Hypertension

Renal and Hormonal Responses to Direct Renin Inhibition With Aliskiren in Healthy Humans

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Background—Pharmacological interruption of the renin-angiotensin system focuses on optimization of blockade. As a measure of intrarenal renin activity, we have examined renal plasma flow (RPF) responses in a standardized protocol. Compared with responses with angiotensin-converting enzyme inhibition (rise in RPF ≈ 95 mL · min⁻¹ · 1.73 m⁻²), greater renal vasodilation with angiotensin receptor blockers (≈ 145 mL · min⁻¹ · 1.73 m⁻²) suggested more effective blockade. We predicted that blockade with the direct oral renin inhibitor aliskiren would produce renal vascular responses exceeding those induced by angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

Methods and Results—Twenty healthy normotensive subjects were studied on a low-sodium (10 mmol/d) diet, receiving separate escalating doses of aliskiren. Six additional subjects received captopril 25 mg as a low-sodium comparison and also received aliskiren on a high-sodium (200 mmol/d) diet. RPF was measured by clearance of para-aminohippurate. Aliskiren induced a remarkable dose-related renal vasodilation in low-sodium balance. The RPF response was maximal at the 600-mg dose (197 ± 27 mL · min⁻¹ · 1.73 m⁻²) and exceeded responses to captopril (92 ± 20 mL · min⁻¹ · 1.73 m⁻²; P < 0.01). Furthermore, significant residual vasodilation was observed 48 hours after each dose (P < 0.01). The RPF response on a high-sodium diet was also higher than expected (47 ± 17 mL · min⁻¹ · 1.73 m⁻²). Plasma renin activity and angiotensin levels were reduced in a dose-related manner. As another functional index of the effect of aliskiren, we found significant natriuresis on both diets.

Conclusions—Renal vasodilation in healthy people with the potent renin inhibitor aliskiren exceeded responses seen previously with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. The effects were longer lasting and were associated with significant natriuresis. These results indicate that aliskiren may provide more complete and thus more effective blockade of the renin-angiotensin system. (Circulation. 2008;117:3199-3205.)

Key Words: renin ▪ drugs ▪ angiotensin ▪ kidney ▪ hypertension

Pharmacological interruption of the renin-angiotensin-aldosterone system (RAAS) has evolved from its original focus on whether blockade provides therapeutic benefit to the current goal of optimizing blockade. New therapeutic regimens are being promoted as evidence mounts to suggest that greater blockade results in improved clinical outcomes.¹⁻⁵ Most recently, the direct renin inhibitor aliskiren, which blocks the system at its rate-limiting step, has been approved for the treatment of hypertension. Aliskiren is as effective at reducing blood pressure but not more so than angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).⁶⁻¹⁰ Blockade at the tissue level, however, is equally important for organ protection, and animal data suggest target-organ protection with aliskiren.⁸

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We have successfully used a model to test the efficacy of blockade of RAAS activity in the kidney by measuring renal vasodilator responses in subjects in whom the system has been activated by restriction of sodium chloride intake to very low levels. A subset was studied on a high-sodium diet. We hypothesized that direct renin inhibition would block the RAAS more completely than other available agents and manifest as larger renal vasodilator responses. As other functional indices, we also measured natriuresis induced by the drug, its effect on glomerular filtration rate, and hormonal effects.

Methods

Twenty healthy subjects (15 men, 5 women) ranging in age from 19 to 52 years (mean 34 ± 3 years) were studied on a low-sodium diet.
An additional 6 healthy subjects (3 men, 3 women; mean age 33.8 ± 5.2 years) were studied on a high-sodium diet. All were white, except for 2 Hispanics. All had normal blood pressure (117/70 ± 3/2 mm Hg) and were free of cardiovascular, renal (creatinine 1.0 ± 0 mg/dL), and endocrine disease. All were within 20% of ideal body weight (72.4 ± 3.2 kg; body mass index 24.2 ± 0.8 kg/m²). After an outpatient evaluation, which included history, physical examination, screening chemistry, and hematology laboratory tests, all subjects were studied during an 8-day admission to a metabolic ward, the Clinical Research Center of the Brigham and Women’s Hospital. Written informed consent was obtained from each patient, and the protocol was approved by the Human Subjects Committee of the institution.

The 20 subjects placed on low-sodium constant isocaloric diets throughout the study consumed 10 mmol of sodium daily, the first several days as outpatients. Daily dietary potassium (100 mmol) and fluid intake (2500 mL) were constant. Twenty-four-hour urine samples were collected daily; when urinary sodium matched sodium intake (usually day 5), the first study was initiated. Each subject was tested on 3 separate study days (Monday, Wednesday, and Friday) separated by a rest interval of 48 hours; drug/placebo was only administered on study days. Phlebotomy limitations prevented subjects from undergoing more than 3 studies each.

Studies began at 7 AM. Subjects had been recumbent and fasting overnight and remained recumbent throughout the study. Renal plasma flow (RPF) was measured by the clearance of inulin (Inutest Polyclad) and plasma flow (RPF) was measured by the clearance of para-aminohippurate (PAH; Clinalfa, Lauffelfingen, Switzerland) and glomerular filtration rate by the clearance of inulin (Inutest Polyclad, Fresenius Pharma, Linz, Austria) by autoanalyzer methods described previously. After a 60-minute control period to establish basal RPF, the drug was dosed by mouth. Each subject received at least 2 separate escalating doses of aliskiren, ranging from 75 to 600 mg (Novartis Pharmaceuticals, Basel, Switzerland). Subjects were blinded to activity or dose of their pills. Twelve subjects received 3 aliskiren doses; 7 received 2 doses and 1 placebo pill as a control. All subjects received the 300-mg dose on 1 of their study days. One subject was withdrawn from study after he developed transient hypotension after the 75-mg dose.

Six additional subjects (3 men, 3 women; mean age 36 ± 1.8 years) received a single dose of captopril 25 mg on the low-sodium diet, demonstrated previously to exceed the top of the renal vascular dilator activity.9,10 These subjects were then changed to a high-sodium (200 mmol/d) diet and were given a single 300-mg aliskiren dose 4 days later, by which time they were in steady high-sodium balance. Limited resources prohibited readministration of captopril on the high-sodium diet in this protocol; however, we have recently reported a group of 69 healthy control subjects who received the identical dose of captopril, 25 mg, in an identical protocol from our laboratory, under the same dietary and study conditions with the same study personnel.11 These subjects are treated statistically as historical controls for the particular high-salt aliskiren versus captopril analysis.

Blood pressure during each infusion was recorded by an automatic recording device (Dinamap, Critikon Inc., Tampa, Fla) at 15-minute intervals. Blood pressure fall was analyzed from the lowest single

blood pressure reached after each dose compared with the mean of 4 measures taken at the predose baseline on that study day.

Blood samples were collected on ice at the start of the PAH infusion, at 90-minute intervals throughout, at the end of each study, and 24 hours after each aliskiren dose. Samples were only drawn in 2 subjects at the 24-hour time point after the 75-mg dose because of phlebotomy concerns; therefore, this time point at this dose only was eliminated from analysis. Samples were spun immediately, and the plasma was frozen until the time of assay. PAH was measured by an autoanalyzer technique. Plasma aliskiren levels were determined by a high-performance liquid chromatography/mass spectrometry-mass spectrometry method with a lower limit of quantification of 0.5 ng/mL (Novartis Laboratories).15 Renin concentration was measured with a commercial immunoradiometric kit (Renin III, Cibisio, Gif-sur-Yvette, France).16 Total renin concentration was determined simultaneously with the same kit after the induction of a conformational change in the prorenin molecule with aliskiren (10 μmol/L for 48 hours at 4°C), which enabled its recognition by the active site-directed radiolabeled antibodies applied in the Cibisio kit.17,18 Subtraction of the renin concentration from the total renin concentration yielded the estimated prorenin concentration. Plasma renin activity was measured by the trapping of generated angiotensin (Ang) I by high-affinity antibodies and by subsequent radioimmunoassay.19 Plasma Ang I and Ang II were measured specifically by radioimmunoassay after solid-phase extraction and subsequent high-performance liquid chromatography separation.20,21

Statistical Analysis

Peak response was taken as the average of the 2 highest consecutive values for PAH clearance and compared with baseline PAH clearance at the beginning of day 1 of the study. Data were examined by dosage of aliskiren, with an accounting for varied dosing regimens and nonindependence of observations. Linear mixed models were used to model the change in response to aliskiren across the study days of varied dose regimens, with an unstructured covariance for the correlation within subjects. An F test is presented for the overall significance of the linear mixed model. For all comparisons, group means have been presented with the SEM as the index of dispersion, and an α-level of 0.05 was used to determine statistical significance. All analyses were performed in SAS version 9.1.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Aliskiren induced a significant dose-dependent renal vasodilation on the low-sodium diet (Figure 1). Baseline RPF before the 300-mg dose (received by all subjects) was 575 ± 23 mL · min⁻¹ · 1.73 m². Responses to 75, 150, and 300 mg of aliskiren were increases in RPF of 93 ± 20,
The rise in RPF was maximal at the 600-mg dose, an increase of 197 ± 27 mL · min⁻¹ · 1.73 m²⁻. The relationship between dose and RPF response was highly significant (P < 0.01, mixed model).

For those studies performed on Mondays and Wednesdays, basal RPF could be measured 48 hours after each dose, before the next-higher dose. Significant residual vasodilation was observed 48 hours after each aliskiren dose, which was greater with higher doses (Figure 2). The correlation between dose and increment in basal RPF 48 hours later was highly significant (r = 0.9, P < 0.001). Analysis of only those RPF studies that were not preceded by a dose of aliskiren 48 hours earlier, conducted to eliminate the contribution of a carryover effect, revealed that the dose-response trend remained.

The plasma concentration of aliskiren was measured at regular intervals after each dose on the low-sodium diet (Figure 3). It was also obtained at time zero of each subsequent dosing day, representing a 48-hour postdose value. Peak concentrations were reached at 2 hours; drug levels were still elevated but falling at 5 hours. By 24 hours after each dose, concentrations were nearly back to baseline.

Six subjects received a single dose of captopril (25 mg) at the top of the renal vascular dose-response curve on this low-sodium diet. Mean RPF response to captopril was 92 ± 20 mL · min⁻¹ · 1.73 m²⁻, consistent with past investigations. This value was significantly less than the peak response to aliskiren, dosed at the top of its dose response (600 mg), which was 197 ± 27 mL · min⁻¹ · 1.73 m²⁻ (P < 0.01; Figure 4).

These 6 subjects also received a single dose of aliskiren (300 mg) on a high-salt diet. Mean RPF response to aliskiren was 47 ± 17 mL · min⁻¹ · 1.73 m²⁻. This response was quantitatively greater than the high-salt responses to captopril in normal subjects that were seen previously in an identical protocol. Natriuresis was also apparent on the high-salt diet. Urinary sodium for the 2 days before aliskiren administration was steady (180.1 ± 40 and 183.2 ± 16 mmol/24 hours), but on the day after aliskiren administration, it rose to 219 ± 15 mmol per 24 hours. As with the low-sodium diet, a fall in the filtration fraction was found (∆−0.043 ± 0.01).

Plasma concentrations of renin and prorenin were assayed at zero, 5, and 24 hours after each dose on the low-sodium diet (Figure 5). Placebo was never given on the first study day; it always followed at least 1 dose of aliskiren. As anticipated, plasma renin rose after administration of aliskiren and was still elevated 24 hours after drug administration. Even 48 hours after dosing, before administration of the next-higher dose and when plasma drug concentrations were no longer detectable, basal renin was elevated moderately. Concentrations of prorenin measured by this commercial assay showed sluggish and small responses to the renin inhibitor. Plasma renin activity measured by the antibody trapping technique was high at baseline (low-sodium balance).

Table. Functional Effects of Aliskiren on a Low-Sodium Diet

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 20)</th>
<th>Placebo (n = 7)</th>
<th>75 mg (n = 7)</th>
<th>150 mg (n = 15)</th>
<th>300 mg (n = 19)</th>
<th>600 mg (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Na, mmol/24 h</td>
<td>7.2 ± 2.3</td>
<td>15.6 ± 6.2</td>
<td>30.2 ± 11.5</td>
<td>34.8 ± 9.3</td>
<td>34.2 ± 8.1</td>
<td>31.9 ± 13.0</td>
</tr>
<tr>
<td>Δ GFR, mL · min⁻¹ · 1.73 m²⁻</td>
<td>...</td>
<td>−6.1 ± 10.0</td>
<td>1.6 ± 6.0</td>
<td>2.6 ± 5.0</td>
<td>1.4 ± 5.0</td>
<td>3.1 ± 3.0</td>
</tr>
<tr>
<td>Δ Filtration fraction</td>
<td>...</td>
<td>−0.018 ± 0.01</td>
<td>−0.035 ± 0.01</td>
<td>−0.039 ± 0.01</td>
<td>−0.051 ± 0.01</td>
<td>−0.015 ± 0.01</td>
</tr>
<tr>
<td>Δ Systolic/diastolic BP, mm Hg</td>
<td>...</td>
<td>4.4/2.8 ± 4.0/3.0</td>
<td>−2.4/1.4 ± 6.0/3.0</td>
<td>−0.4/1.8 ± 2.0/1.0</td>
<td>−4.8/1.9 ± 2.0/1.0</td>
<td>−4.4/1.9 ± 3.0/1.0</td>
</tr>
</tbody>
</table>

GFR indicates glomerular filtration rate; BP, blood pressure.

Values are mean ± SEM.
and fell sharply after each dose of the renin inhibitor but not after placebo (Figure 6A). A dramatic fall in plasma renin activity was evident after each active dose of the renin inhibitor. At 24 and 48 hours after drug administration, plasma renin activity had not fully returned to baseline. The subsequent predose plasma renin activity (0 hours) continued to decrease and manifested a carryover effect of the long-acting renin inhibitor. The plasma angiotensin concentrations confirmed these results and were well correlated (Figure 6B).

On a high-sodium diet, baseline concentrations of plasma renin activity, Ang I, and Ang II were much lower than those during the low-sodium diet, as anticipated (Figure 7). Nonetheless, the aliskiren-induced changes were qualitatively identical, although more modest.

**Discussion**

The present study uncovered several unanticipated features of the renal response to RAAS blockade with the direct renin inhibitor aliskiren that have significant clinical implications. First, a dose-related renal vasodilator response was present that peaked at $\approx 200 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^2$, approximately double the influence of ACE inhibition and 40% larger than our previous experience with ARBs.\(^5,22\) Although we anticipated greater blockade with an agent that acts at the rate-limiting step, no model would have predicted this large a response (discussed below). Second, the influence of aliskiren on the kidney was very prolonged. Unambiguous evidence of blockade was identified 48 hours after single doses, and the effect was dose related. This prolonged response is consistent with tissue studies in animal models that have shown a persistence of aliskiren in the kidney 2 weeks after drug withdrawal.\(^23\) The return of plasma aliskiren concentrations to baseline at a time when a sustained renal response is present lends further support to the existence of persistent local intrarenal activity. Third, we documented a brisk natriuresis during the 24 hours after exposure to individual doses in subjects on a restricted salt intake with very low urine sodium.

Although we have noted a modest natriuresis in response to interruption of the RAAS in the past,\(^24\) the natriuresis documented in the present study was substantial and could well be clinically important. As anticipated, we found no change in glomerular filtration rate with individual doses of aliskiren, as has been described for other agents that block the RAAS.\(^23\) The placebo studies showed no influence of our protocol on RPF, as expected, and the response to captopril was approximately half the response to the top dose of aliskiren. Responses to the renin inhibitor on a high-sodium diet, including a rise in RPF, a rise in urinary sodium, and a fall in plasma renin activity and angiotensins, were similar qualitatively although necessarily smaller in magnitude than those that occurred in low-sodium balance conditions.

What mechanisms can account for this enhanced renal vascular response? The rationale for this hypothesis is 2-fold. First, conversion of angiotensinogen to Ang I by renin is the initial and rate-limiting step in the cascade that results in the generation of Ang II, and its direct inhibition may be more efficient. Second, (pro)renin binding to the recently discov-
levels that occurs.28–30 This scenario would also account for renin is low, which perhaps reflects the increase in prorenin.

Evidence of RAAS activation in the kidney, although active normal control mechanism and an enhanced role for prorenin type 1 and type 2 diabetes mellitus. A role for prorenin as a plasma prorenin concentration than with plasma renin activity. Response to RAAS blockade showed a better correlation with plasma renin activity and levels of angiotensins I and II in subjects on a high-sodium diet after aliskiren exposure (500 mg). Note that baseline levels of all components were much lower than those during the low-sodium diet (Figures 5 and 6) but that the aliskiren-induced changes were identical (although more modest) than those that occurred during the low-sodium diet.

Provenance: The recent identification of a binding site for renin and renin/prorenin receptor26 may generate locally considerable amounts of Ang II, and direct blockade of the active site of receptor-bound (pro)renin should reduce local Ang II concentrations significantly by blocking the enzymatic generation of Ang I. Although aliskiren does act at the rate-limiting step, which should provide it with an advantage in achieving more complete blockade, no current model would have predicted a 40% larger response than that to ARBs, or 2-fold the response to ACE inhibitors. One commonly invoked explanation for a difference in response involves tissue penetration into compartments that might be difficult to reach. Typically, agents that show such a feature are highly lipophilic and thus have greater access to some compartments protected by cell membranes. Aliskiren, however, is highly hydrophilic. Indeed, its remarkable effectiveness in blocking renin reflects this hydrophilicity.27 Thus, a preferentially accessed compartment appears to be an unlikely explanation.

As an alternative, we are interested in the possibility that prorenin at the tissue level is involved in the control of the renal circulation, as suggested recently by our studies in individuals with diabetes mellitus.13 In that study, the renal response to RAAS blockade showed a better correlation with plasma prorenin concentration than with plasma renin activity in normal subjects, and even more strikingly in patients with type 1 and type 2 diabetes mellitus. A role for renin as a normal control mechanism and an enhanced role for prorenin in diabetes could account for the fact that patients show evidence of RAAS activation in the kidney, although active renin is low, which perhaps reflects the increase in prorenin levels that occurs.28–30 This scenario would also account for the fact that prorenin predicts microvascular complications in patients with diabetes mellitus.31–33

The recent identification of a binding site for renin and prorenin in human kidney mesangium and arteries has created a new interest in a role for prorenin in health and disease.26 Until recently, prorenin, despite circulating at plasma concentrations 10-fold higher than those of renin, was thought to play a role in physiology only as a precursor to renin. Circulating prorenin is proteolytically inactive. The identification of a renin/prorenin receptor that binds prorenin equally as well as renin, and in so doing confers full catalytic activity on prorenin, has significant implications, especially in view of its high plasma concentrations. Abundant evidence exists for interactions between renin inhibitors and prorenin.16,17,34–37 Including studies with aliskiren.16 Prorenin functions enzymatically to generate Ang I when bound to its receptor and also functions in direct angiotensin-independent signaling pathways. No data exist to suggest that aliskiren blocks the binding of (pro)renin to its receptor. Evidence suggests that aliskiren acts by blocking the enzymatic activity. One likely possibility is that aliskiren may inhibit the catalytic activity of receptor-bound activated prorenin after a conformational change. In addition, binding of renin to its receptor induced a 4-fold increase in the catalytic efficiency of conversion of angiotensinogen to Ang I,18 which would be expected to be effectively inhibited by aliskiren. Thus, greater blockade of the intrarenal renin system by aliskiren could be explained by the consequences of effective inhibition of receptor-bound renin and prorenin.38,39 ACE inhibitors and ARBs may not be able to inhibit very high local tissue concentrations of Ang II optimally. The sluggish prorenin responses to aliskiren in the assay in the present study are not surprising; prorenin has been recognized to change concentration much more slowly than renin in response to ACE inhibition and also to upright posture.39,40

The duration of the influence of aliskiren and the kidney is also likely to have clinical importance. The more sustained the blockade of the RAAS, the more likely it is to be successful. Persistence of the effect of aliskiren on RPF up to 48 hours after a single dose (at a time when plasma drug levels returned toward baseline) provides evidence for sustained inhibition of the intrarenal renin system. One explanation for this seemingly dissociated pharmacokinetic-dynamic effect is that aliskiren has a very high affinity for renin; a slow kinetic off-rate could explain the observation. The in vitro IC50 of aliskiren for human renin is 0.6 nmol/L, which is equivalent to an aliskiren concentration of 0.4 ng/mL, just below the lower limit of the assay used in the present study. Another possibility is that aliskiren may be bound to structures other than renin and therefore be retained in the kidney. Aliskiren can be detected in the rat kidney up to 2 weeks after drug withdrawal.21 Still unclear is what the aliskiren is bound to and whether it is biologically active. The fact that it was present for weeks suggests a very-high-affinity binding site that clearly merits further investigation.

The dose-related rise in RPF was not paralleled by a change in mean glomerular filtration rate. Like reports on earlier studies on RAAS blockade, glomerular filtration rate did not change significantly with aliskiren dose. The present hemodynamic measurements on the kidney were not made primarily to assess renal hemodynamics but rather to explore an index of RAAS blockade at the tissue level.

The present protocol used a severely restricted sodium intake for the majority of subjects, very different from the typical consumption found in a Western diet; however, relevant physiological lessons can still be learned. We have been interested for

Figure 7. Renin and prorenin levels (left), plasma renin activity (PRA), and levels of angiotensins I and II (right) in subjects on a high-sodium diet after aliskiren exposure (500 mg). Note that baseline levels of all components were much lower than those during the low-sodium diet (Figures 5 and 6) but that the aliskiren-induced changes were identical (although more modest) than those that occurred during the low-sodium diet.
many years in heightened activity of the RAAS and its contribution to pathology in such diseases as diabetes mellitus and congestive heart failure, in which the system is inherently overactive. In clinical studies of these diseases, it is not necessary to use a low-sodium diet, because the system is already activated. Healthy humans do not inherently exhibit an activated RAAS but rather a suppressed one in the kidney. Therefore, we used an extremely low-sodium intake to stimulate the system and to augment the range of renal vascular responses seen. Our laboratory has used these measurements of renal vasodilation with success on both low- and high-sodium diets, and they have enabled predictions of renal responses in diabetes mellitus and in heart failure, as well as the increased risk of renal disease conferred by ethnicity, obesity, and oral contraceptive use. Furthermore, a subset of subjects also received aliskiren on a high-sodium diet. These subjects demonstrated responses far in excess of what we have demonstrated with captopril in a cohort of 69 healthy individuals of similar age under identical protocol conditions.

One weakness of the present study involves the focused and necessarily indirect nature of our measure. Of the many actions of the RAAS, we have studied those in the kidney. Furthermore, we have not actually measured intrarenal RAAS activity but rather the renal hemodynamic response to blocking the system. Although the index is indirect, it is difficult to account for the present findings on the basis of an effect of aliskiren unrelated to its action of inhibiting renin directly. On the positive side, the present findings are anchored by a placebo response that was negative and our recapitulation of the response to ACE inhibitor blockade with captopril. Renal vascular responses in the subset of subjects who received captopril in the present study are in complete accord with a historical database numbering well over 100 subjects that used the identical protocol. Although captopril dose ranging was not performed in the present protocol, we have previously demonstrated that the renal vasodilator response to captopril peaked at 10 mg; responses to 25 mg were no greater. Furthermore, responses to other ACE inhibitors, including lisinopril and ramipril, have been very similar in our model. Likewise, all comparisons made to ARB responses depend on historical controls. Hormone-level changes in response to aliskiren have been documented in careful studies and are compatible with extensive blockade of the RAAS with aliskiren doses identical to those used in the present study.

The present data were collected during short-term studies in healthy normotensive humans, and care must be taken in extrapolating these observations to long-term administration in diseased populations. Nonetheless, they indicate that direct renin inhibition holds the promise of significantly greater blockade of the RAAS than has been possible previously. They are necessarily preliminary to studies in disease. The promise of increased blockade in the kidney implies the potential for greater organ protection, translated clinically into improved clinical outcomes such as protection against both proteinuria and a decline in renal function. We speculate that this protection might be more marked in hypertensive patients with underlying cardiovascular disease. These data encourage assessment of the organ protection conferred by aliskiren, especially in patients with renal disease or diabetes mellitus.

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References


CLINICAL PERSPECTIVE
New pharmacological regimens that interrupt the renin-angiotensin-aldosterone system (RAAS) are being promoted as evidence mounts to suggest that greater blockade results in improved clinical outcomes. Most recently, the direct renin inhibitor aliskiren, which blocks the system at its rate-limiting step, has been approved for the treatment of hypertension. Blockade at the tissue level is important for organ protection; we investigated a measure of RAAS blockade in the kidney, our model quantifies renal vasodilator responses in subjects in whom the RAAS is activated by restriction of sodium chloride intake to very low levels. We hypothesized that direct renin inhibition would block the RAAS more completely than other available agents, which would manifest as larger renal vasodilator responses. Aliskiren induced a remarkable dose-related renal vasodilatation in 20 healthy subjects. The renal plasma flow response was maximal at the 600-mg dose (157±27 mL·min⁻¹·1.73 m²) and exceeded responses to captopril noted in previously performed studies (92±20 mL·min⁻¹·1.73 m²; P<0.01). Significant residual vasodilation was observed 48 hours after each dose along with significant accompanying natriuresis. These results indicate that aliskiren holds the promise of significantly greater blockade of the RAAS than has been possible previously.
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