

CLINICAL AND EXPERIMENTAL EFFECTS OF RESERPINE IN PATIENTS WITH ESSENTIAL HYPERTENSION

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Since our studies on the acute effects of single dosages of parenteral reserpine are still in the exploratory stages, it should be clearly understood that the results reported here are not to be taken as definitive but rather as tentative and preliminary observations. In the early stages of this investigation, we failed to observe significant hypotensive effects until we reached a dosage range of 25 μg . per kgm. or higher. Hence, in the 19 hospitalized hypertensive patients reported here, 4 received dosages of 25 μg . per kgm. and the remainder 40 μg . per kgm.; in other words, approximately 2.5 to 3 mgm. as a single intravenous dose. This came dissolved in approximately 5 cc. of propylene glycol and was further diluted with 125 cc. of normal saline. The resulting solution was given intravenously over a period of 10 to 15 minutes. Five normotensive patients were treated similarly, also.

All of the 19 hypertensive patients exhibited Grade I to II changes in the optic fundi and were suffering from hypertension of moderate severity. FIGURE 1 shows the reductions of blood pressure observed in this group. In four there was less than 10 per cent reduction of "mean" $\left(\frac{\text{systolic plus diastolic}}{2}\right)$ arterial pressure, and in 12 there were moderate reductions of mean arterial pressure of 10 to 25 per cent. In only three patients were marked reductions of blood pressure observed varying between 25 and 35 per cent. The average reduction of mean arterial pressure for the entire group was 14.5 per cent. It is interesting that, in no instance, did the blood pressure fall to collapse levels and none of the patients complained of faintness or weakness.

The hypotensive response was delayed in the 15 patients who exhibited a reduction of blood pressure. Maximum hypotension occurred between one and two hours in six patients, between two and three hours in five patients, and between three and four hours in four. The duration of the hypotensive effect was quite variable; but in most instances in which observations were made, the blood pressure would begin to increase after the fifth hour and, in most instances, had disappeared completely at the end of 24 hours. Five normotensive patients also were given reserpine in dosages of 40 μg . per kgm. Three of these patients showed reductions of mean arterial pressure varying between 13 and 20 per cent. Thus, the hypotensive effects of the drug are not limited to patients with hypertensive diseases.

A significant decrease in heart rate was uncommon after acute intravenous administration of the drug (FIGURE 2). Only 4 patients exhibited reductions of heart rate greater than 10 beats per minute at the time that the drug was having its maximum hypotensive effect. Bradycardia has been reported to occur commonly with crude extracts of the drug or whole powdered root administered orally. Our failure to observe significant or frequent bradycardia

suggests the need for further studies to determine whether this is due to the experimental methods employed or to the presence in the crude drug of a factor other than reserpine which produces bradycardia.

A definite flushing of the skin which was not noted after oral reserpine was seen in 14 of the 19 patients given the drug intravenously. The flushing was marked in seven patients and was seen over the entire body. Dilation of conjunctival vessels accompanied the erythema of the skin (FIGURE 3). The flush usually was most intense approximately one hour after reserpine had been administered, sometimes preceding the fall of blood pressure, but in a few patients the erythema reached its peak in two or three hours.

Stuffiness of the nose also occurred at this time. It was present in eight patients and was severe in four. Our previous experience with the oral drug indicated that nasal stuffiness could be relieved by administering antihistaminics, either by local intranasal nebulization or by oral administration. For this reason, it occurred to us that perhaps the flushing of the skin and congestion of the conjunctiva and nasal mucosa may all be due to the release of histamine, and, therefore, reserpine may in addition to its other actions

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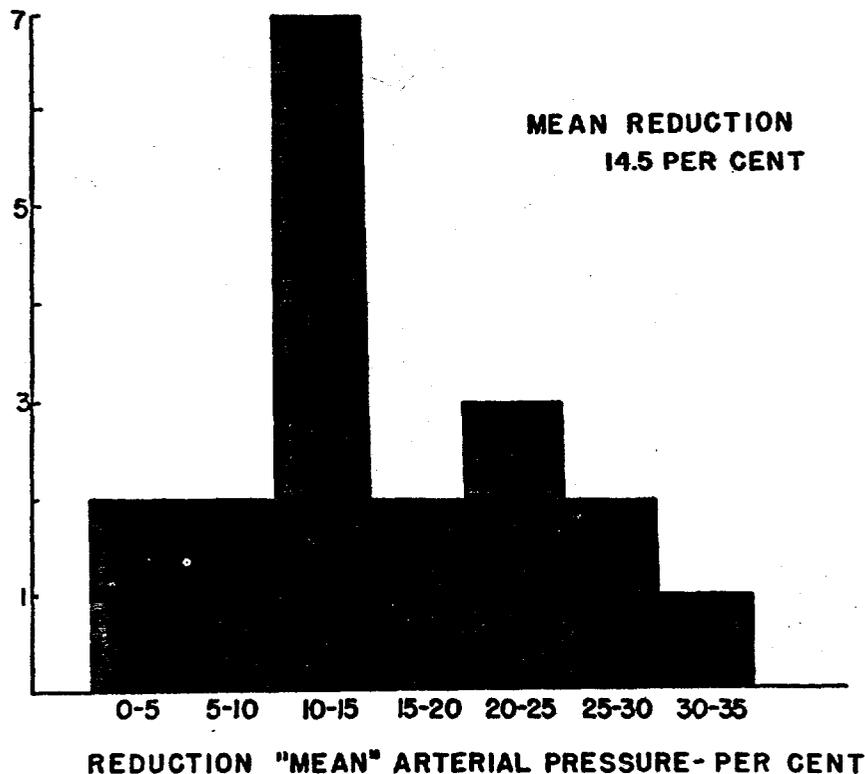


FIGURE 1

fall into that group of compounds known as "histamine liberators." The intravenous injection of tripeleannamine hydrochloride (Pyrebzamine) at the height of the flush in a few cases suggested that the erythema receded more quickly. However, in later experiments we were unable to prevent the development of erythema by pretreating the patient with 100 mgm. of Pyrebzamine orally and 50 mgm. of diphenhydramine hydrochloride (Benadryl) intravenously at the time of administering reserpine. Therefore, we are unable to demonstrate that vasodilation of skin, and conjunctival and nasal mucosal blood vessels is due to release of histamine. Injection of the propylene glycol alone without reserpine fails to induce any of these effects.

Various preliminary studies have been carried out to determine whether reserpine has any adrenergic blocking properties. Although studies have not yet been carried out in a constant-temperature room, digital skin temperatures were measured in 10 patients, but failed to show any consistent or significant changes. The overshoot of blood pressure following the Valsalva maneuver was not significantly inhibited after reserpine (FIGURE 4). It should be pointed out, however, that these dosages were at the 25 μ g. per kgm. level and further studies are necessary at higher dosages of reserpine. Marked postural

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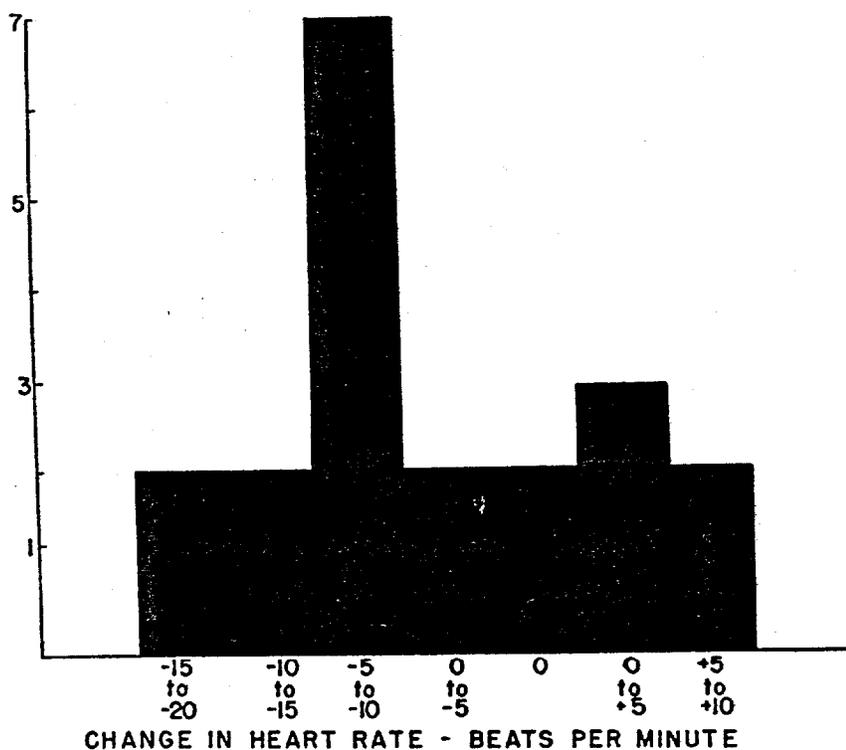


FIGURE 2



FIGURE 3

hypotension, such as is seen after the ganglionic blocking agents, was not observed in these patients. It is of interest, however, that nine of the 19 patients on standing erect showed a reduction of systolic pressure but not of diastolic that was greater than the systolic fall observed in the erect position during the control. The systolic hypotension, however, was not of the degree seen following the exhibition of the adrenergic blocking agents. In contrast to observations made in animals, the pupils did not change significantly in size. Thus, these various observations fail to indicate that reserpine inter-

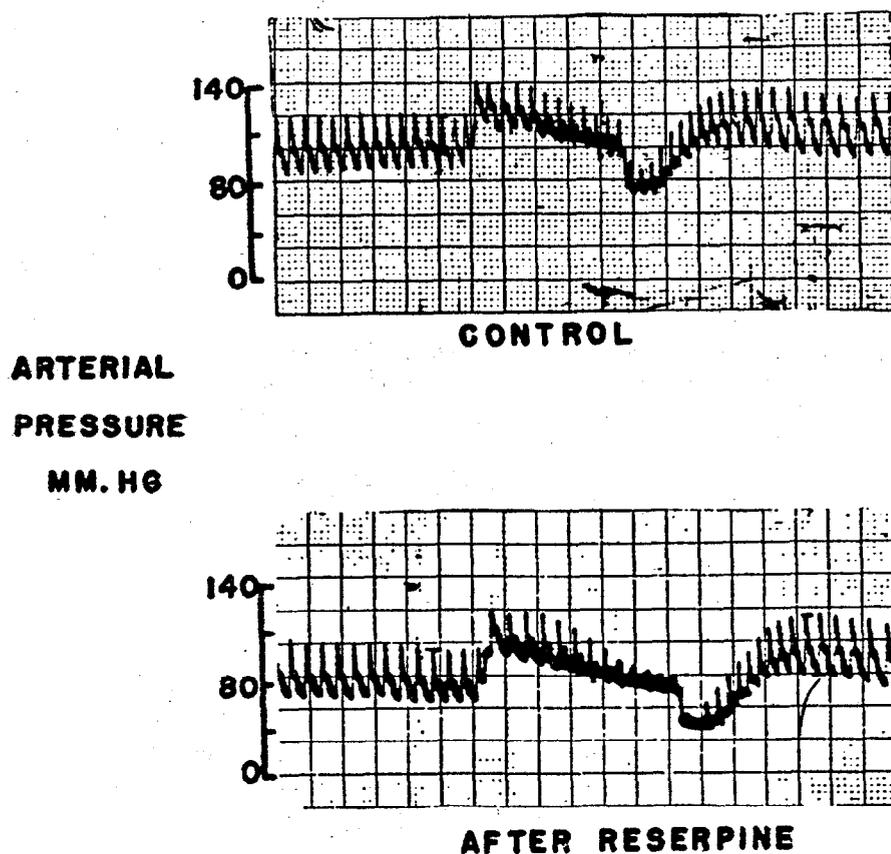


FIGURE 4

feres markedly with the normal activity of the sympathetic nervous system, although a slight or moderate inhibition has not yet been ruled out.

Because of the suggestion that reserpine may act on hypothalamic centers, we were interested in determining whether the drug had any effect on body temperature. Oral temperatures were recorded before and for several hours after the drug in seven patients while rectal temperatures were obtained in three cases. In the seven patients in whom oral temperatures were recorded, one showed a fall of 0.3° while the others exhibited a rise of 0.1° to 1.0° (mean, 0.3°). Since the tests were begun in the morning, the trend toward slight elevation of oral temperature could be explained by the usual diurnal variation of body temperature; that is, the tendency for body temperature to rise during the late morning hours. In the three patients in whom rectal temperatures were recorded, a slight elevation occurred in two and a slight decrease in one, all variations being within the normal range.

When questioned directly, eleven patients commented on slight drowsiness

and a few dropped off to sleep. However, these latter patients usually napped during the day. Certainly, a marked hypnotic action was not apparent.

To summarize these observations on acute intravenous administration of reserpine, the effective dosage range as found originally by Gross and his co-workers in animals is 25 μg . per kgm. or higher. Dosages as high as 40 μg . per kgm. may not produce a reduction of blood pressure in resistant patients, but in most individuals are followed by moderate reductions of blood pressure. Severe hypotension has not occurred in this small series.

Bradycardia was unusual after intravenous administration, but erythema of the skin and congestion of the bulbar conjunctiva and nasal mucosa were common. Only the nasal stuffiness could be relieved by antihistaminic agents. We have not yet demonstrated marked inhibition of sympathetic vasoconstrictor reflexes, but slight or moderate inhibition has not been ruled out. Body temperature did not seem to be significantly altered in man in the dosage ranges employed.

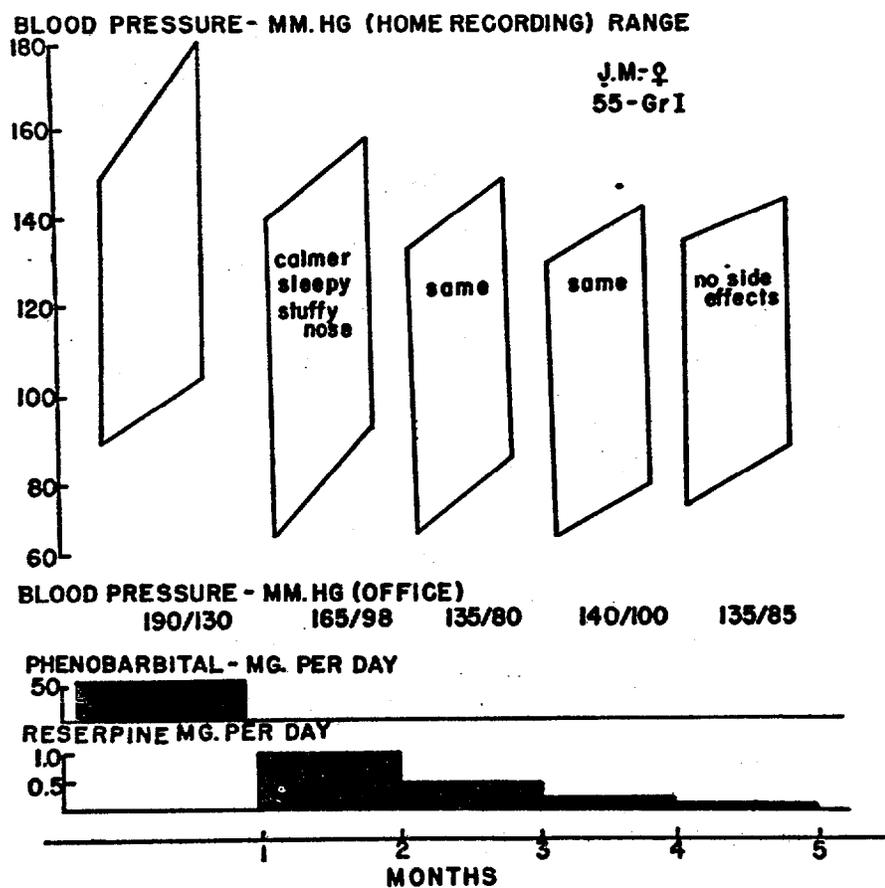


FIGURE 5

In regard to the use of reserpine clinically, our results are in essential agreement with previous reports by Wilkins and others. Not only the reserpine produced by the Ciba group, but also those of the Squibb and Riker investigators, all seemed to have about equal activity. In addition, providing that we used sufficient dosage, our clinical results seemed to be as good with the cruder preparations as they were with reserpine. Our average initial effective dose was 1.0 mgm. per day. At this dose level, significant hypotensive effects were seen at times as soon as 48 hours after beginning therapy. After several weeks of therapy, however, it was possible to reduce the dosage to 0.2 to 0.5 mgm. per day. As has been the experience of others, reserpine alone seemed to be most effective in mild, labile hypertension and, even in this group, slightly more than half were not satisfactorily controlled. The following case represents a successful result (FIGURE 5). This is a white female, age 55, with essential hypertension. The optic fundi were Grade I, and there was no cardiac enlargement. Routine renal function tests were normal. The blood pressure recorded in the office while the patient was taking phenobarbital was 190/130 mm. Hg, but frequent recordings taken by the nurse at the government in-

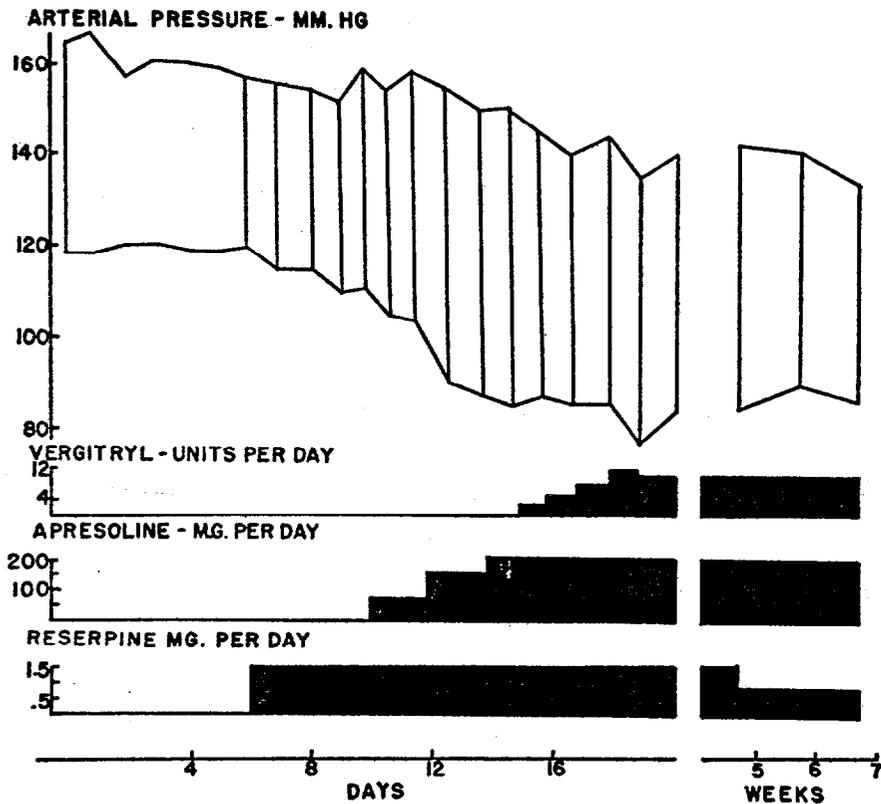


FIGURE 6

stallation where the patient worked were considerably lower, ranging between 150-180/90-105 mm. Hg. Reserpine was begun in a dose of 0.5 mgm. twice daily with a fall of blood pressure to the near normal range. The patient noted that she felt calmer but complained of sleepiness and a stuffy nose. The dosage was reduced progressively and, by the fourth month, was only 0.25 mgm. per day. At this dosage level, the side effects disappeared but the blood pressure remained normal. Although it is not shown on this chart, treatment with reserpine was discontinued five weeks ago and the blood pressure has remained within the normal range. This tendency in the mild cases for the blood pressure to remain at a lower level for a considerable period after discontinuing the drug makes evaluation of therapy difficult with such techniques as alternating periods of administering drug and placebo.

In the majority of cases of moderately severe and severe hypertension, however, and as originally noted by Wilkins, reserpine has been of more value in

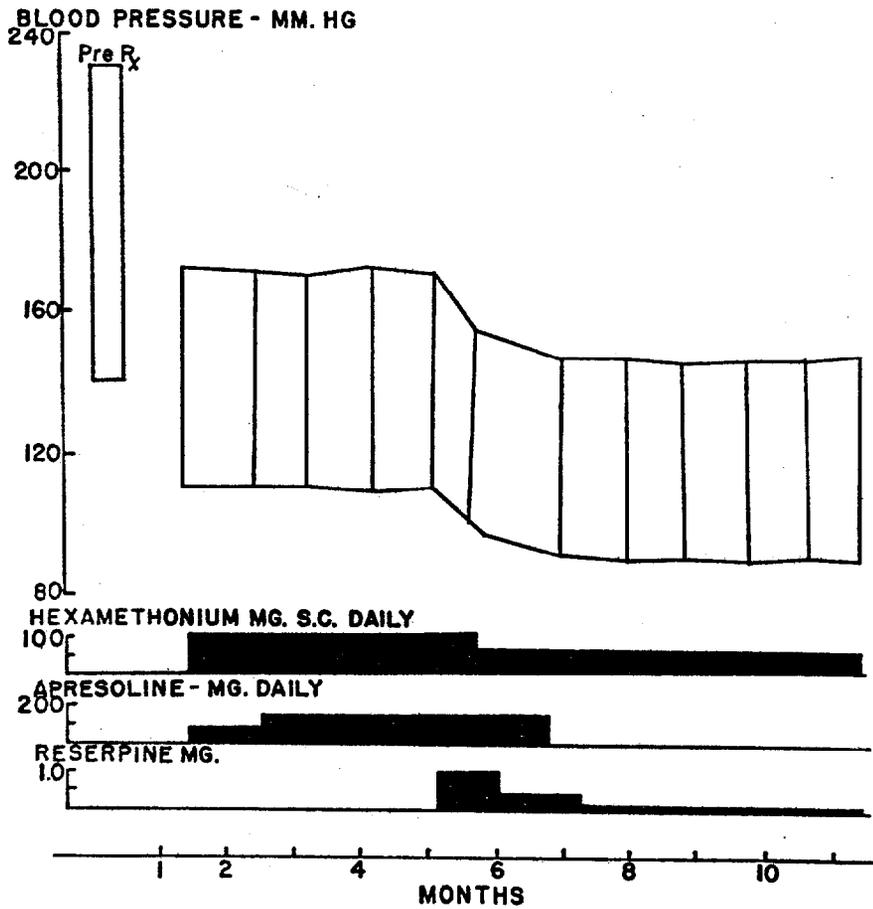


FIGURE 7

conjunction with other agents than when used alone. The patient whose response is charted in FIGURE 6 is an example of combining reserpine, 1-hydrazinophthalazine, and *Veratrum viride* in a patient with moderately severe hypertension. This was a 22-year-old white male with a persistent elevation of diastolic blood pressure to 120 mm. Hg even with home and hospital recordings of blood pressure. The fundi showed Grade II changes. Cardiac and renal functions were essentially normal. In this case, reserpine was begun first because of its tendency to counteract the tachycardia and palpitation produced by Apresoline. During the past six months of observation, this patient's blood pressure has been maintained at normotensive or nearly normotensive levels and he has no side effects.

The final case (FIGURE 7) illustrates the additive effect of reserpine with the ganglionic blocking agents. This is a 34-year-old white male who had Grade IV changes in the optic fundi. With subcutaneous hexamethonium administered twice daily and oral Apresoline the blood pressure fell from average values of 230/140 to 170/110 mm. Hg. Home but not office blood pressures showed that the hypotensive effect continued and the fundi regressed from Grade IV to Grade I. After five months, reserpine was added with an immediate further reduction of average blood pressure to 150/90 mm. Hg. It was possible to discontinue Apresoline entirely and reduce the dosages of hexamethonium and reserpine. Experience has shown that a relatively high percentage of patients show an additive hypotensive response when reserpine is added to the ganglionic blocking drugs.

To summarize the clinical data, it would seem that *Rauwolfia* and the pure alkaloid reserpine are agents of relatively low hypotensive potency. However, because of their freedom from severe side effects and ease of administration they may be useful in some cases of mild hypertension and, because of their additive effects, may be of value as an adjunct to other more potent drugs in the treatment of moderately severe and severe hypertension.