Effect of Methyldopa on Plasma Renin Activity in Man

By Shakil Mohammed, M.D., Ph.D., Alfred F. Fasola, M.D., Ph.D.,
Philip J. Privitera, Ph.D., Raymond J. Lipicky, M.D.,
B. L. Martz, M.D., and Thomas E. Gaffney, M.D.

ABSTRACT

The effect of methyldopa on plasma renin activity was studied in one hypertensive and four normotensive human volunteers. Peripheral venous blood for the estimation of plasma renin activity was obtained with the subjects supine and in a 70° head-up tilted position before, during and, in two subjects, after treatment with oral methyldopa. Despite a reduction in mean arterial pressure, the plasma renin activity was decreased by methyldopa in each subject. The increase in plasma renin activity associated with tilting, however, was not significantly suppressed by methyldopa. These results indicate that treatment with methyldopa can simultaneously decrease mean arterial pressure and plasma renin activity and it is possible that these effects may be causally related.

ADDITIONAL KEYWORDS renin-angiotensin system pressure-control antihypertensive drug hypotensive mechanism

It is generally believed that the mechanism of the hypotensive effect of methyldopa is partial sympathetic nerve blockade due to replacement of the natural transmitter norepinephrine by a less potent “false” transmitter α-methyl-norepinephrine (1). However, both substances have been shown to have identical pressor potency in dogs (2, 3) and rats (4). These observations suggest that the hypotensive effect of methyldopa, at least in some species, may not be explained on the basis of a reduced potency of α-methyl-norepinephrine. Although the pressor potency of norepinephrine was reported to be more than that of α-methyl-norepinephrine in man (5), only a small range of doses of these two amines has been tested.

Recently, Mohammed et al. (3) found that, in contrast to reserpine or guanethidine, chronic treatment with methyldopa significantly reduced the vascular resistance of denervated hindlegs of dogs. Mohammed et al. (6) also found that methyldopa decreased the renal vascular resistance in hypertensive patients in the supine position, a position presumed to be associated with minimal reflex sympathetic activity. Cannon et al. (7) also observed a decrease in renal vascular resistance in 5 of 7 supine hypertensive patients treated with methyldopa and suggested that this drug might have a direct effect on renal vessels. In contrast, the adrenergic neuronal blocking drug guanethidine does not decrease renal vascular resistance in supine man (8). These results viewed collectively suggest that methyldopa may attenuate a mechanism of pressure control other than the sympathetic nervous system, e.g. the renin-angiotensin system. This possibility was investigated in human volunteers in the present study.

Methods

Four normotensive healthy males aged 23 to 28 years, and one 45-year-old woman with essential hypertension were studied. The investigative nature of the study was explained to each subject and written consent to participate was obtained.
The subjects were hospitalized in air-conditioned rooms, remained ambulatory, and were maintained on fixed diets. The dietary contents of sodium and potassium in milliequivalents per day were: (a) low-sodium diet: 12.7 to 17.3 Na⁺ and 73 to 77 K⁺ given to two normotensive volunteers (C.S. and J.T.) and to the hypertensive subject (G.T.); (b) regular sodium diet: 149 Na⁺ and 109 K⁺ given to the other two normal subjects (B.S. and E.T.). Water intake was not restricted. Brachial artery pressure and apical heart rate were measured 4 or 6 times daily while the subjects were supine after 30 minutes of bed rest and after 3 minutes of quiet standing. These measurements were done at about the same time every day.

Plasma renin activity was estimated during a control period of placebo administration, after at least 5 days of treatment with methyldopa, and in two subjects (B.S. and E.T.) during a period of placebo administration after treatment. The dose of methyldopa was adjusted to reduce arterial blood pressure in each subject while standing. Oral doses of methyldopa at the time of renin measurements ranged from 500 to 1500 mg/day. The total number of tablets, either placebo alone or methyldopa mixed with placebo, was the same throughout the study in each subject. The subjects and the nursing personnel who made the blood pressure measurements were not aware of the study design.

Peripheral venous blood (20 ml) was obtained for the estimation of plasma renin activity before, during, and after methyldopa therapy after the subjects had been resting in the supine position for 30 minutes, and after 30 (G.T. and C.S.), 18 (B.S.), or 8 (E.T. and J.T.) minutes of 70° head-up tilt. The duration of tilt was intended to be 30 minutes in each subject but dizziness developed in some subjects and accounts for the differences in the duration of tilt between subjects; the duration for each subject, however, was the same before, during, and after methyldopa therapy. Blood for the estimation of plasma renin activity was obtained in the morning before breakfast.

Plasma renin activity of blood samples was determined by the method of Helmer and Judson (9). Plasma was adjusted to pH 5.5 and dialyzed overnight against cold running water. After dialysis, the plasma was readjusted to pH 5.5 and centrifuged. The supernatant fluid was made isotonic and then incubated at 37 °C for 1 hour; the resultant product was stored frozen until bioassay was performed. The constrictor activity of prepared plasma was assayed on rabbit aortic strip and compared with standard concentrations of synthetic angiotensin II. Plasma renin activity is expressed in terms of nanograms of angiotensin equivalents per milliliter of plasma. Normal values of plasma renin activity by this method range from 0.35 to 2.8 ng/ml in subjects on unrestricted sodium intake. Reproducibility of determinations of plasma renin activity was within 6 ± 2% (mean ± SE).

---

**FIGURE 1**

The effect of oral metyldopa on plasma renin activity in 1 hypertensive and 4 normotensive subjects in supine and tilted positions. Asterisks identify two normotensive subjects, B.S. and E.T., who were given regular sodium diet.
Body weights were determined every morning before the subjects ate breakfast and after they voided. Serum Na, K, and creatinine and their daily urinary excretion were determined throughout the study. Daily creatinine clearances were calculated and were regarded as estimates of glomerular filtration rates. Student's t-test for paired data was used for statistical analyses.

**Results**

Methyldopa reduced plasma renin activity in both the supine and tilted positions in each of the five subjects (Figs. 1 and 2), even though mean arterial pressure was also reduced. The percent reduction (mean ± se) in plasma renin activity during treatment with methyldopa was 40.0 ± 8.0 (P < 0.01) and 45.3 ± 7.9 (P < 0.005) in the supine and tilted positions, respectively. The magnitude of this reduction was the same in the supine and in the tilted position. The plasma renin activity (ng/ml) during the initial placebo administration was 2.6 ± 0.8 with the subjects supine and 8.2 ± 2.5 when they were in the tilted position. During methyldopa therapy, these values were 1.5 ± 0.4 (P < 0.05) and 3.9 ± 0.8 (P < 0.1). Plasma renin activity was measured in a period of placebo treatment after methyldopa therapy in two subjects, E. T. (Fig. 2) and B. S. In each of these two subjects, in the supine and tilted positions, plasma renin activity increased after discontinuation of methyldopa.

On the day blood was obtained for estimation of plasma renin activity, mean arterial pressure was less during methyldopa therapy than on the corresponding day during the period of placebo administration (Fig. 3); the percent decrease was statistically significant in both the supine (P < 0.05) and standing (P < 0.01) positions.

Although the plasma renin activity was

---

**FIGURE 2**

The effect of methyldopa on plasma renin activity, daily average arterial pressure (subject standing), urine sodium excretion, creatinine clearance, and body weight in a normotensive subject, E.T., who was given a 149-mEq sodium diet. S and T refer to the supine and tilted positions respectively.

*Circulation Research, Vol. XXV, November 1969*
The effect of oral methyldopa on mean arterial pressure of subjects in the supine and tilted positions. These pressures were measured on the days blood was obtained for the estimation of plasma renin activity.

reduced in the supine and tilted positions during treatment with methyldopa, neither the percent nor the absolute increase in this activity produced by tilting was significantly suppressed by methyldopa. The percent increase produced by tilting during the control period was 228 ± 53 and that during methyldopa therapy was 243 ± 112. The absolute increase in plasma renin activity (ng/ml) produced by tilting in the control period was 5.5 ± 1.8, whereas during methyldopa treatment it was 2.5 ± 0.8 ($P<0.2$).

The urinary excretion of Na and K, creatinine clearance, and body weight were not affected by methyldopa.

**Discussion**

These results suggest that treatment with methyldopa can simultaneously decrease plasma renin activity and mean arterial blood pressure, and it is possible that these effects are causally related. The finding that methyldopa has an effect on the renin-angiotensin system is also supported by our observation that methyldopa decreased plasma renin activity in the supine and tilted positions in a child with Bartter's syndrome who had markedly elevated plasma renin activity (unpublished observations). After discontinuation of methyldopa, plasma renin activity increased in this child as it did in the two subjects in whom these observations were made in the present study. Indirect support for an effect of methyldopa on the renin-angiotensin system is offered by our observation that chronic treatment with methyldopa produced supersensitivity to the pressor action of angiotensin in the denervated perfused hindleg of dog (unpublished observations). Bunag et al. (10) have suggested that the enhanced pressor responsiveness to angiotensin after bilateral nephrectomy is due to depletion of endogenous renin.

Several factors might be responsible for the observed reduction in plasma renin activity during treatment with methyldopa. It is possible that the stabilizing effects of prolonged hospitalization or prolonged sodium deprivation might be related to the reduction in plasma renin activity. However, treatment with methyldopa was associated with a decrease in plasma renin activity in two subjects who were on a normal sodium intake; it increased after methyldopa was discontinued in these subjects. Furthermore, in one subject (C.T.) maintained on a 12.7-mEq sodium diet, methyldopa was not administered until the thirty-seventh day of sodium deprivation. The plasma renin activity measured on the thirty-first and thirty-fifth days of hospitalization were higher than the values observed on the eleventh day of sodium deprivation. These observations suggest that the reduction in plasma renin activity seen during methyldopa administration is not simply the result of prolonged sodium deprivation or hospitalization. Similarly, the possibility that sodium retention might be related to the decrease in plasma renin activity seems unlikely, since body weight and urinary sodium excretion were not affected by methyldopa.

Adrenergic mechanisms play an important role in the control of plasma renin activity.
role in the control of renin release (11), and methyldopa can produce at least partial adrenergic nerve blockade in man (6, 12). Although there is no evidence that methyldopa impaired sympathetic reflexes in the present study, it is possible that the reduced plasma renin activity may be related to an effect of this drug on sympathetic neurones. The fact that methyldopa reduces plasma renin activity equally in subjects in the supine and the tilted positions, and that the increase in plasma renin activity associated with tilting was not significantly suppressed may be taken as some evidence against the thesis that the reduced plasma renin activity is due simply to adrenergic nerve blockade. Furthermore, the adrenergic neuronal blocking drug reserpine has been shown to increase plasma renin activity in dogs (13). The possibility that methyldopa may decrease plasma renin activity through a nonsympathetic, intrarenal mechanism should be considered.

The observation in this study that methyldopa decreased arterial pressure and simultaneously decreased plasma renin activity is in contrast to the effects of other antihypertensive drugs which increase plasma renin activity as they decrease arterial pressure. Sodium nitroprusside (14, 15), diazoxide (16), hydralazine (17), and reserpine (13) have each been shown to increase plasma renin activity in normotensive or hypertensive subjects or dogs. These increases may simply be in response to a diminished renal perfusion pressure, since Vander et al. (18) and Skinner et al. (19) have shown that a reduction in renal perfusion pressure is an effective stimulus for renin secretion. Treatment with methyldopa was associated with a decline in plasma renin activity, even though the drug also activated a known stimulus for renin secretion, i.e., a decrease in mean arterial pressure.

It has been demonstrated that methyldopa can produce partial adrenergic nerve blockade in man (6, 12) and it is likely that this contributes to the hypotensive effect of this drug. Our observation that methyldopa can decrease plasma renin activity raises the possibility that this effect may also contribute to the hypotensive effect of this drug. An analog of methyldopa, L-dopa, has also been observed to produce hypotension in patients with parkinsonism, and recently Barbeau et al. (20) reported that treatment of patients with parkinsonism with L-dopa is associated with a decline in plasma renin activity. These observations with methyldopa and dopa suggest that these drugs may influence the renin-angiotensin system through a mechanism that, if better understood, might have important practical and theoretical implications, e.g. an alternate approach to the treatment of some types of hypertension.

Acknowledgments
The authors are indebted to Miss Faye Kurtz, R.N., Mrs. R. Maynard, and Mr. R. Sanders for assistance during the study.

References


Effect of Methyldopa on Plasma Renin Activity in Man
SHAKIL MOHAMMED, ALFRED F. FASOLA, PHILIP J. PRIVITERA, RAYMOND J. LIPICKY, B. L. MARTZ and THOMAS E. GAFFNEY

doi: 10.1161/01.RES.25.5.543

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1969 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/25/5/543

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/