably the biggest problem with

Mecamylamine, even more than with other agents. This can usually be prevented or relieved by vigorous therapy.

Prevention: (1) Prostigmin 15-20 mg orally and/or
(2) Milk of magnesia 15-30 cc

Treatment: (1) 1 mg Prostigmin every hour until ileus relieved.
(2) General treatment of bowel obstruction and paralytic ileus.

3. Individualization of dose.

The drug must be started a small dose and individualized to the patient to prevent hypotensive episodes. As a rule, Mecamylamine is retained at night so if a large dose is given at bedtime, faintness will be experienced in the morning. The largest dose is usually given in mid-day.

In Table 11 is a recommended routine cited by Moyer, Ford, Kinard and Dennis[11]

TABLE 11

| Week | 7 AM | 12 Noon | 5 PM | 10 PM |
|---|---|---|---|---|
| 1 | 2.5 | -- | 2.5 | -- |
| 2 | 5 | -- | 5 | -- |
| 3 | 5 | 5 | 5 | 5 |
| 4 | 5 | 10 | 5 | 5 |
| 5 | 5 | 10 | 10 | 5 |
| 6 | 5 | 15 | 10 | 5 |
| 7 | 10 | 15 | 10 | 5 |

4. Tolerance

A partial tolerance usually develops after one to three weeks. If at this period the drug is increased 10-30%, usually no further tolerance develops and the dosage remains stable.

5. Decreased response in supine position.

This occurred in a number of patients but, as a rule, they still obtained benefit from a decreased blood pressure during the day when up and about.

6. Marked early morning reactivity

This is relieved by reducing or discontinuing the night dose and often adding a small breakfast dose.

7. Fluctuation of dosage with stress and strain.

This occurs often and the only solution is to fluctuate the dosage with stress situation of business and the like.

8. Treatment of hypertensive emergency.

Moyer and others[7] recommended in this situation to begin treatment with Reserpine intramuscularly, 10 mg every 6 hours. Later, the dose is changed to 8 mg daily by oral route.

On the fifth day, Mecamylamine is begun in oral doses of 5 mgm twice daily and gradually increased to 30 mg daily. On the sixth week

Mecamylamine is reduced to 20 mg daily and on the eleventh to 10 mg daily. This routine will usually lower blood pressure in most emergency situations.

9. Schneckloth, Corcoran, Dunston and Page[14] reported 7 cases of unusual muscular tremor and convulsions with Mecamylamine therapy. All had diffuse vascular damage. No similar episodes were ever noted with other drugs. (This was supported by Schroeder and Perry at Barnes Hospital in seven patients with malignant hypertension and uremia.)

It can not be definitely decided if this reaction is secondary to the drug itself or secondary to cerebral vascular damage and uremia present in all severe cases. Probably when this reaction occurs another hypotensive agent should be substituted for Mecamylamine.

Symptomatic Relief from Mecamylamine

In the series of Moyer and others,[7] heart failure and headaches were relieved in 10 out of 13 cases. Angina was also improved in these cases. One-half showed a decrease of the pulse rate of 10 or more after taking Mecamylamine and Rauwolfia for four or more months. One-third showed improvement of ECG's and 31%

had decreased heart size. One-fourth of the cases showed improvement of renal status. Little symptomatic change was noted with prolonged treatment. The initial decrease in blood pressure had the most dramatic effect upon symptomatic relief.

Fries, Wilson and Ilse[3] reported the following symptomatic improvement:

(a) Ocular fundi

Grade IV - 8 patients

Grade III after therapy - 2

Grade II after therapy - 6

Grade III - 15 patients

Grade II after therapy - 13

Grade I after therapy - 1

Grade II - 13 patients

Grade I after therapy - 6

Unchanged after therapy - 2

(b) Cardiac status

Of 31 cases with increased heart size, 21 had no change after Mecamylamine therapy, three had further enlargement and seven had a decrease of heart size. ECG's were abnormal in 30 cases and became normal in only four cases after Mecamylamine therapy. No change was noted in 23 cases.

(c) Renal function

In a series of 28 cases exhibiting albuminuria, 11 showed improvement, 11 were unchanged and 6 became worse after treatment with Mecamylamine. No change was noted in the specific gravity or urinary sediment. Elevation of the BUN was decreased in five cases to normal. One case approached normal, two had no further change and one patient with severe renal impairment had a further increase of the BUN after Mecamylamine therapy.

## VII. RECOMMENDED THERAPY OF ESSENTIAL HYPERTENSION[4]

1. Reassurance, weight reduction, mild sedation and deemphysis of the blood pressure in those with Grade I and IA hypertension.
2. If the disease is advancing and complications of progressive hypertension are becoming evident, the risk of therapy must be weighed against the prognosis.
   (a) Rauwolfia and/or Apresoline for less severe cases.
   (b) Mecamylamine in combination with Rauwolfia is the best treatment for severe, progressive cases.
3. In progressive cases having intolerable, uncontrolled symptoms from ganglionic block therapy should be considered for surgical sympathectomy.

## VIII. SUMMARY AND CONCLUSION

The problem of severe, progressive essential hypertension has been reviewed and likewise the agents available for treatment. The value of treatment has been considered. The physiology, pharmacology and clinical use of Mecamylamine (Inversive), a potent, oral ganglionic blocking agent, has been studied in the treatment of advanced, severe hypertension.

Treatment has been found life saving in the majority of malignant cases. It often arrests the progress of advanced disease and prevents progressive damage in milder disease.[15]

Mecamylamine (Inversive) seems the most reliable agent today for the treatment of severe, progressive hypertension. Its complete absorption from the gastro-intestinal tract seems to improve control of dosage and hypotensive effect. The lack of control over dosage was the main objection to Hexamethonium and Pentolinium, both of which are absorbed incompletely.

Combination with Rauwolfia seems to produce the best results with fewer side effects. Reasonably good results are obtainable in cases without severe renal damage and azotemia. When uremia is present, no agent has been found of much value and the disease usually progresses to a fatal outcome.

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