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17 October 1960

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ON RENAL HEMODYNAMICS IN HYPERTENSION

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THE EFFECT OF RAUWOLFIA ALKALOIDS
ON RENAL HEMODYNAMICS IN HYPERTENSION

Following is the translation of an article by P. I. Mishchenko entitled "Vliyaniye Alkaloidov Rauvol'fii na Pochechnuyu Gemodinamiku pri gipertonicheskoy Bolezni" (English version above) in *Terapevticheskiy Arkhiv* (Therapeutic Archives), Vol 32, No 5, Moscow, 1960, pages 7-12.

From the Chair of Propedeutics of Internal Diseases (Head -- Professor A. M. Damir) of the Second Moscow Medical Institute imeni N. I. Pirogov

The role of the renal-ischemia factor in the pathogenesis of hypertensive disease is undoubted. Therefore, it is understandable that it is important to clarify how the new hypotensive agents influence the renal blood flow and the renal filtration. The latter assumes special significance in the late stages of hypertensive disease.

From experience in treating hypertensive disease with modern hypotensive agents it is well known that the reduced

arterial pressure achieved thereby is not uncommonly associated with an improvement in the renal circulation (A. Kh. Adyrkhayev, Reubi, Stunkard and Eurman, Mader and Iseri and others). There are very few studies devoted to the influence of rauwolfia alkaloids on the functional state of the kidneys (blood flow and filtration), either foreign or Soviet.

Such authors as Moyer and others, prescribing reserpine by mouth for prolonged courses of treatment, noted various effects of it on the renal circulation, whereby Moyer, as well as Andrea and Smith believe that rauwolfia alkaloids do not exert any direct effect on the renal hemodynamics. In four out of seven patients with hypertensive disease treated with reserpine Wothinger noted an increase in the renal blood flow; in three, a reduction of it. Reubi and co-workers found a noticeable reduction in the renal circulation (in four it was unchanged) after the intravenous infusion of 3-7.5 milligrams of reserpine which was accompanied by a marked and rapid fall in the blood pressure. The reduction in the renal blood flow following intravenous infusion of large doses of reserpine (0.025-0.05 milligrams per kilogram of weight) has been noted in patients with hypertensive disease also by Krogsgaard, whereas Corcoran and Page

published examples demonstrating a considerable improvement in the functional condition of the kidneys (blood flow and filtration) as the result of the use of hexamethonium, serpasil and other new hypotensive agents in malignant hypertension. They consider the considerable improvement in renal hemodynamics the result of a reduction in blood pressure and emphasize that it is possible to achieve an improvement in the renal circulation even in patients with pronounced nephrosclerosis.

Dutz and Voigt, in experimental hypertension, also noted not only a hypotensive effect of reserpine but also a vasodilating influence of it on the renal arterioles.

Lanz and Hochuli studied the condition of the renal circulation after a single use of reserpine depending on the rapidity and degree of fall in the blood pressure. According to their observations, a slow reduction of it to a certain degree leads to an improvement in the renal circulation; a considerable reduction may cause a reflex spasm of the renal blood vessels, which worsens their blood supply.

Rauwolfia alkaloids, according to some authors (N. A. Ratner and others), have a beneficial influence on the renal hemodynamics; according to others (Andrea and others and

Dennis) use of them not only does not bring about any change in the renal hemodynamics but can even impoverish them.

We also made a study of the effect of rauwolfia alkaloids on the renal blood flow and filtration of the kidneys in patients with hypertension. In all, 88 patients were examined; of these, 41 were men and 47 were women. In eight the disease was in the first stage; in 70, in the second stage; and in 10, in the third stage. With respect to age, the patients were distributed as follows: from 17 to 50, 41 persons; from 51 to 60, 38; and over 60, nine persons.

In all the patients we found the value for glomerular filtration and reabsorption by the endogenous creatinine, and we determined the renal circulation dynamically by means of diodrast.

Treatment with rauwolfia alkaloids was begun after an appropriate clinical examination of the patients for three to five days. Chiefly, reserpine or serpasil was used, and only individual patients were given raupine [hypotensive alkaloid isolated from *Rauwolfia serpentina*] and hendone. Reserpine and serpasil were prescribed in tablets in a dose of 0,25 milligram per day and, if the patient tolerated the preparations well, the dose was gradually increased to three-six or more tablets a day,

that is, the 24-hour dose varied from 0.75 to 1.5 milligrams, and individual patients received two milligrams. The course of treatment lasted three to four weeks. Side effects occurred rarely in treatment with rauwolfia alkaloids.

As has already been mentioned, there were eight patients with hypertensive disease stage I. In some of them, there was a slight enlargement of the heart to the left. The blood pressure before treatment was, on the average, 145/90 millimeters of mercury. The optic fundus was normal. Clinical analysis of the urine and the Zimnitskiy test [concentration] did not show any abnormalities.

The renal circulation proved to be decreased in five out of eight persons and, on the average, amounted to 481.2 cubic centimeter/minute; in three persons it was within normal limits (763 cc/minute).

After treatment the renal blood flow increased to normal (761 cc/minute) and even higher not only in patients in whom it had been decreased but also in those in whom it had been normal (1037 cc/minute). The value for the glomerular filtration in three patients before treatment was normal (94-104 cc/minute), and in five persons it showed a tendency toward an increase (126-172

cc/minute). After treatment it proved to be normal in all patients. Resorption was normal both before and after treatment. Increase in the renal blood flow to normal or higher and the reduction in glomerular filtration to normal usually coincided with a reduction in the blood pressure to normal, as is seen in Fig. 1.

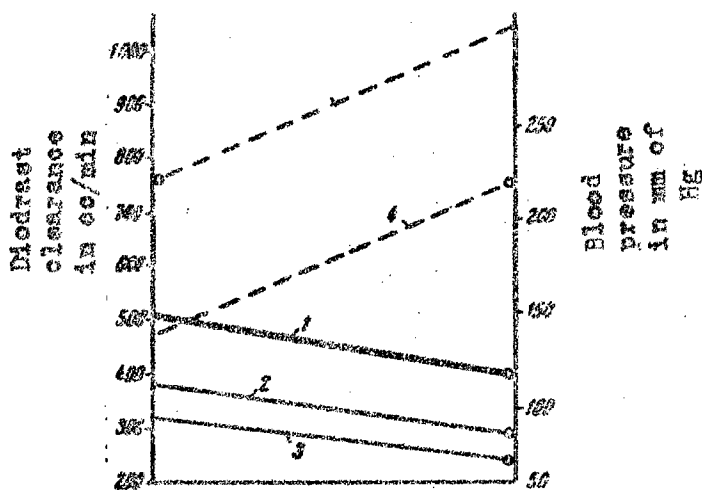


Fig. 1. Change in Renal Blood Flow and Blood Pressure in Patients with First-Stage Hypertension Treated with Rauwolfia Alkaloids:

1--systolic pressure; 2--mean pressure; 3--diastolic pressure; 4--renal blood flow. On the left, before treatment; on the right, after treatment. The normal indices are designated by circles.

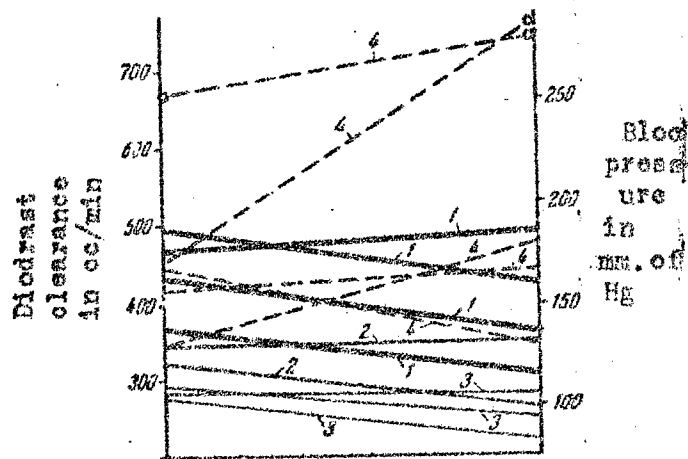


Fig. 2. Change in Renal Blood Flow and Blood Pressure in Patients with Second-Stage Hypertension Treated with Rauwolfia Alkaloids.

The key is the same as for Fig. 1.

Therefore, in patients with hypertensive disease in the stage of functional vascular disturbances the rauwolfia alkaloids

apparently not only eliminate the total peripheral resistance but even, simultaneously, reduce the tone of the renal blood vessels, which can lead in its turn to normalization of the renal circulation and glomerular filtration along with a reduction in the total blood pressure.

In 70 persons the hypertensive disease was in the second stage. The blood pressure varied from 140/100 to 220/130 millimeters of mercury. In patients of this group cardiac and aortic changes characteristic of the second stage were found. In 65 out of 70 changes were found in the optic fundus (Salus I and II). Clinical signs (inconstant albuminuria, microhematuria, casts in the urine, as well as nycturia) of kidney involvement were found in 50 out of 70 patients.

The renal blood flow before treatment was reduced in the majority (56) to 547.8-240 cc/minute, and it was normal in only 14. After treatment, it increased to normal (753.1 in place of 451.4 cc/minute) in 25 patients; increased by 56-289.2 cc/minute and, on the average, reached 471.9 in place of 346.6 cc/minute before treatment in 20; remained almost unchanged (418.4-439.4 cc/minute) in nine; and decreased by 51.2-159 cc/minute in two patients.

The influence of rauwolfia alkaloids on the renal circulation is shown particularly clearly in the younger patients with the shorter histories. The renal blood flow in them increased markedly or rapidly reached normal, whereby the increase of it in the great majority of patients (33 out of 45) coincided with a gradual reduction in the blood pressure or normalization of it (Fig. 2). Similar data have been obtained by N. A. Ratner and Yu. D. Vadkovskaya, S. K. Kiseleva.

Ten patients in this group deserve special attention; in them, after treatment with rauwolfia alkaloids the blood pressure was practically unchanged, whereas the renal circulation increased, and in four out of the 10 it reached normal (Fig. 3). These observations speak for the fact that the circulation in the kidneys is improved not only because of the reduction in the blood pressure but also apparently because of the capacity of the rauwolfia preparations of dilating blood vessels of the kidneys earlier and more markedly than the peripheral blood vessels, and this is very important in the treatment of hypertensive disease. At the same time, in nine patients after treatment with rauwolfia alkaloids the renal circulation remained reduced with a normal blood pressure in four and an elevated blood

pressure in five (Fig. 4). These observations indicate a more persistent renal ischemia which occurred in connection with more profound changes in the renal blood vessels. Apparently, it is not always possible to eliminate it with such new hypotensives as the rauwolfia alkaloids.

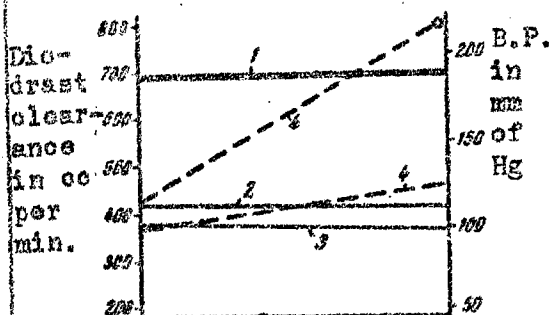


Fig. 3. Change in the Renal Blood Flow and Blood Pressure in 10 Patients with Second-Stage Hypertension Treated with Rauwolfia Alkaloids.

Key is the same as for Fig. 1.

Glomerular filtration in patients with hypertensive disease, stage II, was normal both before and after treatment, except for 11 persons in whom a tendency was noted toward an elevation (124.6-172 cc/minute). This increase was usually encountered in younger patients who had had the disease for a shorter time. After treatment the glomerular filtration decreased to normal

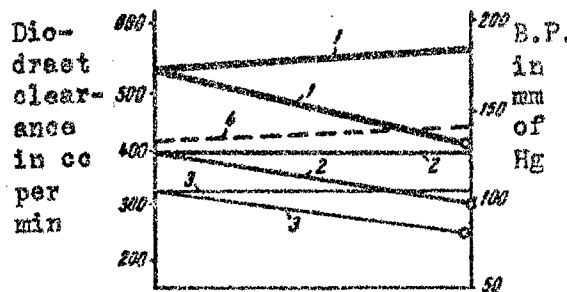


Fig. 4. Change in Renal Blood Flow and Blood Pressure in Nine Patients with Hypertension Treated with Rauwolfia Alkaloids.

Key is the same as for Fig. 1.

figures in those in whom it had been elevated.

Tubular resorption was within normal limits both before and after treatment.

Therefore, among patients with second stage hypertensive disease the renal blood flow in the great majority increased considerably, and in many reached normal after treatment with rauwolfia alkaloids; the glomerular filtration dropped to normal if there had been a tendency toward an increase before treatment; in the majority, it varied within normal limits; resorption was normal both before and after treatment.

Ten persons from 44 to 63 years of age suffered from third stage hypertensive disease. In them, the blood pressure varied from 150/100 to 250/140 millimeters of mercury. In this group cardiac and aortic changes characteristic of hypertensive disease were also noted. In eight persons definite changes in the optic fundus were also found. Clinical symptoms of renal involvement (slight, almost constant albuminuria, microhematuria, and casts in the urine) were found in nine persons. The specific gravity of the urine varied within normal limits. In all patients there was nycturia. The renal circulation proved to be reduced in eight out of ten patients, whereby it was moderate (to 494-420 cc/minute)

in five and marked (to 342.9-110.5 cc/minute) in three. In two patients the renal circulation was normal (647 cc/minute).

After treatment the renal blood flow increased in seven patients (on the average, to 437.8 cc/minute instead of 340 cc/minute before treatment), and in one it even reached normal (629 instead of 494 cc/minute). In two patients with a normal renal blood flow it also increased, on the average, by 161.8 cc/minute, as seen in Fig. 5.

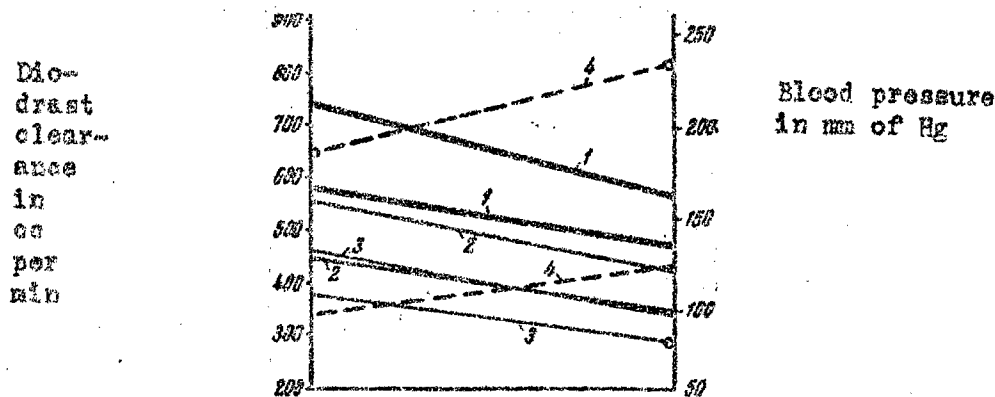


Fig. 5. Change in Renal Blood Flow and Blood Pressure in Patients with Third-Stage Hypertension Treated with Rauwolfia Alkaloids.

Key is the same as for Fig. 1.

Even in this group of patients a definite increase in the renal blood flow was noted in the younger patients. As far as the glomerular filtration is concerned it was almost normal both

before and after treatment, with the exception of three patients in whom a tendency was shown toward a reduction (65-60 cc/minute).

As in the early stages of hypertensive disease the resorption did not deviate from the normal. Therefore, in the great majority of patients with hypertensive disease, stage III (seven out of 10) the renal circulation was reduced both before and after treatment, which indicates more persistent changes in the renal blood vessels.

In comparing the value of the effective renal blood flow with the blood pressure before and after treatment with rauwolfia alkaloids, we found a parallelism between these figures only in the first stage of hypertensive disease. In the patients of this group there was a gradual reduction in the blood pressure and an increase in the renal blood flow. Among patients with hypertensive disease, stage II, the reduction in the blood pressure and increase in the renal circulation were noted only in 33 out of 45. In 10 patients of this group the renal circulation increased and even became normal with a high blood pressure; in 9 patients, conversely, the blood pressure decreased in the presence of an almost unchanged renal blood flow.

In the third stage we did not find any parallelism either between

the reduction in blood pressure and the increase in the renal circulation. Lanz, Hochuli, Trapold, Plummer and Fonkman did not find any parallelism either between the reduction in blood pressure and the increase in the renal blood flow.

Thus, our observations show that in the great majority of patients with hypertensive disease following treatment with rauwolfia alkaloids the blood pressure gradually decreases, and the renal blood flow increases and frequently reaches normal. However, in a number of patients the renal blood flow can increase and even become normal in the presence of a high blood pressure. These data speak for the fact that the renal hemodynamics is improved not only because of reduction in the arterial pressure but also, apparently, because of the capacity of the rauwolfia alkaloids for dilating the renal blood vessels much earlier and more markedly than the general hypotensive effect. Therefore, we cannot agree with Moyer, Andrea and Smith that the rauwolfia alkaloids do not exert any direct effect on the renal hemodynamics.

In generalizing on our own observations and the opinions of a number of Soviet and foreign authors, we may conclude that the new hypotensive agents such as rauwolfia alkaloids have a

beneficial influence on renal hemodynamics and therefore are indicated in hypertensive disease. Use of them in the majority of patients, by producing a gradual reduction in blood pressure not uncommonly to normal, improves the renal circulation, and this can stop the progress of hypertension and possibly lead to a regression of it.

Conclusions

1. In patients with stage I hypertensive disease following treatment with rauwolfia alkaloids the renal blood flow and glomerular infiltration become normal.
2. In hypertensive patients with stage II hypertension following such treatment the renal circulation increases frequently to normal, and some remains persistently reduced and even decreases persistently. The glomerular filtration in almost all the patients is within normal limits.
3. In patients with hypertensive disease, stage III, following treatment there is a slight increase in the renal blood flow and only in some of them does it become normal. The glomerular filtration varies within normal limits.
4. The increase in the renal blood flow in the majority of patients with hypertensive disease coincides with a gradual

reduction or normalization of the blood pressure.

5. The increase in the renal blood flow or normalization of it with a high blood pressure indicates the fact that rauwolfia alkaloids dilate the renal blood vessels sooner and more markedly than the general hypotensive effect produced by them occurs.

6. Resorption both before and after treatment was within normal limits at all stages of hypertensive disease.

7. Treatment with rauwolfia alkaloids is indicated in hypertensive disease. In the majority of patients these preparations, producing a gradual reduction in the blood pressure not uncommonly to normal, improve the renal circulation, and this can stop the progress of hypertension and possibly lead to a regression of it.

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Received 22 December 1959

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