Acute Vascular Effects of the Angiotensin II Receptor Antagonist Olmesartan in Normal Subjects: Relation to the Renin-Aldosterone System

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The extent to which the clinical effects of angiotensin receptor blockers (ARB) are related to ambient renin system activity remains poorly defined. Therefore, we measured blood pressure (BP), large (C1) and small (C2) arterial compliance, systemic vascular resistance (SVR), plasma renin activity (PRA), and the 24-h urinary excretion of sodium (UNaV) and aldosterone before and 1, 2, 4, and 24 h after administration of single doses of placebo, and 5, 20, and 40 mg of the ARB olmesartan medoxomil to 12 unmedicated normotensive subjects.

In the basal state, SVR was inversely related to UNaV ($r = -0.3$, $P = .04$); the greater the UNaV, the more vasodilated the subject. Indices of arterial compliance, both C1 ($r = -0.32$, $P = .03$) and C2 ($r = -0.35$, $P = .02$) were inversely related to the basal PRA. Renin also predicted olmesartan-induced changes in C1 ($r = 0.43$, $P = .004$) and C2 ($r = 0.33$, $P = .04$). The greater the basal PRA, the less the arterial compliance, and the more compliance improved after olmesartan.

Both systolic ($P = .003$) and diastolic ($P < .0001$) BP fell significantly on olmesartan compared with placebo (MANOVA with time), and relations were observed between the basal PRA and olmesartan-induced changes in pressure (systolic BP: $r = -0.414$, $P = .012$; diastolic BP: $r = -0.561$ $P < .0001$)—the greater the initial PRA, the more olmesartan lowered BP. Furthermore, the more pressure fell, the more PRA rose reciprocally ($r = -0.44$, $P = .007$). Finally, aldosterone excretion fell (sig $= 0.05$) on each dose of olmesartan compared with placebo.

We conclude that 1) the inverse relation of UNaV and SVR illustrates the reciprocal role of volume versus constrictor factors in maintaining normal BP; and 2) PRA is a physiologic determinant of arterial compliance in normal individuals and of the response to the ARB olmesartan. Measurement of PRA may help to predict clinical ARB responses in individual subjects. Am J Hypertens 2004; 17:203–208 © 2004 American Journal of Hypertension, Ltd.

Key Words: Plasma renin activity, arterial compliance, aldosterone, volume–vasoconstriction analysis of blood pressure.
less, although the mechanism of these drugs has been well defined on the basis of their specific blockade of the angiotensin I (AT1) receptor for angiotensin II, the extent to which their antihypertensive effects depend on the endogenous activity of the renin-angiotensin system remains unclear. Furthermore, although demonstrated with CEI, the ability of ARB to suppress aldosterone production has been less well documented.

Therefore, 1) to investigate the operation of vasoconstriction in comparison with volume factors in normal man under free-living circumstances, 2) to test the renin-system dependence of ARB action in man, and 3) to study ARB effects on aldosterone, we report here a preliminary, randomized, double-blinded, placebo-controlled study of the AT1 antagonist olmesartan, administered acutely in different doses to normal human subjects. We compared ARB effects on BP and other hemodynamic variables with concomitant measurements of plasma renin activity and urine aldosterone and electrolyte excretion. Our results support the volume-vasoconstriction analysis of BP regulation, demonstrate that the acute BP and other vascular effects of ARB administration depend closely on plasma renin activity, and that aldosterone levels are clearly suppressed by ARB administration. These results strongly suggest a potentiated benefit of olmesartan in subjects with activated renin system activity.

Methods

Healthy volunteers (n = 12) with no known medical conditions, and on no medications were recruited at the Hypertension Center of the New York Presbyterian Hospital/Cornell Medical Center. After a screening history, physical examination, and basal blood tests to exclude disease and pregnancy, each subject was randomized to receive a single pill (labeled A, B, C, or D) once a week thereafter, containing either a placebo or one of three doses (5, 20, and 40 mg) of the angiotensin II–AT1 receptor blocker, olmesartan medoxomil (Benicar). On each such occasion, subjects arrived after an overnight fast, and basal blood tests, BP, and other hemodynamic measurements were obtained before and 1, 2, 4, and 24 h after receiving each pill. In addition, a 24-h urine sample was collected by each subject the day of drug (or placebo) administration and was delivered after an overnight fast to the Hypertension Center before completion of the 24 blood tests and hemodynamic measurements mentioned above.

Plasma renin activity values and 24-h urine aldosterone excretion (ImmunoChem double antibody aldosterone RIA kit; ICN Pharmaceutical Inc, Costa Mesa, CA) were analyzed by standard radioimmunoassay techniques. Blood pressure and other hemodynamic values (two components of arterial compliance, C1 and C2, and systemic vascular resistance, [SVR]), were measured by oscillometric techniques and calculated by computerized pulse waveform analysis using applanation tonometry applied to the radial pulse (CR-2000, Hypertension Diagnostics, Inc, Eagan, MN).

After the coded doses were unblinded, data were analyzed using Statview 5.1 (Abacus Concepts, Berkeley, CA) and JMP (SAS Institute, Inc., Cary, NC) statistical software. Techniques included general summary statistics for mean values for the group, one-way ANOVA, and post hoc t testing for determining statistical significance among the different treatment subgroups (placebo and 5, 20, and 40 mg doses), and MANOVA between subjects for time, to determine the statistical significance of serial values measured over the 24-h period. Linear regression analysis with Pearson correlation coefficients were used to compare relations between the variables reported.

Results

Demographic and clinical data for the 12 normal subjects are listed in Table 1. Subjects were generally young and slightly overweight. There were no differences in the ethnic distribution of the group, although a preponderance of female subjects (8 v 4) were present.

Systemic Vascular Resistance

In the basal state for all subjects analyzed before drug administration, significant relations were observed between 24-h urinary sodium excretion and systemic vascular resistance (Fig. 1). The greater the average 24-h
sodium excretion, broadly indicative of dietary salt intake, the lower the SVR, or the more vasodilated the subject ($r = -0.30, P = .044$). This relation was equally significant when analyzed on each treatment separately, including placebo.

**Arterial Compliance**

Significant relationships were observed between plasma renin activity and basal levels of vascular compliance (stiffness), both for basal large artery compliance ($C_1, r = -0.315, P = 0.03$) and small artery compliance ($C_2, r = -0.350, P = .015$) (Figs. 2a, 2b). Furthermore, continuous relationships were observed between basal PRA values and olmesartan-induced changes in vascular compliance 24 h after drug administration ($\Delta C_1, r = 0.431, P = .004; \Delta C_2, r = 0.327, P = .035$) although compliance did not change for the group as a whole (Figs. 2c, 2d). Similarly, renin levels also predicted olmesartan-induced changes in another index of vascular compliance, pulse pressure, $r = 0.348, P = .016$. Thus, the greater the PRA, the stiffer the vasculature, and the more olmesartan improved vascular compliance.

**Blood Pressure and Urine Aldosterone**

Blood pressures, urinary aldosterone excretion, and plasma renin activity values on placebo and each dose of olmesartan are indicated in Table 2. Despite these subjects being normotensive, BP fell significantly on each dose of olmesartan compared with placebo. Whereas SBP fell significantly over time for the group as a whole on all doses tested ($P = .0026$, MANOVA for time), this trend was not significant for the individual doses, although single time points differed significantly for the 5 and 40 mg doses (Table 2). The maximal fall in diastolic BP ($P < .0001$, MANOVA for time) was similar for the three doses studied (Fig. 3a). Conversely, plasma renin activity rose on olmesartan, but not placebo (Fig. 3b). Maximal PRA values were similar on the different doses studied. However, the time course of renin responses differed for different doses, more prolonged increases in renin being observed with higher doses at 24 h ($P = .014$ for 40 vs 5 mg doses; $P = .16$ for 20 vs 40 mg doses). Finally, compared with placebo, aldosterone levels were significantly lower on each dose of olmesartan (Fig. 3c).

Although no relationships were observed between plasma renin activity and basal BP per se, olmesartan-induced changes in BP changes were significantly related to the activity of the renin-angiotensin system. Basal levels of plasma renin activity predicted the fall in BP on the three doses of olmesartan, both for systolic ($r = -0.414, P = .0121$) and diastolic ($r = -0.561, P < .0001$) BP—the greater the renin, the more the pressure fell (Fig. 4). This was also true reciprocally of the olmesartan-induced fall in pressure—ie, the more the pressure fell, the more renin rose ($r = -0.440, P = .0072$).
Discussion

The rationale for this preliminary study was to investigate the relevance of the renin-angiotensin-aldosterone system in assessing the in vivo clinical effects of the ARB olmesartan in normotensive control subjects. First, if the volume–vasoconstriction analysis of BP regulation correctly reflects clinical physiology, then the normal inverse relation between volume and constrictor factors in maintaining normal BP also ought to be apparent when comparing dietary salt intake and peripheral vascular resistance, which we measured in this study. Second, if the well defined mechanism of action of ARB is relevant to their observed effects, then greater effects on BP and other vascular parameters measured ought to be observed with greater basal renin system activity. Conversely, subjects with suppressed renin system activity should be less responsive. Although this has been reported for other antihypertensive drug classes, the dependence of ARB action on the activity of the circulating renin-angiotensin system has not been previously reported. Finally, although angiotensin II is the chief physiologic regulator of adrenal aldosterone production, and although inhibition of aldosterone is a well documented feature of angiotensin converting enzyme action, the action of ARB drugs on aldosterone is less well defined. We therefore also assessed olmesartan effects on daily urinary aldosterone excretion, which provides an integrated assessment of the inherently variable adrenal aldosterone output over time.

The results of this preliminary study support the above rationale. First, consistent with the physiologic definition of BP and its clinical reformulation as the volume–vasoconstriction model, SVR was inversely related to 24-h urinary sodium excretion values. Thus, as expected, the normal circulation maintains a normal BP by vasodilating to accommodate an increased sodium volume status. This study, among free-living normal subjects on chronic unrestrained dietary salt intakes, thus complements previous intervention studies in which no changes in BP were observed in normal subjects studied after short-term administration of different dietary salt intakes.

Second, we found that renin system activity helps to determine the vascular response to the angiotensin receptor-blocking agent olmesartan. This was observed in different ways. For one thing, the higher the basal, pretreatment PRA, the greater the drug-induced fall in BP. This has not been previously reported for the ARB drug class and is consistent with the greater dependence of ambient BP on the renin-angiotensin system in “higher renin” subjects, as observed in response to other antihypertensive drug classes. For another thing, in addition to BP, levels of arterial compliance, both in the basal state and after olmesartan, were also predicted by basal plasma renin activity values. The higher the PRA, the lower the basal arterial compliance (increased stiffness), and the more compliance rose after AT1R blockade with olmesartan. The clinical influence of renin activity on arterial compliance (stiffness) has also not been previously reported, and these data suggest the relevance of the renin-angiotensin system to this vascular function as well. These results may also help to explain the reported utility of

### Table 2. Blood pressures, renin activity, and urinary excretion data in 12 Ni subjects

<table>
<thead>
<tr>
<th>Dose</th>
<th>Placebo</th>
<th>5 mg</th>
<th>20 mg</th>
<th>40 mg</th>
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<tr>
<td><strong>Systolic BP (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t = 0</td>
<td>123 ± 4</td>
<td>122 ± 4</td>
<td>120 ± 4</td>
<td>121 ± 3</td>
</tr>
<tr>
<td>t = 60</td>
<td>126 ± 3</td>
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<tr>
<td>t = 120</td>
<td>124 ± 3</td>
<td>115 ± 3*</td>
<td>117 ± 4</td>
<td>119 ± 4</td>
</tr>
<tr>
<td>t = 240</td>
<td>125 ± 4</td>
<td>118 ± 3</td>
<td>118 ± 3</td>
<td>116 ± 3*</td>
</tr>
<tr>
<td>t = 24 h</td>
<td>120 ± 3</td>
<td>118 ± 3</td>
<td>117 ± 3</td>
<td>118 ± 4</td>
</tr>
<tr>
<td><strong>Diastolic BP (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t = 0</td>
<td>73 ± 2</td>
<td>71 ± 2</td>
<td>71 ± 2</td>
<td>71 ± 2</td>
</tr>
<tr>
<td>t = 60</td>
<td>74 ± 2</td>
<td>71 ± 2</td>
<td>67 ± 2*</td>
<td>65 ± 3*</td>
</tr>
<tr>
<td>t = 120</td>
<td>72 ± 2</td>
<td>67 ± 2*</td>
<td>67 ± 2*</td>
<td>67 ± 2*</td>
</tr>
<tr>
<td>t = 240</td>
<td>73 ± 2</td>
<td>66 ± 2*</td>
<td>66 ± 2*</td>
<td>65 ± 2*</td>
</tr>
<tr>
<td>t = 24 h</td>
<td>72 ± 2</td>
<td>67 ± 2*</td>
<td>67 ± 2*</td>
<td>66 ± 2*</td>
</tr>
<tr>
<td><strong>PRA (ng/mL/h)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t = 0</td>
<td>3.4 ± 0.5</td>
<td>2.1 ± 0.4</td>
<td>2.9 ± 0.6</td>
<td>2.9 ± 0.4</td>
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<tr>
<td>t = 60</td>
<td>3.1 ± 0.5</td>
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<td>7.1 ± 1.3*</td>
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<td>3.2 ± 0.5</td>
<td>6.2 ± 1.1*</td>
<td>11.7 ± 3.2*</td>
<td>11.8 ± 2.5*</td>
</tr>
<tr>
<td>t = 240</td>
<td>3.2 ± 0.6</td>
<td>11.1 ± 3.0*</td>
<td>13.7 ± 4.6*</td>
<td>12.2 ± 3.1*</td>
</tr>
<tr>
<td>t = 24 h</td>
<td>3.1 ± 0.7</td>
<td>5.1 ± 0.9*</td>
<td>9.2 ± 2.2*</td>
<td>14.7 ± 3.5*</td>
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<tr>
<td>24 h UNaV (mEq/day)</td>
<td>122 ± 19</td>
<td>163 ± 19</td>
<td>146 ± 19</td>
<td>150 ± 19</td>
</tr>
<tr>
<td>24-h UCrV (g/day)</td>
<td>1.57 ± 0.17</td>
<td>1.44 ± 0.17</td>
<td>1.60 ± 0.17</td>
<td>1.54 ± 0.17</td>
</tr>
<tr>
<td>24-h UAlDoV (µg/day)</td>
<td>10.6 ± 1.6</td>
<td>6.1 ± 1.6†</td>
<td>3.7 ± 1.6†</td>
<td>3.7 ± 1.6†</td>
</tr>
</tbody>
</table>

* sig = 0.05 both v t = 0 and placebo.
† sig = 0.05 v placebo.

BP = blood pressure; PRA = plasma renin activity; t = time in minutes unless indicated otherwise; UAlDoV = urinary excretion of aldosterone; UCrV = urinary excretion of creatine; UNaV = urinary excretion of sodium.
ARB therapy in isolated systolic hypertension,\textsuperscript{18,19} where decreased arterial compliance (increased stiffness) is the predominant underlying pathophysiologic feature.\textsuperscript{20} Olmesartan induced a reactive rise in plasma renin activity that was itself proportional to the degree of BP fall induced by the drug—the more the pressure fell, the more the renin rose. Indeed, the higher the dose of olmesartan administered, the greater and more persistent was the renin response; PRA levels 24 h after olmesartan were significantly higher at the highest dose, indicating the persistence of drug effects on the renin system over the 24-h period, as has also been described previously for BP in hypertensive subjects.\textsuperscript{21} The clinical literature on the adrenal aldosterone effects of ARB agents is incomplete, and the lesser rise in serum potassium after therapy with ARB in comparison with converting enzyme inhibitors has been attributed to lesser suppression of aldosterone.\textsuperscript{24,25} This in turn is supported by data suggesting a role for the AT2 receptor in aldosterone secretion that would not be affected by AT1 receptor blockade.\textsuperscript{26,27} Nevertheless, this study demonstrates, at least in the short term, that aldosterone excretion is suppressed by olmesartan in normal individuals.

Certain caveats should be considered before applying these results clinically in using olmesartan or other ARB in hypertension. First, and most obviously, this study was performed in a small number of normal subjects, but nonetheless has identified a role for the renin-angiotensin system in determining the clinical response to ARBs under normal physiologic circumstances. Similar studies need to be performed in hypertensive subjects to determine the applicability of these observations in more commonly encountered clinical situations. Second, we studied responses to isolated single doses of olmesartan administered acutely. Hence, these studies also need to be repeated in the setting of more chronic olmesartan administration. Third, these studies need to be repeated with other angiotensin receptor blocking agents to determine whether qualitatively or quantitatively similar results are obtained, and thus whether our results are class specific or unique to olmesartan. Finally, as all of the current subjects were free of other medications, the relevance of our conclusions also need to be studied under circumstances in which multiple other antihypertensive drug therapies are being administered concurrently.
The above notwithstanding, our present results may be clinically relevant. The current failure to choose antihypertensive drugs on the basis of matching the known mechanism of drug action with the relevance of these mechanisms in maintaining elevated BP in different individual hypertensive subjects may contribute to the disappointing overall long-term control rates of clinical hypertensive disease. Indeed, large clinical trials in which different combinations of antihypertensive drugs are allocated randomly to all subjects has fostered the notion that almost all of the available drugs possess equivalent or nearly equivalent BP or longer-term clinical benefit, leaving little other than cost and convenience as determining factors for drug choice in the average hypertensive subject. Accordingly, less attention has focused on physiologic measurements that might make the choice of drug therapy less arbitrary and more effective. The present study suggests that the practicing physician can, by measuring plasma renin activity levels, assess the contribution of different mechanisms to the regulation of BP among individual subjects in a manner that also predicts clinical responsiveness to drug therapy not only with other previously studied drug classes but also with the ARB olmesartan.

References