a "raised blood-pressure" repeated visits to hospital and blood-pressure measurements reassured him quite considerably.

We were not particularly impressed by the sedative or so-called "tranquillizing" action of the drug when given in the doses used by us.

From our experience in this clinical trial we felt that this was by far the most effective and useful orally administered agent for reducing blood-pressure which we have yet used. In our opinion this substance is fully worthy of a trial in every case of essential hypertension in which treatment is thought to be necessary. The severe cases, which always need treatment, are as likely to respond as the mild.

I am grateful for the constant help I received from my house-physicians and registrars, Mr. Williams, the hospital pharmacist, and the staff of the dispensary, as well as from Sister Willis and the nursing staff of the out-patient department of Oldchurch Hospital, while making these observations. This work would, however, never have been possible had it not been for the willing and active co-operation of all the hypertensive patients who have participated. I wish to thank Mr. J. A. Lumley and Riker Laboratories Ltd. for providing an adequate supply of rauwolfia extract and, later, total active alkaloids, control tablets, and *Veratrum viride* extract which enabled this work to be carried out. Finally, I am indebted to Dr. W. S. M. Grieve for many discussions and criticisms, and to my secretary, Mrs. E. D. Price, for her patience and excellent secretarial assistance.

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RESERPINE IN HYPERTENSION

BY

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Reserpine ("serpasil") is a colourless, crystalline, ester-alkaloid derived from the roots of *Rauwolfia serpentina*, crude and unstandardized preparations of which have been used in the treatment of hypertension for the past 20 years or so. It has a melting-point of 266 to 270° C., and its empirical formula, $C_{33}H_{40}O_9N_2$, contains a pentacyclic nucleus.

It is claimed that reserpine is a single entity and does not produce any of the undesired effects of the unknown alkaloids of the whole root, but possesses only its sedative and antihypertensive actions. The fall in blood pressure is characterized by a gradual beginning and a prolonged duration, and occurs in about two-thirds of all cases of essential hypertension, and may occur in renal hypertension and hypertension associated with hyperthyroidism. The desired effect is obtained even in severe cases and in cases of hypertension which have remained at a fixed level for a considerable time.

The fall of blood pressure is sustained, so that sharp fluctuations do not occur, and the effect may not disappear for several weeks after the drug has been discontinued. Experiments in anaesthetized cats show that

the hypotensive effect cannot be increased beyond a certain point despite the increase in dosage. This is taken to suggest that the drug acts mainly by protecting from abnormal tensile stimuli the autonomic nerve centres which regulate blood pressure. Postural hypotension has not been observed.

The fall in blood pressure is always associated with slowing of the pulse rate and, in some patients, with improved cardiac output. The depth of respiration is somewhat increased, but the rate remains more or less unaltered. Intestinal motility is increased in dogs but not in monkeys or rats. Diarrhoea may occur in human beings.

Reserpine produces a pronounced central sedative effect in cats, rabbits, and dogs. The animals remain quiet and sleep unless disturbed. The sedative effect is not a narcotic effect, and no electroencephalographic changes have been recorded in rats. It also does not protect against convulsant drugs. In man the lethargy is easily counteracted by caffeine or dextro-amphetamine sulphate in small doses. It occurs generally in the earlier stages of administration of larger doses, but even then it usually abates with time. Lower maintenance doses are well tolerated. In most patients there is subjective improvement associated with a sense of well-being.

The minimum lethal dose in rabbits and rats is about 10 mg. per kg., whereas its pharmacological effects are noticeable with doses of 1 µg. per kg. daily for five days. Thus the drug in recommended dosage (see below) has a wide margin of safety. In rabbits the prolonged administration of 0.1 mg. per kg. daily for 12 days or on alternative days for 24 days did not produce any changes in the heart, spleen, liver, kidneys, adrenals, stomach, or intestines. Side-effects in human beings with recommended dosage are mild and tolerable. They consist of nasal congestion—which is relieved by local vasoconstrictors—nausea, anorexia, more frequent or looser stools, headache, dizziness, heaviness of legs, and urticaria, which is relieved by antihistamines.

The initial therapeutic dose is 0.25 mg. three or four times daily, and is continued till the blood pressure falls. This occurs after a latent period, and the cause of delayed action is not known. Massive doses as used in acute experiments are not recommended. Subsequently the daily maintenance dosage may be 0.1 to 1 mg. Patients do not develop tolerance, and withdrawal symptoms do not occur. The drug is not habit-forming and there are no known contraindications to its use.

Literature

Recent clinical reports substantiate the above claims to varying extent. Löffler *et al.* (1953), using reserpine in doses varying from 0.75 to 1.5 mg. a day on 51 hypertensive patients, found that its hypotensive effect was insignificant in 27 and the blood pressure actually was higher than before in 6. In 14 the lowered pressure lasted only 12 days in spite of continued dosage, and in only 4 was the lower pressure sustained throughout the period of observation in hospital. Increase of dosage above 1.5 mg. a day did not increase the hypotensive activity, but it increased the incidence and severity of side-effects: 17 felt fatigued, 11 were depressed, 8 complained of heaviness of the limbs, 5 saw flickers in front of the eyes, 2 had bradycardia, 2 became mentally excited, 1 complained of dryness of the mouth, and 1 had miosis.

Vakil (1953) treated 25 cases with 0.5 mg. twice a day after meals for four weeks followed by a similar two-weeks course after an interval of a fortnight. After four weeks' treatment the systolic pressure dropped by 25 to 68 mm. Hg

in 11 cases, by 10 to 24 mm. in 7, and by less than 10 mm. in 3. In 1 case the systolic pressure was unaltered and 3 showed a rise of 2 to 16 mm. In 5 cases the diastolic pressure dropped by 15 to 26 mm., in 12 by 5 to 14 mm., and in 2 by less than 5 mm. Hg. In 2 cases it was unaltered and 4 showed a rise of 2 to 8 mm. During the two weeks' cessation of treatment, in 2 out of 19 cases the blood pressure fell further, in 9 it continued to remain at the lowered level, in 7 it rose but remained below the pre-treatment level, and in 1 case it returned to the original.

During the second course there was a drop in systolic pressure in 23 cases, but there was a rise in 2. There was a drop in the diastolic pressure in 21 cases, in 2 it remained unaltered, and in 2 it was higher than before. Both the systolic and the diastolic pressures fell in 19 cases. In 1 case, however, the systolic pressure rose and the diastolic pressure fell; the opposite occurred in another case. Four cases responded well to the first course but did not respond to the second; the opposite occurred in 2 cases. Side-effects were mild and infrequent: 4 had weakness, 3 suffered from excessive drowsiness, 2 had diarrhoea, 2 complained of anorexia, 1 had nasal congestion, 1 had frontal headache, and in 1 the existing vertigo was aggravated. Vakil concluded that a good result was likely in one-half to two-thirds of cases of systolic hypertension under 200 mm. Hg, and in practically all cases with pressures above 200.

Doyle and Smirk (1954) found that single doses of 2 or 3 mg. of reserpine by mouth produced a significant fall of blood pressure about four to six hours later. In 6 out of 9 patients the systolic pressure fell by 40 mm. Hg and the diastolic by 20 mm. or more. When 2 or 3 mg. was given thrice daily the blood pressure fell on the first or second day in 16 out of 20 patients. In all of these 16 cases the systolic fall was over 40 mm. Hg, and in 12 of them it was over 60 mm. The diastolic fall was over 25 mm. in 17 out of 20 cases, and more than 45 mm. in 7 of them. Some of the lowest pressures recorded were well below the basal blood-pressure levels. Slight postural hypotension was noticed when the blood pressure had fallen to normal or below normal levels. After discontinuance of the drug the blood pressure continued to remain at a significantly lower level for 12 to 24 hours. With these large doses, however, side-effects were severe. Combination with hexamethonium or pentolinium tartrate ("ansolysen") gave an additive effect, and the lowered blood pressure was more steady than with hexamethonium alone.

Douthwaite (1954) treated 12 cases of chronic benign hypertension with basal blood pressures ranging between 210/120 and 250/160 mm. They had symptoms of high blood pressure for five years or more and associated secondary cardiovascular changes; 2 had retinal haemorrhages and exudate. A sustained reduction of systolic pressure of 30 to 40 mm. and of diastolic pressure of 10 mm. was obtained with a daily dose of 4 mg. in 2 cases and with a daily dose of 8 mg. in 8 cases. Doses of 16 and 8 mg. were ineffective in 2 cases. Bradycardia occurred within three days of treatment, but had no relationship with blood-pressure readings. With a daily dose of 8 mg. 2 cases developed coarse tremor with occasional twitching of limbs, chattering of teeth, and mental distress.

Present Clinical Trial

Reserpine was administered to 24 patients with benign hypertension and to 2 with malignant hypertension. In addition it was given to 1 case of hypertension associated with chronic nephritis, to 2 cases associated with advanced arteriosclerosis, to 1 case associated with thyrotoxicosis, and to 3 cases associated with severe anxiety state.

One case of malignant hypertension and one case of chronic nephritis had advanced renal failure and characteristic changes in the fundus. The second case of malignant hypertension had early renal failure, tachycardia, cardiac asthma, and characteristic fundus changes. Eleven cases of chronic benign hypertension had associated cardiovascular changes, five of them had albuminuria with slightly impaired

renal function; five had fundus changes only, and one suffered badly from cardiac asthma.

Apart from two cases of malignant hypertension and one case of chronic nephritis, all patients were ambulant and went about their ordinary daily work. There were no restrictions in diet or salt intake. Blood-pressure readings were taken immediately the patient reported and subsequently every five minutes till they were constant for at least three readings. To begin with they were taken daily. Later, when the patients were stabilized, they were taken twice or thrice weekly.

All cases had already been under care for periods varying from two months to seven years. Their normal blood-pressure variations were therefore known. All previous treatment, if any, was reasonably discontinued before reserpine was tried. The initial dosage was 0.25 mg. three times a day for systolic pressures below 200 and 0.5 mg. three times a day for systolic pressures above 200.

Results

The effect of reserpine varied a good deal, and depended on the type of hypertension treated and individual susceptibility. The main results are summarized in Table I.

TABLE I.—*Effect of Reserpine Treatment in Various Types of Hypertension*

Type of Hypertension	Initial B.P.	No. of Cases	Fall of B.P. below				Maintenance Dose of Reserpine (mg./Day)
			145/90	160/100	170/110	185/115	
Benign	165/95 - 180/115	4	4	4	4	4	0.2 to 0.5
	180/90 - 200/115	10	7	10	10	10	0.3 to 1
	180/110 - 220/120	4	0	2	2	0	0.3 to 0.75
	170/100 - 240/140	4	1	0	0	3	0.75 to 1.5
	210/140 - 260/150	1	0	0	0	0	1.5
	140/230 - 150/290	1	0	1*	0	0	1.25
	125/165 - 130/250	2	0	0	0	0	1.5
	110/185 - 150/225	1	0	0	0	0	1.5
	165/70 - 265/95	2	1	0	0	1	0.75
	165/85 - 195/95	1	0	1	0	0	0.5
Anxiety state	165/165 - 185/105	3	1	2	0	0	0.5 to 0.75

* During periodic fluctuations the basal blood-pressure levels rose to 220/110-120 mm. Hg.

Response in Malignant Hypertension and Chronic Nephritis

With daily doses of 1.5 mg. it was not possible to lower the blood pressure appreciably in malignant hypertension and advanced chronic nephritis. The drop in systolic pressure varied from 20 to 50 mm., and in diastolic pressure from 5 to 25 mm. But these readings were almost within normal fluctuations before treatment, and the net drop did not exceed 20/10 mm. in any case. Gross fluctuations, however, appeared to be less frequent. In all these three cases it was possible to maintain more or less a constant blood pressure between 125/80 and 135/90 throughout the day along with hexamethonium bromide, 25 mg. intramuscularly three-hourly. With the same dose of hexamethonium bromide alone the fluctuations were greater and tolerance was often produced, the lowest readings varying from 125/85 to 170/100.

Response in Benign Hypertension

In benign hypertension it was possible to bring the blood pressure to normal or within reasonable limits in less severe

TABLE II.—*Effect of Reserpine Therapy on a Patient's* Blood Pressure*

Day:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	27	29	33	36	40	44	47	50	55	57
S. . .	180	185	180	175	170	140	150	145	130	140	140	130	135	125	120	125	125	138	120	120	135	125	170	130	125	135	125	130	125	150	130	125	150
D. . .	110	110	105	100	90	85	85	80	80	95	95	85	85	80	80	80	85	85	85	80	90	90	110	85	85	85	90	90	90	85	90	85	95
	0.75 mg. reserpine daily							0.3 mg. reserpine daily							0.75 mg. reserpine daily																		

S. = Systolic. D. = Diastolic.

* A man aged 38, height 5 ft. 11 in. (180 cm.), weight 198 lb. (90 kg.), with moderate cardiac hypertrophy and normal renal function. Fluctuations in blood pressure before treatment varied from 170/100 to 195/115 mm. Hg.

and less chronic cases, whereas in the more severe and more chronic cases the results obtained were similar to those obtained in malignant hypertension. Periodic fluctuations up to plus 45/20 mm. Hg continued to occur, and to keep the blood pressure at the lower levels the dosage had to be adjusted from time to time. In some individuals rises occurred at irregular intervals on any day for no obvious predisposing cause (Table II). To these fluctuations the rises associated with the ordinary day's work were additive.

Sometimes fluctuations chiefly affecting the systolic pressure also occurred when the patient was resting in bed. Owing to these variations it was impossible to record the basal blood pressure in such cases. These fluctuations during rest were especially noticeable a few days before the blood pressure started falling and during the transition period, when it was actually falling. The systolic and diastolic pressures were not necessarily always proportionately affected either during the transition period or finally when lowered—for example, a case with an initial blood pressure varying from 185/120 to 230/140 finally settled between 140/115 and 150/115, whereas another case with fluctuations between 170/110 and 185/110 settled between 120/80 and 160/100.

With the dosage employed the blood pressure started falling between the fourth and the nineteenth day and continued to do so amidst variations till the lowest level for a particular individual was reached. This took altogether from 9 to 40 days. In 5 out of 24 individuals there was a further fall of blood pressure after it had been more or less constant for periods varying from 6 to 20 days. With the dosage used, however, readings below 115/75 were not obtained in any case. Trials with higher doses at this stage were not undertaken. In seven cases which reached blood-pressure levels round about 120/80 the drug could be discontinued for 3 to 13 days before the blood pressure started to rise again.

The time taken for the blood pressure to fall and the decision whether reserpine could be discontinued for a few or more days were dependent on individual response and were quite unpredictable. It certainly did not depend on the initial blood-pressure level or the duration of the blood pressure, the emotional set-up of the individual, or his weight, age, or sex. For example, in a rather highly strung woman aged 34, who was known to have had hypertension for about two years, the initial basal blood pressure of 185/110 took 19 days to drop to 160/100, 25 days to drop to 130/90, and 40 days to drop to 125/85–90 with reserpine 0.75 mg. daily. Reserpine was discontinued when the blood pressure was 125/85–90, and she showed the first rise to 135/95 after 13 days. On the other hand, a man aged 38 with a similar blood pressure (180/110) for about the same duration, with the same dose, dropped to 130/80 in five days. He required a maintenance dose of 0.3 mg. of reserpine daily, but had a tendency to periodic rises every three to four weeks, during which he required a daily dose of 0.75 mg. The maintenance dose could not be omitted at all in this case, and a day's omission caused an immediate rise to 150/95 or more.

A case of myocardial infarction with two attacks within two years showed a poor response to 0.75 mg. of reserpine daily for 35 days. His blood pressure, which was initially 175/95 to 185/110, continued to fluctuate between 160/95 and 175/105.

In severe cases of benign hypertension in which reserpine alone was not very effective in lowering the blood pressure,

combined therapy with phenobarbitone, mannitol hexanitrate, and hexamethonium had the following effects: phenobarbitone did not aid, mannitol seemed to help, but hexamethonium compounds were very effective. In one case, in which the original basal blood pressure of 230/115 was reduced to 160/90 with reserpine, the equivalents were: 0.25 mg. of reserpine six times daily equalled 0.25 mg. of reserpine plus 375 mg. of hexamethonium bromide three times daily, equalled 50 mg. of hexamethonium bromide intramuscularly four to six times daily, and equalled 750 mg. of hexamethonium bromide six times daily by mouth.

Other Results

Response in Arteriosclerotic Hypertension.—In arteriosclerotic cases both systolic and diastolic pressures fell, as a result of which the pulse pressure still remained relatively high and symptoms such as giddiness, throbbing in the head, and insomnia, were only partially relieved. Day-to-day variations in pressure were greater than in cases of benign hypertension due probably to effects of arteriosclerosis itself.

Response in Hypertension with Anxiety State.—In hypertension associated with anxiety state gross daily fluctuations were mostly controlled, but maintenance doses were relatively high.

Effect of Ordinary Day's Work.—The effect of an ordinary day's work, so far as could be ascertained, showed that fluctuations in blood pressure were quite common when readings were recorded at different times of the day. The fluctuations affected the systolic as well as the diastolic pressures, and rises of 10–35/5–20 mm. Hg were seen. The tendency was to revert towards the pre-treatment basal levels, although usually the rise was not so great. The effect of subsequent rest varied. Some patients took a few minutes to return to pre-exertion levels, while others took two to three hours. For example, a man of 39 suffering from chronic benign hypertension of six years' duration with lowest pre-treatment basal blood pressure of 175/110 and with lowest basal blood pressure of 130/95 under reserpine, 0.75 mg. daily, showed rises up to 165/110, which took nearly three hours to revert to 130/95, whereas a woman of 45, suffering from chronic benign hypertension of about seven years' duration with lowest pre-treatment basal blood pressure of 170/120, and with lowest basal blood pressure of 130/90 under the same dose of reserpine, showed rises up to 140/110, which took only five minutes to revert to 130/90.

Effect of Standard Exercise.—In those patients who reverted to the pre-exertion levels within a few minutes of a standard exercise-tolerance test, reserpine *per se* did not influence the types of responses to exercise. The responses depended entirely on the blood-pressure levels. As the blood pressure fell the patterns described by Fowler and Guz (1954) progressively reverted towards the normal (see Table III).

Postural Hypotension.—Some degree of postural hypotension was present in nearly all patients, especially those with systolic blood pressure above 200 who received reserpine 1.5 mg. daily. The maximum difference recorded between pressures taken lying supine on a bed and sitting up on a chair was plus 20/15 mm. Hg. Under the influence of 1/50 gr. (1.3 mg.) of atropine intravenously this effect was abolished. But the change affected mostly the diastolic pressure, which rose to pre-treatment or almost pre-treatment levels. Thus in one case the blood pressure rose from 220/100 before atropine to 220/120 after atropine.

TABLE III.—*Responses to Standard Exercise at Various Blood-pressure Levels in a Case of Chronic Benign Hypertension Under Reserpine Treatment 1.5 mg. Daily. Blood-pressure Readings were Taken in Supine Position*

Initial B.P. Level	B.P. Levels at One-minute Intervals							
	0	1	2	3	4	5	6	7
225	195	205	235	230	225	220	215	210
100	105	100	100	100	95	95	105	100
190	215	215	220	212	200	192	185	185
90	100	100	100	100	95	95	95	95
160	195	190	180	175	165	160	155	155
90	95	95	90	90	85	85	85	80

Side-effects

The severity of side-effects was a matter of individual tolerance and the dosage of reserpine used. Nasal congestion, anorexia, dryness of the mouth, depression, muscular weakness, heaviness of limbs, giddiness, diminished vision associated with miosis, and drowsiness occurred with varying severity and frequency. They were more frequent and more pronounced when the dose of reserpine was above 0.75 mg. daily. However, it was possible to tell the patient confidently that these would abate with time. With doses below 0.75 mg. daily, most patients could tolerate the drug comfortably after a few days, usually less than a week. A chronic alcoholic did not complain of any side-effects with 1.5 mg. daily.

Under the influence of the drug slowing of the pulse rate from 20 to 36 beats was a consistent finding. In seven cases the pulse rate slowed down to between 46 and 52 a minute. In one case with a pre-treatment pulse rate of 48 to 52, however, no further reduction took place. It increased with exercise, but remained relatively low. The bradycrotic effect was completely overcome by atropine, 1/50 gr. (1.3 mg.) intravenously. This was less noticeable in the supine position and became maximum when the patient assumed the upright posture. The bradycrotic effect was also influenced by infection. In a patient who developed pneumonia the pulse rate rose from 68 to 110 a minute.

There was no direct relationship between the bradycrotic effect and the degree of fall of blood pressure. For example, in the case mentioned above, although the pulse rate remained constant between 48 and 52, the blood pressure fell from 230/125 to 160/90 with reserpine, 1.5 mg. daily. This patient also complained of precordial discomfort, which was not complained of before. An electrocardiogram showed a prolonged S-T interval. This was also the only change in six other individuals with bradycardia. The second case of malignant hypertension mentioned above, however, developed a silent posterior infarct during the course of treatment. This may be a coincidence, but it does raise a point whether the excessive bradycrotic effect along with the fall of blood pressure favours coronary thrombosis.

The excessive bradycrotic effect caused giddiness in three of the patients with pulse rates between 46 and 52.

When the initial side-effects began to pass off all patients showed subjective improvement. Among the symptoms that were most relieved were headache, giddiness, insomnia, palpitation, and worry. The subjective improvement was not always related to fall of blood pressure or the actual state of the patient, but also appeared to occur independently of them. Thus a patient with malignant hypertension and another with severe chronic benign hypertension who died had felt well during reserpine treatment. A gratifying side-effect was relief from constipation.

Conclusion

Reserpine is a useful drug in the treatment of all types of hypertension. It lowers the blood pressure to normal or to within reasonable limits in all cases of less chronic and less severe benign hypertension, and the same effect may also be obtained in some of the more chronic and severe cases.

In the remaining chronic and severe cases and in malignant hypertension subjective symptoms and early cardiac failure are relieved and treatment with hexamethonium is facilitated. The blood-pressure readings are more steady and the dosage of hexamethonium is lowered. This is a great advantage, as adverse effects of large doses of hexamethonium are avoided.

Summary

Thirty-three cases of hypertension were treated with reserpine—24 had benign hypertension, 2 had malignant hypertension, 1 was associated with chronic nephritis, 2 with arteriosclerosis, 1 with thyrotoxicosis, and 3 with anxiety state.

Fifteen patients whose basal systolic blood pressure at the time of treatment was above 200 mm. Hg were treated with reserpine 1.5 mg. daily. Eighteen patients whose basal systolic blood pressure was below 200 were treated with 0.75 mg. daily. In the former group 2 patients were reduced to below 145/90, 5 below 160/100, 7 below 170/110, and 10 below 185/115. In the latter group 12 patients were reduced to below 145/90 and 18 below 160/100.

More details in relation to previous fluctuations and diastolic pressures are given in Table I.

Lack of adequate response was associated with chronicity of hypertension and myocardial and/or renal failure.

Periodic fluctuations up to plus 45/20 mm. Hg continued to occur, and required suitable adjustment of dosage. In some subjects irregular rises of blood pressure of about the same degree occurred on any day. Fluctuations chiefly affecting the systolic pressure occurred in some patients during rest, and it was not possible to record the basal blood pressure in them. Rises associated with routine daily work varied from plus 10–35 systolic to 5–20 mm. diastolic. The tendency in these circumstances was to revert towards pre-treatment levels, but the rise was never so great.

The blood pressure started falling between the fourth and the nineteenth days, reaching its lowest in 9 to 40 days. Sometimes after being constant for a few days it fell further, but readings below 115/75 were not obtained. In some cases it was possible to discontinue the drug for 3 to 13 days before a rise started again.

Some degree of postural hypertension was present in those who received reserpine in doses of 1.5 mg. daily.

Appreciable additive effects with hexamethonium were obtained.

Side-effects occurred with varying severity and frequency, especially with doses above 0.75 mg. daily. Within a week or so, however, they either cleared or were tolerable. When the side-effects abated there was marked subjective improvement in most cases. Constipation had a tendency to be relieved.

In some patients the bradycrotic effect was very marked and precordial discomfort was complained of. Only a prolonged S-T interval was observed in the electrocardiogram.

The bradycrotic effect was abolished by atropine, but exercise had much less effect on it.

Atropine also abolished postural hypertension. The effect was mainly on the diastolic pressure.

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THE TREATMENT OF ESSENTIAL HYPERTENSION WITH PENTOLINIUM TARTRATE COMBINED WITH RAUWOLFIA ALKALOIDS

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The autonomic ganglion-blocking agent pentolinium tartrate (pentapyrrolidinium; "ansolysen") is acknowledged to be an effective agent in the control of hypertension (Smirk, 1953). Difficulties have been experienced in its continued use because of the unpleasant effects of its indiscriminate ganglion-blocking activity—for example, constipation, dry mouth, visual disturbances, etc.—which accompany the hypotensive activity. The rauwolfia alkaloids have been in extensive use in India for a variety of conditions for many years. Vakil (1949)

showed that the drug has hypotensive properties. It is a central sedative and also stimulates the smooth musculature of the intestinal tract. The combined use of a rauwolfia alkaloid (reserpine) with pentolinium tartrate was described by Smirk, Doyle, and McQueen (1954), who found that less of the latter was required and that the effect was more sustained. They recommend a method of control by these drugs.

We have used this method, and present a short series of cases in which stabilization had been achieved on pentolinium tartrate alone and which were later restabilized on that drug with the addition of rauwolfia alkaloids ("rauwiloid" 4 mg.), taken in a single dose each evening.

All the patients had essential hypertension. Their blood pressure before treatment varied from 300/160 to 240/130. None had evidence of renal involvement. The average dose of pentolinium tartrate when given alone was 840 mg. a day. The average daily dose of that drug when combined with rauwolfia alkaloids was 240 mg., a reduction of over two-thirds. One patient who required 440 mg. of pentolinium tartrate a day was restabilized on the combination with 60 mg. a day.

The corresponding decrease in the undesirable effects of the ganglion-blocking agent was very great, and some patients who had found it impossible to continue with pentolinium tartrate alone are now well stabilized and able to live active lives.

Discussion

The combined use of pentolinium tartrate and rauwolfia seems to offer a promising treatment of hypertension. In

Case No.	Sex and Age	B.P.	Clinical Features	Control by Pentolinium Tartrate Alone			Control by Pentolinium Tartrate and Rauwiloid		
				Daily Dose of P.T. (mg.)	B.P.	Results	Daily Dose of P.T. (mg.)	B.P.	Results
1	F 50	260/150	Dyspnoea	420	120/80	Tired and faint	120	140/80	Doing full-time work
2	F 50	280/150	Cerebral encephalopathy. Congestive failure	720	170/100	Intolerably dry mouth and constipation. Blurred vision	60	170/90	Dryness of mouth slight only. Regular bowel action
3	F 63	290/130	Dyspnoea. Headaches	540	240/120	Constipation	60	200/100	Normal bowel action
4	F 59	260/150	Dyspnoea. Retinal sclerosis	480	140/80	Postural hypotension. Constipation	120	150/110	Feeling well
5	F 62	260/135	Congestive failure. Gross cardiac enlargement	120	200/100	Blurred vision. Constipation	Rauwiloid alone	190/90	Symptom-free
6	M 48	260/150	Headaches. Visual failure. Gross retinal sclerosis	840	190/125	Refused further treatment. Dry mouth. Constipation. Postural hypotension	420	135/90	Bowels easily controlled. At work
7	F 56	280/170	Cardiac asthma	Hexamethonium bromide, oral 1,500	240/140	Dry mouth. Constipation. Postural hypotension	240	190/110	Mouth not dry. Constipation easily controlled. No faintness
8	F 66	250/140	Dyspnoea	900	150/100	Dry mouth. Postural hypotension	120	170/105	Mouth less dry. No postural hypotension
9	F 63	290/150	Dyspnoea, visual failure	240	220/140	Refused further treatment	120	190/110	Minimal side-effects
10	M 59	290/150	Angina. Heart grossly enlarged	600	200/115	" "	300	210/110	Less constipation
11	F 55	270/170	Subarachnoid haemorrhage. Encephalopathy. Gross cardiac enlargement	960	170/110	Postural hypotension. Dry mouth. Constipation. Blurred vision	720	190/110	Constipation easily controlled
12	F 40	225/140	Congestive failure	360	190/130	Intolerant of higher dosage	120	180/110	Tolerable side-effects. At work
13	F 60	230/140	Dyspnoea. Retinal sclerosis	360	180/120	Postural hypotension	240	200/110	Tolerable side-effects
14	F 39	300/160	Dyspnoea. Visual failure	720	220/120	Refused further treatment	240	160/90	Minimal side-effects. At work
15	F 49	270/150	Cardiac enlargement	1,020	190/110	Dry mouth. Blurred vision. Constipation	360	190/105	Less constipation. Feels very well
16	F 48	240/130	" "	720	170/110	Dry mouth. Constipation. Fainting	300	190/110	Less constipation. Mouth not dry. Feels well
17	F 48	250/140	Visual failure. Congestive heart failure	900	150/100	Dry mouth. Fainting	360	160/115	Mouth not dry. Less tendency to faint

P.T. = Pentolinium tartrate.