Prolonged Duration of Blood Pressure Response to Enalkiren, the Novel Dipeptide Renin Inhibitor, in Essential Hypertension


The effects of sustained renin inhibition by repeated administration of enalkiren (A-64662), the novel dipeptide renin inhibitor, were evaluated in a randomized, double-blind, placebo-controlled, parallel-group study of 32 inpatients (eight per group) with essential hypertension who were maintained on a diet containing 60 meq/day sodium. Three different dosage regimens of enalkiren were studied: 1) 1.2 mg/kg quotid., 2) 0.3 mg/kg q.i.d., and 3) 0.1 mg/kg q.i.d. Each patient received an intravenous infusion every 6 hours for 1 week. Placebo infusions were used to mimic the 4 times/day dosing schedule. Blood pressure was measured periodically via 24-hour automated monitoring equipment. Mean plasma renin activity in the patient groups ranged from 1.58 to 2.68 ng/angiotensin I/ml/hr. Plasma renin activity was promptly suppressed in all groups receiving enalkiren. Prolonged duration of plasma renin activity suppression (≥24 hours) was demonstrated after the administration of 1.2 mg/kg enalkiren. The 0.3 mg/kg q.i.d. and 1.2 mg/kg quotid. regimens produced statistically significant reductions (p<0.05) in systolic and diastolic blood pressures with clear evidence of persistent antihypertensive activity for 12 hours or more when compared with the placebo group. Despite relatively large reductions in mean systolic and diastolic blood pressure, mean pulse rates were essentially unchanged. The prolonged reduction in blood pressure with enalkiren without evidence of tachyphylaxis after 1 week of treatment suggests that renin inhibitors may emerge as useful therapeutic agents for the treatment of hypertension. (Hypertension 1990;15:835–840)

The renin-angiotensin system is an important modulator of blood pressure and extracellular fluid volume. Manipulation of the renin-angiotensin system has emerged as a valuable tool in the evaluation of physiological mechanisms of blood pressure control and fluid and electrolyte homeostasis and as a new therapeutic approach to the management of hypertension and congestive heart failure. Angiotensin converting enzyme inhibitors block the conversion of angiotensin I (Ang I) to angiotensin II (Ang II). However, angiotensin converting enzyme inhibitors also exert actions on other endogenous systems, such as the kallikrein-kinin system, and prostaglandins and therefore are not specific physiological probes of the renin-angiotensin system.

The action of renin on angiotensinogen is the first and rate-limiting step in the renin-angiotensin system and is highly specific. The potential advantages of renin inhibition have been recognized for many years, and progress in this field has been reviewed recently. Clinical studies with renin inhibitory peptide and renin inhibitor H142 demonstrated that renin inhibition could reduce blood pressure, but these early renin inhibitors were relatively large molecules. More recently, enalkiren (A-64662) and CGP 38560A have been shown to produce dose-related reductions in plasma renin activity (PRA) and Ang II in normal human subjects.

Enalkiren is a dipeptide transition-state analogue with an IC₅₀ of 14 nM at pH 7.4 against human plasma renin; it is capable of lowering blood pressure in supine hypertensives and exhibits enhanced antihypertensive effects in patients pretreated with diuretics. The current study examines the antihypertensive effect of repeated administration of three different dosing regimens of the renin inhibitor enalkiren: 1.2 mg/kg quotid., 0.3 mg/kg every 6 hours (q.i.d.), and 0.1 mg/kg q.i.d.

Methods

Thirty-two patients with uncomplicated mild to moderate essential hypertension (diastolic blood pressure between 100 and 114 mm Hg) were selected.
for participation in this randomized, double-blind, placebo-controlled, multiple-dose study. The study was reviewed and approved by the appropriate Institutional Review Board. Informed consent was obtained, and patients were instructed to follow a diet containing 60 meq/day sodium for 2 weeks before, as well as during, confinement in the clinical testing unit. Patients were assigned to receive one of four treatments: 1.2 mg/kg enalkiren quotid. at 6:00 AM (with placebo infusions at noon, 6:00 PM, and midnight); 0.3 mg/kg q.i.d.; 0.1 mg/kg q.i.d., or placebo q.i.d. All patients received four intravenous infusions each day for 7 days (days 1–7). On day 8 patients received only one infusion at 6:00 AM. Each of the 29 infusions was administered over a 10-minute period in a volume of 120 ml. The 480-ml total volume per day provided 18 meq sodium/day. Twenty-four–hour urine collections for sodium excretion were obtained on the day before the first dose (baseline day) and on days 2 and 6.

Blood samples for PRA (measured at pH 5.7 for 1.5 hours), assessed by use of a radioimmunoassay kit (GammaCoat, Baxter Healthcare Corporation, Cambridge, Massachusetts), were obtained before and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours after the 6:00 AM infusion on days 1 and 8. On days 3 and 6, samples were obtained before and 0.25 hours after the 6:00 AM infusion. The lower limit of detection for this PRA assay is 0.15 ng Ang I/ml/hr.

Automated 24-hour monitoring devices (model 90202, SpaceLabs, Inc., Redmond, Washington) were used to record blood pressure and pulse rate on the baseline day and on days 1, 4, 7, and 8. Blood pressure was measured every 20 minutes from 6:00 AM until 10:00 PM and every 30 minutes from 10:00 PM until 6:00 AM the following day. Statistical analysis of the change in blood pressure and pulse rate from the baseline day to the corresponding time on each study day was performed with a one-way analysis of variance; pairwise comparisons of placebo and each active treatment were made by least significant difference tests.

**Results**

Two patients were excluded from all analyses presented below; one exclusion was due to technical difficulties with the blood pressure monitoring device and the other due to withdrawal from the study because of liver function abnormalities associated with Epstein-Barr virus infection. Of the remaining 30 patients, 24 were male and six were female. Nineteen patients were white, eight were black, two were Hispanic, and one was Oriental. The patients ranged from 32 to 61 years of age with a mean age of 49 years. Average body weight was 83 kg (range 63–100 kg). There were no significant differences among the demographic profiles of the treatment groups.

Mean sodium excretion of the 30 patients was 66 meq/day on the baseline day and 89 and 88 meq/day on days 2 and 6; these values reflect the increased sodium intake in conjunction with test infusions. Before dosing on day 1, the mean PRAs for the various treatment groups ranged from 1.58 to 2.68 ng Ang I/ml/hr, and individual PRAs ranged from 0.3 to 8.73 ng Ang I/ml/hr. Although PRA levels in the placebo group showed little change throughout the study, mean PRA in each of the active treatment groups was completely suppressed within 15 minutes of the first dose of enalkiren and remained suppressed for the duration of the study.

Average hourly diastolic blood pressure results are shown in Figure 1. Statistically significant decreases in average hourly diastolic blood pressure (primarily in the 0.3 mg/kg q.i.d. and 1.2 mg/kg quotid. groups) are evident on the first day of dosing and tend to be of larger magnitude on successive dosing days. On day 8 (6:00 AM infusion only), both the 0.3 mg/kg and 1.2 mg/kg groups demonstrated a persistent antihypertensive effect for more than 12 hours. The small decreases seen in the placebo group are consistent with non–drug-related blood pressure decreases that may be observed in hypertensive patients confined to a clinical testing unit.

A similar pattern for average hourly systolic blood pressure is shown in Figure 2. However, the reductions in average hourly systolic blood pressure after 1 week of dosing at 1.2 mg/kg are particularly striking; sustained, statistically significant reductions compared with placebo are present for at least 14 hours on day 8.

Despite the clinically significant changes in average hourly systolic and diastolic blood pressures, pulse rate remained remarkably stable in all enalkiren treatment groups throughout the study with no statistical difference compared with placebo. Enalkiren was well tolerated. One patient was withdrawn from the study because of evidence of Epstein-Barr virus infection. All other adverse events were mild and self-limited.

**Discussion**

Enalkiren has been shown to produce dose-related decreases in PRA and Ang II after acute intravenous administration in normal subjects without definite blood pressure reductions. This finding is consistent with observations in sodium-replete, normotensive subjects treated with captopril and the renin inhibitor CGP 38560A and suggests that blood pressure maintenance in normotensive subjects is not primarily dependent on the renin-angiotensin system. When enalkiren was administered to supine hypertensive patients, a dissociation was noted between PRA suppression and hypotensive response. PRA was suppressed at very low doses (0.001 mg/kg), but higher doses were required before clear blood pressure reductions were apparent. These results parallel similar observations in animal models. The description of a vascular-based renin-angiotensin pathway provides an explanation for understanding how manipulations of the renin-angiotensin system might produce effects on blood pressure that are not closely linked to inhibition of circulating renin. Subsequent studies with enalkiren have demonstrated enhancement of
Figure 1. Graphs showing comparison of the average hourly diastolic blood pressure (in millimeters of mercury) on baseline day (dotted lines) with average hourly diastolic blood pressure on days 1, 4, 7, and 8 (solid lines) by treatment group. *Average hourly diastolic blood pressure change from baseline day to corresponding time on dosing day is statistically significant (p≤0.05). †Change from baseline observed in active treatment group is significantly different from corresponding change from baseline observed in placebo group (p≤0.05).
FIGURE 2. Graphs showing comparison of the average hourly systolic blood pressure (in millimeters of mercury) on baseline day (dotted lines) with average hourly systolic blood pressure on days 1, 4, 7, and 8 (solid lines) by treatment group. *Average hourly systolic blood pressure change from baseline day to corresponding time on dosing day is statistically significant (p<0.05). †Change from baseline observed in active treatment group is significantly different from corresponding change from baseline observed in placebo group (p<0.05).
the hypotensive effect after pretreatment with hydrochlorothiazide.\textsuperscript{22,23} Additionally, in the high renin group a greater blood pressure response was seen after administration of the renin inhibitor enalkiren than was seen after recommended doses of the angiotensin converting enzyme inhibitor enalaprilat.\textsuperscript{31}

The current study provides the first evaluation of the effects of sustained renin inhibition in humans and supports several conclusions. First, clear and pronounced blood pressure reductions are apparent with both the 0.3 mg/kg q.i.d. and 1.2 mg/kg qo.d. regimens. Blood pressure response was excellent despite mean PRAs of 2.23 and 1.58 ng Ang I/ml/hr, respectively, and did not require concomitant diuretic administration. Second, no tachyphylaxis was observed during 1 week of dosing. In fact, the magnitude of blood pressure reduction was greater at the end of 1 week of dosing than it was on the first dosing day. Third, prolonged reduction of blood pressure was observed after administration of 1.2 mg/kg enalkiren qo.d. with statistically significant reductions in systolic and diastolic blood pressure for at least 12 hours after administration.

PRA was suppressed and remained suppressed throughout the week of dosing even in the low dose group. Despite the suppression of PRA in this group, blood pressure reductions were not comparable with those seen in the two groups that received a higher total daily dose. Clearly, suppression of PRA is not sufficient to induce a hemodynamic response. Suppression of plasma renin may not accurately reflect what is happening to tissue renin activity. In addition to the issue of circulating versus tissue renin-angiotensin systems, questions have been raised about using PRA as a marker for in vivo activity of the renin-angiotensin system.\textsuperscript{32} Measurement of PRA depends on the generation of Ang I in an in vitro system frequently performed at the pH optimum for renin (pH 5.6 to 6.0) to maximize sensitivity, but even if the assay is run at pH 7.4, the in vitro conditions may not fully replicate the physiological milieu. Although assays that specifically measure angiotensin-(1–8) octapeptide are difficult, and not widely available, they may be critical for the elucidation of the role of the circulating renin-angiotensin system in supporting blood pressure and the mechanism of action of renin inhibitors.

Another interesting observation is the prolonged suppression of PRA for at least 24 hours after administration of 1.2 mg/kg enalkiren, despite a half-life of only 1.6 hours in humans.\textsuperscript{17} The persistent suppression of PRA at 24 hours suggests that very low levels of the renin inhibitor remain accessible to the circulation. Release of small amounts of enalkiren from tissue depots could contribute to this phenomenon.

Finally, the absence of a reflex rise in pulse rate confirms earlier findings with renin inhibitors in animal models\textsuperscript{9,23,24} and is also characteristic of angiotensin converting enzyme inhibitors in general.\textsuperscript{3} Angiotensin converting enzyme inhibitors do not affect the normal cardiovascular response to autonomic reflexes or exercise.\textsuperscript{35} Several mechanisms for the lack of reflex tachycardia have been proposed including resetting of the baroreflex,\textsuperscript{36} withdrawal of the inhibitory action of Ang II on vagal activity,\textsuperscript{37,38} and reduction of Ang II–potentiated effects on the sympathetic nervous system.\textsuperscript{39}

The prolonged reduction of blood pressure in this study without evidence of tachyphylaxis after 1 week of treatment suggests that renin inhibitors may be useful therapeutic agents for the treatment of hypertension.

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