Kinetic-Dynamic Relations and Individual Responses to Enalapril
Richard Donnelly, Peter A. Meredith, Henry L. Elliott, and John L. Reid

Pharmacokinetic and pharmacodynamic variability largely account for interindividual differences in the response to antihypertensive drugs including angiotensin converting enzyme inhibitors. The factors determining the response to enalapril have been investigated in a placebo-controlled study in essential hypertension. The effects of placebo, the initial dose of enalapril, and long-term (1 and 6 weeks) treatment with enalapril were studied in 13 subjects. By using an integrated kinetic–dynamic model that incorporates a parameter for saturable protein binding, individual responses for blood pressure reduction and angiotensin converting enzyme inhibition were characterized in terms of the maximum effect (Eₘₐₓ) and the drug concentration required to produce 50% of Eₘₐₓ (C₅₀). In individual subjects, plasma enalaprilat concentrations could be correlated with falls in blood pressure and changes in plasma angiotensin converting enzyme activity. For the group, Eₘₐₓ was -46.1 ± 16.5 and -19.7 ± 3.8 mm Hg for systolic and diastolic blood pressure, respectively, and the corresponding C₅₀ values were 66.1 ± 20.2 and 61.6 ± 22.5 ng/ml. For angiotensin converting enzyme inhibition, Eₘₐₓ (%) and C₅₀ (ng/ml) were, respectively, 102.4 ± 5 and 19.8 ± 13 after the first dose, 103 ± 5 and 33.4 ± 20.3 after 1 week, and 101.3 ± 2.2 and 31.3 ± 18.9 after 6 weeks. There was no relation between the responsiveness to enalapril (Eₘₐₓ or C₅₀) and patient age or plasma renin activity, but there was a significant positive correlation between Eₘₐₓ and the pretreatment blood pressure. In individual subjects, Eₘₐₓ (first dose) was directly correlated with Eₘₐₓ after 1 and 6 weeks. This study, which incorporated kinetic as well as dynamic information to characterize the antihypertensive response to enalapril, has identified enalaprilat concentration–effect relations in individual hypertensive subjects. (Hypertension 1990;15:301–309)
cation 6 weeks before entering the study. All patients had a normal serum creatinine and no electrocardiographic evidence of cardiac disease.

After a preliminary drug-free assessment period of at least 6 weeks, the average entry blood pressure (±SD) was 181/101 ±15/8 supine and 175/101 ±13/6 mm Hg erect. Thereafter, in a single-blind design, patients received placebo for 3 weeks followed by 6 weeks of treatment with enalapril (20 mg once daily). Each patient attended four 8-hour study days in the Clinical Pharmacology Research Unit to evaluate the effects of placebo, of the first dose of enalapril (20 mg), and of enalapril therapy (20 mg daily) after 1 week and 6 weeks. On each occasion, after an overnight fast, baseline blood pressure and heart rate were recorded, an indwelling cannula was inserted into an antecubital vein, and then enalapril (20 mg) or placebo was administered orally with 100 ml water. At frequent intervals during each study day, and at 24 hours after dosing, blood pressure and heart rate were measured supine after not less than 10 minutes recumbency and erect after 5 minutes standing. Blood pressure was measured with a semiautomatic sphygmomanometer (Datascope Accutorr, Paramus, New Jersey). At corresponding times (i.e., 0, 0.5, 1.0, 1.5, 2.5, 3.5, 4, 5, 6, 7, 8, and 24 hours) venous blood samples were collected for measurement of plasma enalaprilat concentration and plasma ACE activity. In seven patients (patients 3, 7, 8, 9, 10, 11, and 12), blood pressure was recorded and additional blood samples were obtained at 12 and 32 hours after dosing. On each study day, extra blood samples were collected in all patients at 0, 1.5, and 6 hours for determination of plasma renin activity, aldosterone, and catecholamines.

**Laboratory Methods**

Plasma concentrations of enalaprilat were measured by radioimmunoassay. The inter assay and intra-assay coefficients of variation, across a range of concentrations, for the enalaprilat assay were 8.5% and 7%, respectively, with a limit of detection of 0.4 ng/ml.

Plasma ACE activity was assayed by measurement of the rate of generation of hippuric acid, quantified by high-performance liquid chromatography, with Hip-His-Leu as the artificial substrate. Enzyme activity is expressed as nanomoles of hippuric acid generated per minute (EU), and the normal range in our laboratory for plasma ACE activity is 5–32 EU/ml. The interassay and intra-assay coefficients of variation were 7% and 5.5% for plasma renin activity (normal range 0–12 ng angiotensin I (Ang I)/ml/hr), 11% and 7.3% for plasma aldosterone (normal range 12–125 pg/ml), and 15% and 13% for plasma norepinephrine (normal range 0.3–7.5 nmol/l).

**Pharmacokinetic Analysis**

The pharmacokinetics of enalaprilat were initially evaluated by fitting a hierarchy of conventional kinetic compartmental models, governed by first-order processes. In all subjects, a two-compartment open model was most appropriately fitted to the data, but this did not satisfactorily describe all the features of the disposition, particularly the relative lack of accumulation of enalaprilat on repeated dosing.

Thereafter, in accordance with the findings and recommendations of Till et al and of Francis et al, a one-compartment model with saturable protein binding was found to produce satisfactory fits to the data. In addition, by using a number of criteria of goodness of fit, a unified approach fitting this model simultaneously to acute and steady-state data was found to be superior to both the original "conventional" approach and to independent fitting for each study day. Goodness of fit was judged using the coefficient of determination and the z value for runs in the residuals, while model comparison was based on the Akaike Information Criterion values and by application of the general linear test to the residual sum of squares.

**Concentration–Effect Analysis**

For the concentration–effect analysis, the predetermined pharmacokinetic model was augmented by an "effect" compartment as described previously. The effect, in this case blood pressure reduction or ACE inhibition, was then related to the drug concentration in the effect compartment by means of both linear and nonlinear (Langmuir or maximum inhibition values [E_{max}]) models which define the relation between drug concentration and effect as either linear model

\[ E = mC_e + i \]

or nonlinear Langmuir (E_{max}) model:

\[ E = \frac{E_{max} \cdot C_e}{C_e + 50 + C_e} \]

where E is the measured effect and C_e the drug concentration in the effect compartment. For the linear model, the slope of the relation, m, represents the responsiveness to the drug in terms of effect per unit drug concentration in the effect compartment, whereas for the Langmuir model, E_{max} is the maximum possible effect and C_{50} is the concentration of enalaprilat required to produce 50% of E_{max}. The first-order rate constant of the effect model, K_{eq}, defines the temporal discrepancy between changes in drug plasma concentration and changes in effect.

After the pharmacokinetic model and the appropriate parameters in individual patients were defined, the pharmacodynamic data were then fitted to both effect models by using a nonlinear least-squares fitting procedure. Three measurements of
hemodynamic drug effect were analyzed: 1) the placebo-subtracted change in erect systolic blood pressure, 2) the placebo-subtracted change in erect diastolic blood pressure, and 3) the placebo-subtracted change in plasma ACE activity expressed as percent inhibition. For individual patients, profiles of blood pressure and plasma ACE activity were corrected by subtracting the corresponding placebo value at each individual time point throughout the dosing interval. In all cases, the data were most appropriately described by the \( E_{\text{max}} \) model on the basis of the general linear test. The concentration-effect parameters \( E_{\text{max}}, C_{50}, \) and \( K_{e} \) were derived for individual patients to characterize the response to enalapril in terms of blood pressure reduction and ACE inhibition.

**Statistical Analysis**

Blood pressure and heart rate measurements were evaluated by repeated measures analysis of variance. The concentration-effect parameters and the measurements of plasma renin activity, aldosterone, and catecholamines were compared between treatments by repeated-measures analysis of variance.

Linear regression analysis was used for the correlations between \( E_{\text{max}} \) after the first dose, \( E_{\text{max}} \) after 1 week and 6 weeks of therapy, and for the correlations between \( E_{\text{max}} \) and starting blood pressure, age, and plasma renin activity. Measurements throughout are expressed as mean±SD.

**Results**

**Pharmacodynamics**

**Blood pressure.** The mean changes in blood pressure after placebo and enalapril are shown in Figure 1. After the first dose of 20 mg enalapril, there were significant reductions in both supine and erect blood pressure, maximal at 5–6 hours after dosing \((p<0.01)\). Erect blood pressure fell from a baseline of 171/101±17/10 to 122/80±20/13 mm Hg at 6 hours, compared with a change from 178/106±21/10 to 155/94±11/7 mm Hg after placebo (Figure 1). There was no significant orthostatic component as evidenced by maximal reductions of 46/27 supine and 49/21 mm Hg erect.

The antihypertensive effect of enalapril was sustained during long-term treatment with significant reductions of blood pressure 24 hours after the last dose \((p<0.03)\) and further reductions during the subsequent dosage interval. Supine blood pressure recorded 24 hours after dosing was 153/91±23/12 at 1 week and 157/94±18/12 mm Hg after 6 weeks treatment with enalapril (20 mg daily), compared with 187/105±17/10 mm Hg after placebo. After drug administration, there were further significant reductions in blood pressure that reached a nadir at 6 hours with 118/76±26/10 and 122/77±19/13 mm Hg, respectively, in the supine and erect posture after 1 week and correspondingly 122/73±18/10 and 122/77±19/13 mm Hg after 6 weeks (Figure 1).

**Plasma angiotensin converting enzyme activity.** The first dose of enalapril was associated with a prompt reduction in plasma ACE activity (Figure 2), significant at 1 hour and reaching a nadir at 3–4 hours after drug administration \((p<0.001)\). ACE activity was reduced from a baseline of 39.3±11.9 to 4.1±1.5 EU/ml at 4 hours, and the corresponding placebo values were 36.8±12.6 and 34.9±12.2 EU/ml (Figure 2). Significant inhibition of ACE activity was sustained for up to 24 hours after the first dose: 22.0±8.2 compared with 35.9±12.1 EU/ml 24 hours after placebo \((p<0.01)\).

During long-term treatment with enalapril (20 mg daily), measurements of plasma ACE activity recorded 24 hours after the last dose were not significantly reduced: 33.7±18.9 after 1 week and 32.2±11.1 after 6 weeks compared with 36.8±12.6...
EU/ml after placebo (Figure 2). In addition, although there was significant inhibition of plasma ACE activity during the 8-hour study day, measurements at 24 hours had returned toward placebo values: 31.7±18.5 (1 week) and 32.3±16.9 (6 weeks) EU/ml compared with 35.9±12.1 EU/ml at 24 hours after placebo (Figure 2).

Hormone measurements. Enalapril produced significant increases in plasma renin activity, particularly during long-term treatment (p<0.001) (e.g., plasma renin activity increased progressively from 5.1±7.3 after placebo to 12.4±12.1 after first dose, 50.3±40 after 1 week, and 58.0±177 ng Ang I/ml/h after 6 weeks at 6 hours after dosing). There were modest but significant reductions in plasma aldosterone concentration after 1 week (p<0.01) but not after 6 weeks (e.g., at 6 hours 102±74 after placebo, 58±46 after 1 week, and 71±24 pg/ml after 6 weeks). Enalapril had no significant effects on plasma norepinephrine.

Pharmacokinetics
A one-compartment model incorporating a parameter for saturable protein binding produced the best fit to the plasma enalaprilat concentration data from acute and steady-state study days. The pharmacokinetic parameters calculated for both bound and unbound enalaprilat are shown in Table 1. The mean values for the area under the plasma concentration curve (AUC) and elimination half-life were, respectively, 1,388±451 ng · hr/ml and 2.7±0.5 hours for unbound drug and correspondingly 147±95 ng · hr/ml and 16.8±9.4 hours for bound drug. Independent fits revealed no significant differences in the kinetics of enalaprilat between the first dose and 1 week and 6 weeks. In this group of patients, age did not influence the pharmacokinetics of enalaprilat.

Concentration–Effect Relations
There was no simple direct relation between plasma enalaprilat concentration and effect. The temporal discrepancy between kinetic and dynamic parameters is illustrated for a representative patient in Figure 3.

Plasma angiotensin converting enzyme inhibition. In individual patients, the plasma concentrations of enalaprilat were directly correlated with the inhibition of plasma ACE activity (relative to the placebo day) using the Langmuir equation. The data sets from each active drug study day were fitted independently. The individual fitted parameter values are given in Table 2. The E_max were comparable on all three study days and were not significantly different statistically, with means of 102.4±5, 103±5, and
FIGURE 3. Line graphs representing data for an individual patient (patient 3) after the first dose of enalapril (20 mg) showing temporal discrepancies between profiles of plasma enalaprilat concentration (Cen.) (○) and inhibition of plasma angiotensin converting enzyme (ACE) (●) activity (Panel A) and the placebo-corrected fall in erect systolic blood pressure (BP) (Panel B).

Table 2. Concentration–Effect Parameters for Maximum Inhibition Values and Concentration of Enalaprilat Producing Half of Maximum Inhibition for Changes in Plasma Angiotensin Converting Enzyme Activity

<table>
<thead>
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<th>Patient</th>
<th>E\text{\textsuperscript{\textregistered}} \text{max} (%)</th>
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<td>1 week</td>
<td>6 weeks</td>
<td>First dose</td>
<td>1 week</td>
<td>6 weeks</td>
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<td>102.3</td>
<td>10.2</td>
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<tr>
<td>Mean±SD</td>
<td>102.4±5</td>
<td>103.0±2</td>
<td>101.3±2</td>
<td>19.8±5</td>
<td>33.4±2</td>
<td>31.3±2</td>
</tr>
</tbody>
</table>

E\text{\textsuperscript{\textregistered}} \text{max}, maximum inhibition values; C\text{\textsubscript{50}}, concentration of enalaprilat producing 50% of E\text{\textsuperscript{\textregistered}} \text{max}.

*\textsuperscript{p}<0.01 compared with C\text{\textsubscript{50}} after 1 and 6 weeks.

Blood pressure. There was no simple direct relation between plasma enalaprilat concentration and the fall in blood pressure, and hysteresis was observed to varying degrees in all patients, as illustrated for a representative individual patient (Figure 4). However, by using the effect modeling approach, reductions of both systolic and diastolic blood pressure were correlated with enalaprilat levels in individual patients, yielding good fits of the blood pressure profiles as illustrated in the representative patient in Figure 4. In all cases, the kinetic–dynamic relations after acute and chronic dosing were described most appropriately by the Langmuir–E\text{\textsuperscript{\textregistered}} \text{max} model. For changes in systolic blood pressure, the data sets for the three study days were fitted both independently and simultaneously, and the derived concentration–effect parameters are shown in Tables 3 and 4. No advantage was obtained in fitting the data independently, and therefore simultaneous fitting was used to characterize the changes in diastolic blood pressure (Table 4). The mean values for E\text{\textsuperscript{\textregistered}} \text{max} were −46.1 mm Hg for systolic and −19.7 mm Hg for diastolic blood pressure, and the C\text{\textsubscript{50}} (the concentration of drug calculated to produce 50% of the maximum reduction) was, correspondingly, 66.1 and 61.6 ng/ml.

Relation to age, plasma renin, and pretreatment blood pressure. There were significant correlations between E\text{\textsuperscript{\textregistered}} \text{max} for systolic and E\text{\textsuperscript{\textregistered}} \text{max} for diastolic blood pressure after acute and chronic dosing (r=0.54, p<0.05). The E\text{\textsuperscript{\textregistered}} \text{max} (systolic and diastolic) was directly
related to the pretreatment blood pressure measured on placebo treatment, as illustrated for systolic blood pressure (Figure 5). In addition, there were significant correlations between $E_{\text{max}}$ after the first dose of enalapril and $E_{\text{max}}$ after 1 week and 6 weeks of treatment (Figure 6). There was no relation between $C_{50}$ (or $C_{50}$) and the age of the patients or the pretreatment plasma renin activity (Figure 5).

There was no significant relation between $C_{50}$ for ACE inhibition and $C_{50}$ for blood pressure, and additionally, there was almost an order of magnitude difference in the mean values for these parameters (e.g., 31.3 ng/ml for ACE inhibition after 6 weeks compared with 66.1 ng/ml for systolic blood pressure).

**Table 3.** Enalaprilat Concentration-Effect Parameters for Maximum Inhibition Values, Concentration of Enalaprilat Producing Half of Maximum Inhibition, and Rate Constant for Changes in Erect Systolic Blood Pressure Derived From Fitting Data Sets for Each Study Day Independently

<table>
<thead>
<tr>
<th>Patient</th>
<th>$E_{\text{max}}$ (mm Hg)</th>
<th>$C_{50}$ (ng/ml)</th>
<th>$K_{\text{eq}}$/hr</th>
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<tr>
<td></td>
<td>First dose</td>
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<td>6 weeks</td>
</tr>
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<td>-56</td>
<td>-52</td>
</tr>
<tr>
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<td>-71</td>
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<td>-57</td>
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<td>Mean±SD</td>
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<td>-44±20</td>
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$E_{\text{max}}$: maximum inhibition values; $C_{50}$: concentration of enalaprilat producing 50% of $E_{\text{max}}$; $K_{\text{eq}}$: first-order rate constant of the effect model.

**Discussion**

The role of enalapril in the treatment of essential hypertension is well established, but there is only limited information about the drug's disposition and pharmacokinetic properties and, in particular, about the relations between plasma drug concentrations and pharmacological effects. The principal finding of this study was that, although there was no simple direct relation between plasma enalaprilat concentration and the fall in blood pressure, there were significant correlations in individual patients when a Langmuir ($E_{\text{max}}$) model was used to describe the kinetic dynamic relations. By using the $E_{\text{max}}$ values, it was possible to demonstrate significant correlations...
between the antihypertensive effect of single and multiple doses, to confirm that the reductions in systolic and diastolic blood pressure were comparable, and to show that the magnitude of the antihypertensive effect was directly related to the pretreatment blood pressure but not to the age of the patient or the pretreatment plasma renin activity.

Few studies have examined the relation between plasma drug concentration and effect for ACE inhibitor drugs. It has been suggested that these drugs exhibit shallow, or flat, dose–response relations so that an increase in dosage may result in an extension of the duration of action but without any increase in the magnitude of the antihypertensive effect despite higher plasma drug concentrations. However, previous studies of concentration–effect relations have usually investigated data for groups of subjects or have assessed only maximal changes in blood pressure or peak plasma enalaprilat concentrations. In contrast, the present study investigated individual patients, with multiple measurements of blood pressure and plasma drug levels across a dosage interval, and confirmed and extended the findings of previous single-dose studies in normotensive subjects by additionally defining individual concentration–response relations in hypertensive patients during both acute and long-term treatment.

Although there was no simple direct plasma drug concentration–effect relation, integrated kinetic–dynamic analysis demonstrated that enalaprilat levels in individual patients could be closely correlated not only with changes in plasma ACE activity but also with reductions in systolic and diastolic blood pressure. Consistent with the observations of Tilk et al, a conventional pharmacokinetic model could not be used to satisfactorily describe all the features of the disposition, particularly the accumulation of enalaprilat during chronic therapy. A "physiologically realistic" model, based on the putative saturable binding of drug to ACE, was found to be appropriate for describing both the pharmacokinetics of enalaprilat and the kinetic–dynamic relations. The theoretical basis for this model, and other practical applications, have been investigated extensively, but with enalaprilat and with other ACE inhibitor drugs there is the unusual feature that the binding protein is an enzyme that is associated with the drug's mechanism of action and the therapeutic response. The requirement for an E\(_\text{max}\) model to characterize the concentration–effect relation is consistent with the previous proposal for a flat dose–response curve, as previous studies may have used doses that produced drug levels and antihypertensive effects on the top plateau of the E\(_\text{max}\) dose–effect curve.

What factors influenced the response to enalapril? The single, most important determinant of the hypertensive response to ACE inhibition by enalapril appeared to be the height of the starting (pretreatment) blood pressure. The antihypertensive effect of an ACE inhibitor is influenced by the activity of the renin-angiotensin system, but there is disagreement about the importance of plasma renin activity as a predictive marker of blood pressure response in salt-replete essential hypertensive patients in routine clinical practice. This study has shown that, in an unselected group of essential hypertensive patients on an unrestricted salt intake and with levels of plasma renin activity within the normal range, the response to enalapril cannot usefully and independently be predicted by plasma renin activity. Similarly, the response to enalapril was not significantly influenced by the age of the patient. However, the number of subjects in this study was relatively small and the age range (41–66 years) studied does not permit the extension of this conclusion to elderly patients in whom a reduction in the clearance of...
enalaprilat has been reported. It has been reported, both with captopril and with enalapril, that it takes several weeks to achieve a maximal blood pressure "response," and additionally it has been claimed that the first dose response to an ACE inhibitor drug is not related to the response observed during long-term treatment. In this study, which integrated the plasma drug levels and the measurements of blood pressure throughout the dosage interval, there was no significant difference in responsiveness ($E_{\text{max}}$ or C50) to enalapril when comparing first dose with 1 and 6 weeks of treatment. Thus, the profiles of antihypertensive effect were similar when allowances were made for changes in plasma drug concentration and changes in baseline (predosing) blood pressure during the 6 weeks of treatment.

In conclusion, this study defined concentration–effect relations for enalapril in individual patients with essential hypertension. The parameters derived from the integrated kinetic–dynamic analysis are potentially useful not only for investigating factors that contribute to the intersubject variability in response to ACE inhibition but also as a means of defining the optimal dose range.

Acknowledgments

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