Antiaradrenergic Therapy: Special Aspects in Hypertension in the Elderly

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SUMMARY The effect of antiadrenergic treatment with methyldopa was studied in 17 patients with established essential hypertension who were subdivided with respect to age in a group younger (n = 10; mean age, 47 ± 2.4 (SEM) years; and a group older than 60 years of age (n = 7, mean age, 67 ± 2.8 SEM). The fall in arterial pressure was associated with a significant (p < 0.05) decrease in cardiac output and heart rate in patients over 60 years of age and no change in total peripheral resistance, whereas a (nonsignificant) fall in resistance occurred in younger patients. In both age groups, a significant (p < 0.05 and < 0.01, respectively) decrease in plasma norepinephrine levels was observed, whereas epinephrine and dopamine showed no changes. Pre- and posttreatment values of mean arterial pressure correlated directly with plasma norepinephrine values (r = 0.35 p < 0.05). Regardless of whether cardiac output was reduced or remained unchanged, renal blood flow, plasma and total blood volume did not change in either group with antiadrenergic treatment. Further, reflexive cardiac changes (responses to isometric exercise and upright tilt) remained qualitatively unchanged. It is concluded that antiadrenergic treatment with methyldopa lowers arterial pressure additionally by decreasing circulating norepinephrine levels. The antihypertensive effect is associated with a fall in peripheral resistance in the younger and a decrease in cardiac output in the older patients, and does not compromise renal blood flow or cardiac reflexive responses. (Hypertension 3 (suppl II): 11-226—11-229, 1981)

KEY WORDS • methyldopa • age • elderly • antiadrenergic treatment • hemodynamics

M ETHYLDOPA, a centrally acting antiadrenergic drug, has been available for more than a quarter of a century as a reliable antihypertensive agent. Although its mechanism of action has been elucidated only recently, controversy still exists regarding its hemodynamic effects. Early studies had indicated that the antihypertensive effect occurs by a reduction in cardiac output, whereas other reports suggested that this was mediated by a decrease in total peripheral resistance. Since hypertension in the elderly is associated with distinct hemodynamic, fluid volume, and endocrine alterations, we hypothesized that the age of the patient may significantly influence the mechanisms of the antihypertensive response. Accordingly, the present study was designed to evaluate hemodynamic, circulating humoral, and intravascular volume changes in 17 patients who were subdivided into groups older and younger than 60 years of age.

METHODS

Seventeen patients with established essential hypertension were included in the present study. They were subdivided with respect to age in a group younger (n = 10, mean age 47 ± 2.4 (SEM) years) and older than 60 years of age (n = 7, mean age 67 ± 2.8 SEM). Race, sex, body height, weight, and surface area (2.05 ± 0.06 and 1.97 ± 0.1 M2) were similar in the two groups. Antiadrenergic treatment was discontinued at least 4 weeks before the study was initiated. The research protocol had been approved previously by our clinical investigation committee and informed consent was obtained from all patients. Two hemodynamic evaluations were performed, the first after the patient had remained off treatment for 4 weeks and the second after the patient had taken methyldopa for 4 to 6 weeks. During the treatment period the dose of methyldopa was titrated in the outpatient department gradually from 250 mg twice a day to a maximum of 2.0 g per day according to the response of arterial pressure. The average dose was 0.9 and 0.6 g per day in the younger and older group respectively. Routine laboratory blood and urine tests as well as pulmonary function studies (pulmodigitalizer) were done 1 day before or after the hemodynamic measurements were made.
Hemodynamic assessment was done as previously reported. Cardiac output was measured in triplicate using indicator dilution with indocyanine green dye. Renal blood flows were determined concomitantly with single injections of 131 iodinated-para-aminophenacyl puric acid. Plasma volume and red cell mass were determined with 125 iodinated human serum albumin and 1 chromium-labeled red cells, respectively. Blood was withdrawn for determination of plasma renin activity and catecholamine (epinephrine, norepinephrine, and dopamine) concentrations 1 hour after the insertion of the intravascular catheters. Plasma renin activity was measured according to the method of Sealey et al., and catecholamines were determined by radioenzymatic assay. Responses to isometric exercise (handgrip) and upright tilt (45°) were performed during the hemodynamic study as previously reported. Data before and during antihypertensive treatment were compared statistically by a paired t test, and a linear correlation analysis was obtained between catecholamine values and the hemodynamic findings.

**Results**

In both age groups of patients, methyldopa reduced mean arterial pressure by about 10 mm Hg. The drop in arterial pressure was even more pronounced during supine and 20/10 mm Hg (p < 0.001) supine and 21/10 mm Hg (p < 0.01) upright, and in younger subjects, 20/13 mm Hg (p < 0.02) upright, and in older patients, 21/10 mm Hg (p < 0.001) supine and 20/10 mm Hg (p < 0.001) upright. This fall in pressure was associated with a significant decrease in cardiac output and heart rate in patients over 60 years of age, however, cardiac output did not change in the younger patients. There was no change in total peripheral resistance in the elderly patients; but a slight (but insignificant) fall in resistance was seen in the patients under 60 years. Patients of both age groups demonstrated a significant decrease in plasma norepinephrine levels, whereas epinephrine and dopamine showed no changes. Regardless of whether cardiac output was reduced or remained unchanged, renal and hepatic blood flows remained at pretreatment levels; and plasma and total blood volume did not change in either group with methyldopa treatment. Pre- and posttreatment values of mean arterial pressure correlated weakly with plasma norepinephrine values (r = 0.35 p < 0.05).

A slight fall in mean arterial pressure was observed with upright tilt, but in no instance did an orthostatic reaction occur. Heart rate, cardiac output, stroke index, and total peripheral resistance changed to a similar extent during treatment as compared with the pretreatment measurements (fig. 1). Similarly, the hemodynamic responses to isometric exercise were qualitatively unchanged by methyldopa (fig. 2). Although the forced expiratory volume measurements were lower during methyldopa therapy in the older patients, this decrease was not statistically significant. In one instance, however, a patient complained of an exacerbation of symptoms of his chronic obstructive pulmonary disease, and this was confirmed by a decrease in FEV1. This value most likely explained the overall decreased average of the older patients.

**Table 1. Hemodynamic Humoral, and Respiratory Function Before and After Methyldopa Therapy in Hypertensive Patients Younger (<) or Older (>) than 60 Years of Age (Mean ± 1 SEM)**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Patients under 60 years</th>
<th>Patients over 60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>172 ± 9</td>
<td>153 ± 4*</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>92 ± 3</td>
<td>83 ± 2*</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>118 ± 4</td>
<td>106 ± 2*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71 ± 4</td>
<td>65 ± 3*</td>
</tr>
<tr>
<td>Cardiac output (liter/min)</td>
<td>6.16 ± .48</td>
<td>6.06 ± 47</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>81.1 ± 6.2</td>
<td>94.8 ± 7.8</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>204.2 ± 20</td>
<td>184 ± 15</td>
</tr>
<tr>
<td>(mm Hg liter/min)</td>
<td>3088 ± 186</td>
<td>3090 ± 171</td>
</tr>
<tr>
<td>Plasma volume (ml)</td>
<td>1061 ± 115</td>
<td>1061 ± 77</td>
</tr>
<tr>
<td>Renal blood flow (ml/min)</td>
<td>346 ± 64</td>
<td>160 ± 26*</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>68 ± 27</td>
<td>100 ± 30</td>
</tr>
<tr>
<td>Epinephrine (pg/ml)</td>
<td>51 ± 18</td>
<td>107 ± 35</td>
</tr>
<tr>
<td>Dopamine (pg/ml)</td>
<td>.89 ± .28</td>
<td>.64 ± 24</td>
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<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forced expiratory volume</td>
<td>2.63 ± .15</td>
<td>2.68 ± .21</td>
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<tr>
<td>1st second (liter)</td>
<td></td>
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<tr>
<td>Percent of forced vital capacity</td>
<td>75.8 ± 3.8</td>
<td>74.5 ± 4</td>
</tr>
</tbody>
</table>

*p < 0.05.

*p < 0.01.
Discussion

The present data seem to clarify some previously controversial findings about the hemodynamic effects of methyldopa, particularly on cardiac output and total peripheral resistance.\(^*\)\(^\text{11-18}\) In elderly patients in whom cardiac output is lower and myocardial reserve impaired,\(^*\)\(^\text{18}\) cardiac function may depend more on endogenous adrenergic support than in younger subjects. It is not surprising, therefore, to see some fall in cardiac output in the older patients, since methyldopa, by its central action and also by lowering circulating norepinephrine levels, may interfere with such adrenergic cardiovascular support. Hence, the fall in arterial pressure observed in the elderly patients with hypertension is mediated mainly by a decreased cardiac output and not by a fall in total peripheral resistance.

Alternatively, the fall in cardiac output could reflect an increased venous capacitance. Regardless of the mechanism, the negative inotropic effect of methyldopa should be borne in mind when prescribing the drug in an elderly patient exhibiting a history or symptoms and signs of congestive heart failure. Indeed, a previous report has indicated that cardiac output may be significantly reduced with methyldopa treatment in patients with congestive heart failure.\(^*\)\(^\text{10}\) Hence, unpaired myocardial function and reserve seems to be a prerequisite for maintenance of cardiac output during antiadrenergic therapy. The present data only reflect the hemodynamic changes occurring after 4 to 6 weeks of treatment. Conceivably, the adjustment of the cardiovascular system could take a longer period of time, especially in elderly patients and produce a different picture after several months.

On the other hand, methyldopa also induced a decreased adrenergic outflow in the younger patients, but this effect mainly resulted in a fall of total peripheral resistance without changing cardiac output. In these individuals, despite the decreased adrenergic support, cardiac output was most likely maintained at pretreatment levels by the fall in aortic impedance. Therefore, the overall effect of methyldopa on cardiac output and total peripheral resistance seems to be the combined result of the unloading of the left ventricle.

**Figure 1**. Hemodynamic responses to 45° upright tilt pre- and post-antiadrenergic treatment. MAP = mean arterial pressure; HR = heart rate, CO = cardiac output, and TPR = total peripheral resistance.

**Figure 2**. Hemodynamic responses to isometric exercise (handgrip) pre- and post-antiadrenergic treatment. Same abbreviations as in figure 1.
mino concluded that methylxanthines do not interfere with the positive correlation between mean arterial pressure and circulating norepinephrine. The lack of correlation suggests that methylxanthines do not significantly interfere with these reflexive responses despite the compound’s negative inotropic effect in the elderly patient. Similarly, renal blood flow was not changed in either group. Comparable findings have been reported in patients with essential hypertension and chronic parenchymal kidney disease. The renal circulation in general seems to be less dependent upon endogenous adrenergic support than the myocardium, at least under baseline conditions. Whereas pulmonary function was well-maintained in young patients, a slight (but significant) fall in FEV₁ was observed in older individuals. Thus, similar to cardiac function, endogenous adrenergic support may be more important to maintain patent airways in elderly patients.

Plasma norepinephrine levels showed a distinct fall with methylxanthines in both age groups. This, together with the positive correlation between mean arterial pressure and circulating norepinephrine suggests that methylxanthines exerted its antihypertensive effects at least to some degree through a decrease in circulating norepinephrine levels. Although norepinephrine is known to predominantly mediate peripheral vascular constriction, the fall in plasma norepinephrine did not correlate with a reduction of total peripheral resistance in the present study. This lack of correlation provides indirect evidence that methylxanthines predominantly lower arterial pressure through other mechanisms (such as the central nervous system).

References

4. Van Zwieten PA. Antihypertensive drugs with a central action. Prog Pharmacol 1: 1, 1975