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Comparative Pharmacodynamics of Olmesartan and Azelnidipine in Patients with Hypertension: a Population Pharmacokinetic/Pharmacodynamic Analysis

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Summary: The objectives of this study were to identify the factors influencing antihypertensive response to the angiotensin receptor blocker, olmesartan medoxomil, or the calcium channel blocker, azelnidipine, and to discuss the possibility of utilizing them as predictors for drug selection prior to therapy. A two-way crossover study of olmesartan medoxomil and azelnidipine was conducted in 29 patients with mild to moderate essential hypertension. The 24-hour ambulatory blood pressure measurements (ABPM) and plasma drug concentrations were obtained on the first and at the end of each treatment period, and were analyzed using population pharmacokinetic/pharmacodynamic (PK/PD) modeling approach. The population PK/PD models considering circadian variations in baseline blood pressure well described the observed plasma drug concentrations and 24-hour ABPM profiles. Pre-treatment plasma renin activity (PRA) was identified as a significant covariate on the maximum drug effect (Emax) of olmesartan, whereas azelnidipine Emax was independent of patient background characteristics investigated. No patient was found to have a high Emax to one agent who also had a high Emax to the other. In conclusion, the effects of olmesartan medoxomil and azelnidipine were modestly correlated with pharmacokinetic profiles, and the pre-treatment PRA level could be a useful determinant of responsiveness in selecting olmesartan medoxomil and azelnidipine.

Keywords: antihypertensive agents; individualization; population pharmacokinetics/pharmacodynamics; olmesartan medoxomil; azelnidipine

Introduction

Although the therapeutic guidelines for hypertension management have continued to evolve, the results of the treatment of hypertension still reveal a poor success rate in various nations, and the theoretical basis for a more optimized and individualized treatment strategy has been in demand.1–4) Interest has been focused on the identification of demographic, physiological or genetic factors which influence antihypertensive response.5–7) Pre-treatment plasma renin activity (PRA) has been proposed as one of the most promising predictors which could help guide the selection of antihypertensive therapy.8–10) It has been reported that antihypertensive drugs such as angiotensin receptor blockers (ARB),8–10) angiotensin converting enzyme (ACE) inhibitors,11,12) and β-blockers13) reduce blood pressure more in hypertensive patients with a higher pre-treatment PRA. In contrast, diuretics6,14) and calcium channel blockers (CCB)5) show a more antihypertensive response in patients with a low-renin state. In these studies, however, the antihypertensive agents were not administered in a crossover fashion, and therefore whether the observed average trends are also reproducible in each individual patient has not yet been clearly demonstrated considering that essential hypertension is a heterogeneous disorder. The other drawback of these studies is that the pharmacokinetic (PK) variability, which is another important factor determining antihypertensive response,16–18) was not adequately taken into consideration. Donnelly et al. pointed out that previous stu-
dies on the heterogeneity of antihypertensive response have neglected interindividual variability in the PK and consequently conflicting and, in some cases, misleading statements have been provided.\cite{16}

In this report, a two-way crossover study of the AT\(_1\)-receptor selective ARB olmesartan medoxomil\cite{19,20} and the dihydropyridine-type CCB azelnidipine\cite{21} was conducted in Japanese patients with mild to moderate essential hypertension, and 24-hour ambulatory blood pressure monitoring (ABPM) data and plasma drug levels were applied to covariate analyses by using a population pharmacokinetic/pharmacodynamic (PK/PD) modeling approach.\cite{22} For analyses of 24-hour ABPM data which are subject to circadian rhythms and different sources of variability (interindividual, interoccasionl, and residual variability), the population PK/PD modeling approach has been shown to be suitable because it can decompose these sources of variability in baseline.\cite{23}

Given these considerations, we investigated the factors which influence the antihypertensive response to treatment with olmesartan medoxomil or azelnidipine in essential hypertensive patients, and discussed the possibility of utilizing them as predictors for drug selection prior to therapy.

**Methods**

**Patients**

Thirty Japanese patients with mild to moderate essential hypertension, as defined by mean seated cuff blood pressure \(\geq 140/90\) and \(\leq 180/110\) mmHg and 24-hour ABPM mean blood pressure \(\geq 135/80\) mmHg at the end of a 4-week run-in period, were enrolled in this study. All patients gave written informed consent prior to participating in this study. The informed consent form and study protocol were approved by the local ethics committee.

**Study design**

This study was a single-center, randomized, open-label, 2-way crossover study of olmesartan medoxomil and azelnidipine as a monotherapy, which comprised a 4-week run-in period and two treatment periods of 8 weeks duration with a washout period of 4 weeks between two treatments. Eligible patients entered a run-in period, during which previous antihypertensive therapy was discontinued. Patients who fulfilled the entry criteria at the end of a run-in period were randomized to receive olmesartan medoxomil or azelnidipine for 8 weeks. The initial dosage was olmesartan medoxomil 10 mg once daily or azelnidipine 8 mg once daily. For patients who did not achieve the target blood pressure at the time of 4-week visit, the study drug doses were up-titrated to olmesartan medoxomil 20 mg or azelnidipine 16 mg, respectively. After a 4-week washout, patients receiving olmesartan medoxomil switched to azelnidipine, and vice versa.

**Ambulatory blood pressure monitoring:** The 24-hour ABPM were recorded during the fourth week of both the run-in and washout periods, and on the first (day 1) and at the end (week 8) of each treatment period. Measurements were taken every 30 minutes using a TM–2431\textsuperscript{R} Ambulatory Blood Pressure Monitor (A&D Company).

**Pharmacokinetic sampling:** Blood was sampled for PK from all patients just prior to the last dose and 1, 2, 4, 8, and 24 hours after the last dose on the days corresponding to the 24-hour ABPM measurements in each treatment period. The plasma concentrations of olmesartan and azelnidipine were determined by the validated liquid chromatography tandem mass spectrometry method. The lower limit of quantification for olmesartan was 1.0 ng/mL and for azelnidipine 0.1 ng/mL, with the intra-assay precision (% coefficient of variation) at 4.9% and 14.1% and the accuracy (% bias) at \(-6.0\%\) and \(-4.8\%\), respectively. Olmesartan or azelnidipine was extracted from plasma using a solid phase extraction disk plate Empore\textsuperscript{R} UR (3M Bioanalytical Technologies). The chromatographic system consisted of an Agilent 1100\textsuperscript{R} series pump (Agilent Technologies) and HTC-PAL\textsuperscript{R} auto sampler (CTC ANALYTICS), and an Inertsil\textsuperscript{R} Ph-3 (2.1 \(\times\) 150 mm; GL Science Inc.) was used as the analytical column. A Quattro Premier\textsuperscript{R} triple-quadrupole mass spectrometer (Waters Corporation) was used for mass spectrometric detection.

**Renin-angiotensin-aldosterone-system:** Supine blood samples were collected during the run-in period for the determination of the PRA, plasma renin concentration (PRC), plasma angiotensin I (Ang I) concentration, plasma angiotensin II (Ang II) concentration, plasma aldosterone concentration (PAC), and serum ACE activity. A 24-hour urine sample was collected during the run-in period to determine urinary sodium excretion (UNaV).

**Preliminary analysis**

For the purpose of preliminary analysis only, the ABPM data were averaged hourly for each patient and then used to calculate the mean blood pressure values over the following intervals: 24-hour period, day time (7:00–22:00), and night time (22:00–7:00). The change from baseline was calculated by subtracting the mean blood pressure at the run-in period from the corresponding value at the end of the treatment period, and the relationships between the change from baseline and covariates were confirmed using univariate regression analysis.

**Population pharmacokinetic/pharmacodynamic model building**

Nonlinear mixed-effects modeling\cite{22} was employed to analyze the plasma drug concentrations and 24-hour ABPM measurements. A sequential approach\cite{20} was used to develop the population PK/PD models: first, the PK models were developed and then baseline blood pressure
models to describe the 24-hour ABPM profile without drug treatment were built. Lastly, the drug effect model parameters were estimated using the 24-hour ABPM data with and without treatment, conditioning on the population parameter estimates of the final baseline blood pressure model, and individual Bayesian post hoc estimates of the PK parameters of the final PK model. Before performing the analysis, the number of 24-hour ABPM data was randomly reduced to 70 points per patient, so that at least 1 measurement in an approximately 1.5-hour interval was kept. Separate population PK/PD models were developed for olmesartan medoxomil and azelnidipine and for systolic blood pressure (SBP) and diastolic blood pressure (DBP).

**Software:** NONMEM software version V (double precision, level 1.1) was used to conduct the population analysis. The first-order conditional estimation (FOCE) method with an interaction option was predominantly employed throughout the NONMEM analyses. All other statistical analyses, data handling, and graphing were performed using S-PLUS 7J (Insightful Corporation) and SAS version 8.2 (SAS Institute).

**Population PK model:** Because olmesartan medoxomil is a prodrug that is rapidly and completely de-esterified to the active metabolite olmesartan during its absorption, the PK modeling was based on the plasma olmesartan concentration data. Both 1-compartment and 2-compartment open models with first-order absorption, as implemented in the NONMEM subroutines ADVAN2/TRANS2 and ADVAN4/TRANS4 respectively, were investigated. Interindividual random variability was modeled for as many PK parameters as possible, if parameter identifiability was evident. Intercostational random variability was considered in the absorption-related parameters, because each patient had both single dosing (day 1) and steady state (week 8) profiles available, which were assumed to represent 2 separate occasions. The interindividual variability and intercostational variability were modeled as an exponential function as shown:

$$ \theta = \theta_1 \cdot \exp (\eta + \kappa) $$

(1)

where $\theta$ is the individual estimate of parameter; $\theta_1$ is the typical population estimate; $\eta$ is the interindividual random-effect of mean 0 and variance $\omega_{\eta i}$; and $\kappa$ is the intercostational random-effect of mean 0 and variance $\omega_{\kappa i}$. The residual variability was modeled with an exponential error model as shown:

$$ y_{ij} = \bar{y}_{ij} \cdot \exp (\varepsilon) $$

(2)

where $y_{ij}$ and $\bar{y}_{ij}$ represent the jth observed or predicted concentration for the ith patient, respectively, and $\varepsilon$ is the residual random-effect of mean 0 and variance $\sigma^2$.

**Baseline blood pressure model:** Since the 24-hour ABPM measurements are subject to circadian variations, a baseline blood pressure model to describe the circadian rhythm in blood pressure over a 24-hour period was built using the data from both the run-in and washout periods (two 24-hour profiles per patient). The circadian rhythm was modeled by a cosinor analysis, which characterizes the rhythm by sums of 2 or more oscillators (cosine functions) with different periods. The baseline blood pressure model for the ABPM measurements was represented as follows:

$$ Bsl(t) = (\theta_1 + \eta_1 + \kappa_1) \cdot \left[ 1 + \sum_{i=1}^{n} \theta_{2i} \cdot \exp (\eta_{2i}) \right] \cdot \cos \left( \frac{2 \pi \cdot i \cdot \left( t - \theta_{3i} - \eta_{3i} \right)}{24} \right) + \varepsilon $$

(3)

where $Bsl(t)$ is the baseline blood pressure as a function of $t$ (clock time); $\theta_1$ is the mesor (acronym for the midline estimating statistic of rhythm, that is the rhythm-adjusted mean blood pressure over 24 hours [mmHg]); $\theta_{2i}$ are amplitudes of cosine terms; $\theta_{3i}$ are acrophases (timing of cosine maximum [hr]) of cosine terms; $\eta_1$, $\eta_{2i}$, and $\eta_{3i}$ are the interindividual random variability in the mesor, amplitudes, and acrophases, respectively; $\kappa_1$ is the intercostational random variability in the mesor; and $\varepsilon$ represents the additive residual variability. The optional number of the cosine functions, $n$, was selected based on the objective function values (OFVs; minus twice the log likelihood), parameter identifiability, and prior knowledge.

**Population pharmacokinetic/pharmacodynamic model:** A full population PK/PD model was developed using all the ABPM data with and without drug treatment (four 24-hour profiles per patient for each drug). Three models of blood pressure change from baseline were considered. The first model assumed that the size of drug effect was related to the baseline blood pressure, which included the individual mesor as a covariate as shown:

$$ BP(t) = Bsl(t) - \text{mesor} \cdot E(t) $$

(4)

where $BP(t)$ is the blood pressure; $E(t)$ is the drug effect as a fractional change in the baseline mesor. The second model was the same as the first model except that the circadian rhythm in the baseline was considered as shown:

$$ BP(t) = Bsl(t) - Bsl(t) \cdot E(t) $$

(5)

where $E(t)$ is the drug effect as a fractional change in the baseline blood pressure at the corresponding clock time $t$. The third model assumed that the size of drug effect was independent of the baseline as shown:

$$ BP(t) = Bsl(t) - E(t) $$

(6)

where $E(t)$ is the absolute change from baseline. The drug effect, $E(t)$, was modeled by using a linear, $E_{\text{max}}$, and sigmoid $E_{\text{max}}$ model. The interindividual random variability of the drug effect model parameters was modeled exponentially. Both a direct link model and an effect com-
partment model\(^{30}\) were considered for the relationship between the drug concentration and the drug effect. The effect compartment model was fitted using the subroutines ADVAN4 and ADVAN5\(^{25}\) for the 1-compartment and 2-compartment PK models, respectively. Model selection was based on such criteria as the goodness-of-fit plots, estimates and standard errors of the population parameters, parameter identifiability, and OFVs.

**Covariate model selection:** The influence of covariates was evaluated after each structural model was developed. The covariates considered in the PK model parameters were demographic factors [age, body weight, body mass index, gender], indices of renal function [serum creatinine (SCr) and creatinine clearance (CLcr) predicted with the Cockcroft-Gault equation\(^{31}\)], and indices of hepatic function [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBIL), gamma glutamyl transferase (GGT)]. The dose was also tested as a covariate. The covariates considered in the drug effect model parameters were the PRA, PRC, Ang I, Ang II, PAC, ACE activity, and UNaV at baseline. Gender and dose were the categorical covariates, which were modeled by use of an indicator variable (0/1) as follows:

\[
\theta = \theta _{0} \cdot (1 + K_{COV} \cdot \text{covariate})
\]  

(7)

where \(K_{COV}\) is the covariate scale factor. Continuous covariates were modeled as an exponential function and centered at the patients’ median value (median\(_{COV}\)) as shown:

\[
\theta = \theta _{0} \cdot \left( \frac{\text{covariate}}{\text{median}_{COV}} \right)^{K_{COV}}
\]  

(8)

or modeled as a linear function of the centered covariate value as shown:

\[
\theta = \theta _{0} + K_{COV} \cdot (\text{covariate} - \text{median}_{COV})
\]  

(9)

The parameter-covariate relationships were explored first by visual inspection and a linear regression. The covariates thus screened were tested individually using stepwise inclusion in the NONMEM with the use of a likelihood ratio test (\(p < 0.05\)).

**Model evaluation:** The ability of the final PK and PK/PD models to describe the observed data was investigated via the visual predictive check. Ten thousand patients were simulated with covariates values resampled from those observed in this study for the population PK models and two hundred replicates of the original dataset were simulated for the population PK/PD models using the fixed- and random-effect parameter estimates of the final models. The key parameter estimate was evaluated using the log-likelihood profiling.\(^{32}\) The resulting changes in the OFVs were plotted as a function of the selected parameter estimates and interpolated by using a cubic spline.

### Table 1. Description of patients’ characteristics (\(N = 29\))

<table>
<thead>
<tr>
<th>Characteristics (unit)</th>
<th>Mean (SD)</th>
<th>[Range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>22/7</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>54.4 (7.13)</td>
<td>[36, 64]</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>66.2 (10.6)</td>
<td>[45.5, 93.3]</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>99.3 (24.6)</td>
<td>[55.23, 157.83]</td>
</tr>
<tr>
<td>Plasma renin activity (ng/mL/hr)</td>
<td>0.624 (0.476)</td>
<td>[0.1, 1.8]</td>
</tr>
<tr>
<td>Plasma renin concentration (pg/mL)</td>
<td>4.31 (2.59)</td>
<td>[0, 10]</td>
</tr>
<tr>
<td>Plasma Ang I concentration (pg/mL)</td>
<td>457 (148)</td>
<td>[240, 770]</td>
</tr>
<tr>
<td>Plasma Ang II concentration (pg/mL)</td>
<td>4.62 (2.18)</td>
<td>[0, 12]</td>
</tr>
<tr>
<td>Plasma aldosterone concentration (pg/mL)</td>
<td>125 (34.9)</td>
<td>[81, 228]</td>
</tr>
<tr>
<td>Serum ACE activity (IU/L)</td>
<td>11.8 (3.04)</td>
<td>[2.3, 16.3]</td>
</tr>
<tr>
<td>Urinary sodium excretion (g/24hr)</td>
<td>3.44 (0.945)</td>
<td>[1.54, 5.82]</td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; Ang, angiotensin; SD, standard deviation. The creatinine clearance was estimated using the Cockcroft-Gault equation.

### Results

**Patient characteristics**

Of the 30 hypertensive patients enrolled, there was one patient where the inclusion criteria was not fulfilled and who was therefore excluded. The remaining 29 patients were employed in the analyses. Table 1 summarizes the key demographic characteristics of the patients.

**Preliminary analysis**

The 24-hour mean, daytime mean, and night time mean of the ambulatory DBP and SBP and their changes from baseline are displayed in Table 2. The results of the univariate regression of change from baseline in the 24-hour mean SBP against each covariate are shown in Figure 1. Each bar represents the predicted influence of a single covariate on the 24-hour mean SBP change. The change from baseline in the mean blood pressure for olmesartan appeared to be largely influenced by the renin-angiotensin-related factors (PRA, PRC, Ang I, Ang II, and PAC), whereas that for azelnidipine was relatively stable within the observed range of these factors. The plasma drug exposures (AUC\(_{0-24}\)) for azelnidipine and olmesartan were modestly correlated with their blood pressure responses.

**Population pharmacokinetic/pharmacodynamic model building**

**Population PK model:** A total of 317 measurable plasma concentration data of olmesartan and 308 of azelnidipine were examined. The PK of olmesartan was best described by a 1-compartment linear model with first-order absorption and an absorption lag-time. CLcr was identified as a significant covariate on the apparent clearance (\(CL/F\)) (\(\Delta OFV = -9.285; **p < 0.01\)) and was incorporated into the model as shown:

\[
CL/F = CL/F_{T} \cdot \left( \frac{CLcr}{95.93} \right)^{0.319}
\]  

(10)
Table 2. Mean ambulatory blood pressures and their changes from baseline

<table>
<thead>
<tr>
<th>Variables</th>
<th>Azelnidipine</th>
<th></th>
<th>Olmesartan medoxomil</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 8</td>
<td>ΔBP</td>
<td>Week 8</td>
</tr>
<tr>
<td>24-hour mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>156.8 (10.0)</td>
<td>141.6 (8.7)</td>
<td>−15.2 (8.7)</td>
<td>141.3 (14.9)</td>
</tr>
<tr>
<td>DBP</td>
<td>96.8 (5.8)</td>
<td>89.7 (4.8)</td>
<td>−7.0 (5.2)</td>
<td>89.8 (7.1)</td>
</tr>
<tr>
<td>Day time mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>162.0 (10.0)</td>
<td>147.0 (9.1)</td>
<td>−15.0 (10.5)</td>
<td>146.3 (14.4)</td>
</tr>
<tr>
<td>DBP</td>
<td>100.1 (6.8)</td>
<td>92.7 (5.8)</td>
<td>−7.4 (6.5)</td>
<td>93.4 (7.6)</td>
</tr>
<tr>
<td>Night time mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>148.3 (12.9)</td>
<td>132.3 (10.4)</td>
<td>−15.9 (8.6)</td>
<td>132.9 (17.5)</td>
</tr>
<tr>
<td>DBP</td>
<td>91.1 (6.6)</td>
<td>84.7 (4.8)</td>
<td>−6.3 (5.4)</td>
<td>84.0 (7.6)</td>
</tr>
</tbody>
</table>

ΔBP, change from baseline in mean blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

Values are expressed as the mean (SD).

Change from baseline in 24-hour mean systolic blood pressure [mmHg]

Fig. 1. Sensitivity plot of univariate regression analysis comparing the effect of covariates on change from baseline in 24-hour mean systolic blood pressure.
The labels at each end of the bar represent the extremes of the covariate range. Each bar describes the predicted blood pressure change for individuals with specified characteristics. The values adjacent to each bar on the right are the P values of each coefficient. The solid vertical lines are the mean values. ACE, angiotensin converting enzyme; Ang, angiotensin; AUCss, area under the plasma drug concentration curve for a 24-hour interval at steady state (week 8); BP, blood pressure; CLcr, creatinine clearance; NS, not significant; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PRC, plasma renin concentration; UNaV, urinary sodium excretion.

where CLcr is in mL/min. A decrease in CLcr by half could result in a reduction of olmesartan CL/F of approximately 20%. The interindividual variability in CL/F fell from 28.5% in the basic model to 25.5% in the final model by incorporating CLcr as a covariate.

The PK of azelnidipine was best described by use of a...
Table 3. Population parameter estimates of pharmacokinetic models of olmesartan and azelnidipine

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Estimate (%CV)</th>
<th>IIV (%CV)</th>
<th>IOV (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olmesartan:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>4.92 (5.33)</td>
<td>0.0648 (22.1)</td>
<td>NT</td>
</tr>
<tr>
<td>Effect of CLcr</td>
<td>0.319 (32.9)</td>
<td>0.0470 (34.0)</td>
<td>NT</td>
</tr>
<tr>
<td>$k_a$ (hr)</td>
<td>37.4 (4.97)</td>
<td>0.0470 (34.0)</td>
<td>NT</td>
</tr>
<tr>
<td>Absorption lag-time (hr)</td>
<td>0.911 (2.73)</td>
<td>NE</td>
<td>1.35 (24.4)</td>
</tr>
<tr>
<td>Residual variability ($\sigma^2$)</td>
<td>0.111 (12.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azelnidipine:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>75.6 (10.5)</td>
<td>0.0650 (40.9)</td>
<td>NT</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>557 (9.32)</td>
<td>0.0108 (52.7)</td>
<td>NT</td>
</tr>
<tr>
<td>Q/F (L/hr)</td>
<td>48.2 (10.9)</td>
<td>NE</td>
<td>NT</td>
</tr>
<tr>
<td>$k_e$ (hr)</td>
<td>1090 (10.6)</td>
<td>NE</td>
<td>NT</td>
</tr>
<tr>
<td>Absorption lag-time (hr)</td>
<td>0.971 (0.784)</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>$F_{relax}$</td>
<td>0.8047 (41.8)</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>16 mg compared with 8 mg</td>
<td>1.554 (14.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>female compared with male</td>
<td>1.710 (34.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual variability ($\sigma^2$)</td>
<td>0.141 (12.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

%CV, standard error/parameter estimate X 100; CL/F, apparent clearance; CLcr, creatinine clearance; $F_{relax}$, relative bioavailability using the data from male administered 8 mg as a reference; IIV, interindividual random variability (\(\sigma_{ind}^2\)); IOV, interoccasion random variability (\(\sigma_{occ}^2\)); $k_a$, absorption rate constant; NE, not estimable; NT, not tested; Q/F, intercompartmental clearance; V/F, apparent volume of distribution; Vp/F, apparent volume of distribution in the peripheral compartment.

2-compartment linear model with first-order absorption and an absorption lag-time. The relative bioavailability ($F_{relax}$) was parameterized using the data from male patients administered 8 mg as a reference (i.e. $F_{relax} = 1$). The dose-dependent increase in $F_{relax}$ was estimated to be 55.4% higher at 16 mg than at 8 mg ($\Delta$OFV = -39.046; **p < 0.001). The gender-effect on $F_{relax}$ was estimated to be 71.0% higher in females than males ($\Delta$OFV = -9.855; *p < 0.01), and the interindividual variability in $F_{relax}$ decreased from 38.1% to 29.1% by incorporating the gender-effect. The body weight was also statistically significant ($\Delta$OFV = -4.661; *p < 0.05) as a single covariate on $F_{relax}$, but could not provide further model improvement ($\Delta$OFV = -0.648; p > 0.05). The population parameter estimates of the final models are listed in Table 3.

Figure 2 shows the observed plasma drug concentrations for olmesartan and azelnidipine, together with the 2.5th, 50th and 97.5th percentiles calculated from a simulation based on the final population PK model. The model accurately described the observed data.

Baseline blood pressure model: Baseline blood pressure models and population PK/PD models were separately developed for SBP and DBP. Since the modeling processes and their results for both blood pressure variables were similar, only the results for SBP which showed clearer results than DBP are reported in detail below. The circadian variation in baseline blood pressure was well described by a cosinor analysis. The optimal number of cosine functions was determined to be 3. Introduction of a 4th cosine function (4-hour period) to the model could improve the OFV ($\Delta$OFV = -24.150). However, the parameter identifiability was insufficient. Introduction of the interoccasion variability in the mesor significantly improved the model ($\Delta$OFV = -148.165), but it was later removed from the final baseline blood pressure model because the interoccasion variability in the mesor and interindividual variability in the $E_{max}$ were found to be not separately estimable. The population parameter estimates of the final models are given in Table 4.

Population PK/PD model: An $E_{max}$ model well described the 24-hour ABPM profiles with and without treatment for both olmesartan and azelnidipine. A linear model and a sigmoid $E_{max}$ model did not provide better fits. The three models of blood pressure change from baseline were not clearly distinguishable by the OFVs, but the model with the individual mesor as a covariate (equation 4) was slightly more stable than the other two overall. An effect compartment was needed for olmesartan, and the estimate of the elimination rate constant from the effect compartment ($k_{d0}$) was sufficiently small [$k_{d0} = 0.00329$ (hr)]. As for azelnidipine, the introduction of an effect compartment could not reduce the OFV significantly ($\Delta$OFV = -0.707), suggesting that the delay between the plasma concentration profile and the drug effect time-course was not evident from the data. However, since the earlier clinical trial demonstrated that the response to azelnidipine took 4 weeks to reach its steady state, the following baseline $E_{max}$ model was considered for the steady state data (week 8) to test this delay:

$$E(t) = E_a + \frac{E_{max} \cdot C(t)}{C_{50} + C(t)}$$

for steady state (11)

where $E_{max}$ is the maximum drug effect; $C_{50}$ represents the potency (drug concentration resulting in half of $E_{max}$); $E_a$ represents the baseline change due to the delayed drug response that needs 4 weeks to reach its steady state. Incorporation of $E_a$ as a fixed-effect significantly improved the model ($\Delta$OFV = -13.394). The dose-dependent difference in $E_a$ was further tested but was not statistically significant. The interindividual variability could be estimated in only $E_{max}$, and those in the other drug effect parameters were not introduced due to an identifiability problem or showing no significant decrease in OFV. As a result of covariate analyses, the pre-treatment PRA was identified as a significant covariate on olmesartan $E_{max}$ ($\Delta$OFV = -5.610; *p < 0.05) and was incorporated into
Fig. 2. Visual predictive check of the population pharmacokinetic models of olmesartan and azelnidipine after single dosing (day 1) and at steady state (week 8, for starting doses and up-titrated doses). The datapoints are the observed plasma drug concentrations, and lines are the 2.5th, 50th (bold) and 97.5th percentiles of the simulated plasma drug concentrations.

Fig. 3. (a) Individual predicted maximum drug effect ($E_{\text{max}}$) of olmesartan for ambulatory systolic blood pressure versus pre-treatment plasma renin activity (PRA). The solid line represents the population model equation for olmesartan $E_{\text{max}}$. (b) Log-likelihood profile for the slope parameter describing the relationship between pre-treatment PRA and olmesartan $E_{\text{max}}$.

\[ E_{\text{max}} = E_{\text{max,0}} + 4.56 \cdot (\text{PRA} - 0.45) \]  

where PRA is in ng/mL/hr. An increase in PRA of 1 ng/mL/hr could result in an increase of olmesartan $E_{\text{max}}$ by 4.56% of the mesor. The interindividual variability in $E_{\text{max}}$ decreased from 50.3% in the basic model to 44.4% in the final model. Plots of individual Bayesian post hoc estimates of $E_{\text{max}}$ versus PRA are given in Figure 3a. The likelihood profile for the slope parameter describing changes of olmesartan $E_{\text{max}}$ with PRA (point estimate 4.56 in equation 12) is shown in Figure 3b. Its profile-liekli-
comparative pharmacodynamics of olmesartan and azelnidipine

Table 4. Population parameter estimates of pharmacokinetic/pharmacodynamic models of olmesartan and azelnidipine for systolic blood pressure

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Estimate (%CV)</th>
<th>IIV (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline blood pressure model for SBP:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesor (mmHg)</td>
<td>153 (1.24)</td>
<td>101 (22.7)</td>
</tr>
<tr>
<td>Amplitude, 24-hour period</td>
<td>0.0497 (20.3)</td>
<td>0.500 (63.4)</td>
</tr>
<tr>
<td>Amplitude, 12-hour period</td>
<td>0.0153 (8.78)</td>
<td>NE</td>
</tr>
<tr>
<td>Amplitude, 8-hour period</td>
<td>0.00995 (38.9)</td>
<td>0.923 (59.0)</td>
</tr>
<tr>
<td>Acrophase, 24-hour period (hr)</td>
<td>14.32 (5.16)</td>
<td>1.72 (44.4)</td>
</tr>
<tr>
<td>Acrophase, 12-hour period (hr)</td>
<td>8.93 (14.9)</td>
<td>1.08 (45.7)</td>
</tr>
<tr>
<td>Acrophase, 8-hour period (hr)</td>
<td>10.62 (4.53)</td>
<td>NE</td>
</tr>
</tbody>
</table>

Drug effect model parameters for olmesartan:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (%CV)</th>
<th>IIV (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_{e0} ) (hr)</td>
<td>0.00329 (240)</td>
<td>NE</td>
</tr>
<tr>
<td>( E_{ma0} ) (% of mesor) at PRA = 0.45 ng/mL/hr</td>
<td>7.76 (16.0)</td>
<td>0.197 (57.9)</td>
</tr>
<tr>
<td>Effect of PRA (% of mesor/čg/mL/hr)</td>
<td>4.56 (43.6)</td>
<td>NE</td>
</tr>
<tr>
<td>( EC_{50} ) (ng/mL)</td>
<td>4.84 (264)</td>
<td>NE</td>
</tr>
<tr>
<td>Residual variability (( \sigma^2 ))</td>
<td>270 (8.89)</td>
<td>NE</td>
</tr>
</tbody>
</table>

Drug effect model parameters for azelnidipine:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (%CV)</th>
<th>IIV (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( E_{ma0} ) (% of mesor)</td>
<td>11.2 (27.5)</td>
<td>0.283 (43.5)</td>
</tr>
<tr>
<td>( C_{io} ) (ng/mL)</td>
<td>14.8 (41.4)</td>
<td>NE</td>
</tr>
<tr>
<td>( E_{e} ) (% of mesor)</td>
<td>3.18 (36.5)</td>
<td>NE</td>
</tr>
<tr>
<td>Residual variability (( \sigma^2 ))</td>
<td>255 (7.41)</td>
<td>NE</td>
</tr>
</tbody>
</table>

%CV, standard error/parameter estimate \( \times 100; \) \( C_{io} \), potency; \( E_{e} \), baseline change due to the delayed drug response; \( EC_{50} \), potency for an effect compartment model; \( E_{ma0} \), maximum drug effect; IIV, interindividual random variability (\( \sigma^2 \); \( k_{e} \), elimination rate constant from effect compartment; mesor, rhythm-adjusted mean blood pressure over 24 hours; NE, not estimable; PRA, plasma renin activity; SBP, systolic blood pressure.

Table 4. Population parameter estimates of pharmacokinetic/pharmacodynamic models of olmesartan and azelnidipine for systolic blood pressure

The effects of the selected covariates on the plasma drug concentration profile and the 24-hour ABPM profile at steady state (week 8) were explored using a simulation approach. Figure 5 shows the predicted time course of plasma drug concentrations and blood pressure at steady state (8 weeks) in typical patients with a single covariate altered. For example, Figure 5a depicts the typical plasma olmesartan concentration time-courses in patients with Clcr at median and the extremes of range in the present study, and Figure 5d describes the typical 24-hour ambulatory systolic blood pressure time-courses in patients with pre-treatment PRA at median and the extremes of range. These results demonstrate that pre-treatment PRA could be influential on the antihypertensive response to olmesartan, but the impacts of the covariates influencing PK parameters (i.e., Clcr for olmesartan, gender for azelnidipine) on the antihypertensive response would be considered minimal.

A scatter plot of the individual predicted \( E_{ma0} \) of olmesartan versus that of azelnidipine is shown in Figure 6a. No patient was found to have a high \( E_{ma0} \) to one agent who also had a high \( E_{ma0} \) to the other. Six representative patients who showed a pronounced responsiveness to either drug (patient ID 7, 11, 24 for azelnidipine, and ID 5, 19, 27 for olmesartan) were identified in the plot of pre-treatment PRA versus UNaV (Fig. 6b). Based on the plasma renin-urinary sodium profile classification as defined by Laragh et al.,3,34 3 patients with a pronounced responsiveness to azelnidipine were classified as having a low renin profile, where the low renin profile means that the relation of PRA and UNaV is below the range established by the normotensive volunteers. The 24-hour SBP measurements and the individual predictions for 2 of the 6 representative patients with a pronounced responsiveness are shown in Figure 7.

Discussion

The present study was designed to model the population PK/PD of both the ARB olmesartan medoxomil and the CCB azelnidipine using 24-hour ABPM data, and to identify the demographic or physiological determinants of the antihypertensive response to treatment with olmesartan medoxomil or azelnidipine in Japanese patients with mild to moderate hypertension. It was demonstrated that the pre-treatment PRA level was a significant covariate of the azelnidipine antihypertensive response to olmesartan. As for the CCB azelnidipine, an antihypertensive response was observed in all patients, and patient background characteristics investigated, including pre-treatment PRA, were not identified as a clinically significant covariate of the azelnidipine antihypertensive response. Resnick et al., however, have reported a negative correlation between the extent of blood pressure reduction after nifedipine administration and pre-treatment PRA.35 One reason for this disagreement could be the difference in the distribution of pre-treatment PRA between these studies. It was reported that salt intake was high in the Japanese population and low-renin hyperten-
The Japanese patients in the current study exhibited pre-treatment PRA values which were relatively low and were categorized as having a normal or low renin profile in the classification of hypertensive patients defined by Laragh et al.\(^{3,34}\) (Fig. 6b). Based on the hypothesis contrasting rennin activity-dependent and volume-dependent forms of hypertension,\(^3\) we hypothesized that UNaV was also a likely predictor of responsiveness to olmesartan medoxomil or azelnidipine. However, this study could not detect its clinically significant effect for both drugs. It must be noted that this study involved a relatively small number of patients and type II error in covariate selection cannot be excluded. The results need to be further confirmed by a larger sample.

The major strength of the current study was that it was designed as a crossover trial; consequently, responsiveness to olmesartan and azelnidipine could be compared within individual patients. Interestingly, it was found that there was no patient with a pronounced responsiveness to one drug who associated with a pronounced responsiveness to the other. It was also found that the 3 representative patients with a pronounced responsiveness to azelnidipine were classified as low renin patients\(^{3,34}\) (Fig. 6b). Considering that plasma renin levels change in response to changes in dietary salt to sustain blood pressure,\(^3,34,36\) it is reasonable that the forms of hypertension, renin activity-dependent or volume-dependent, are determined by the statuses of both renin activity and UNaV. Although UNaV was not selected as a significant covariate on drug effect in the present study, this finding indicates a possibility that UNaV, in combination with pre-treatment PRA, may be a predictor of responsiveness to azelnidipine.

The population PK analyses indicated that CLcr was identified as a significant covariate on olmesartan CL\(/F\) and a decrease in CLcr by half could result in a reduction of CL\(/F\) of approximately 20%. These results were similar to those previously reported.\(^{38}\) As for azelnidipine, a gender-related difference in relative bioavailability was indicated, and this could not be explained by body weight. The presence of a gender-difference in bioavailability, higher in females than males, was suggested in some drugs,\(^{39}\) including the dihydropyridine-type CCB amlodipine.\(^{40}\) These covariates were considered less important from the point of view of antihypertensive response (Fig. 5e and 5f). It is not surprising because if a dose of olmesartan medoxomil 20 mg or azelnidipine 16 mg were administered once daily, the predicted effect site drug concentrations at steady state were much higher than the estimated \(EC_{50}\) for olmesartan and azelnidipine. In the preliminary analysis, azelnidipine showed a more pronounced decrease of mean blood pressure in females than in males (Fig. 1). Most of the observed
Fig. 5. Population predicted time-courses of plasma drug concentrations at steady state. (a) in patients with creatinine clearance (CLcr) at median and the extremes of range (olmesartan medoxomil 20 mg once daily), (b) in males and females (azelnidipine 16 mg once daily), (c) after treatment with azelnidipine 8 mg or 16 mg once daily; and population predicted time-courses of 24-hour ambulatory systolic blood pressure at steady state: (d) in patients with pre-treatment plasma renin activity (PRA) at median and the extremes of range (olmesartan medoxomil 20 mg once daily), (e) in patients with CLcr at median and the extremes of range (olmesartan medoxomil 20 mg once daily) [the lines mostly overlap each other], (f) in males and females (azelnidipine 16 mg once daily).

Fig. 6. (a) Scatter plot of individual predicted maximum drug effect ($E_{\text{max}}$) of olmesartan for systolic blood pressure versus that of azelnidipine, where patients are identified by their ID numbers and those with a pronounced responsiveness are shown by closed symbols. (b) Plot of the baseline plasma renin activity (PRA) against urinary sodium excretion (UNaV) where the patients are identified, correspondingly. Dashed lines refer to the border of the normal range of the relation of PRA and UNaV which was previously defined by Laragh et al. 3,34
difference between genders could be explained by the difference in the baseline blood pressure (data not shown), which was compatible with our model implications. However, it remains to be elucidated because the number of female patients enrolled was limited.

The population PK/PD analyses demonstrated that the drug effect of olmesartan at steady state was maintained constantly throughout the dosing intervals, which was well described by an effect compartment model with a small $k_0$ parameter estimate displaying a pronounced hysteresis. This result may partly reflect the slow dissociation kinetics from Ang II receptor, the so-called insurmountable blockade, reported for olmesartan. It should be noted that $k_0$, and in consequence $EC_{50}$, could not be precisely estimated from the data and the coefficient of variation (SE/estimate $\times 100\%$) of these parameter estimates were 240% and 264%, respectively (Table 4), probably because the 24-hour ABPM profiles were obtained at day 1 and week 8 only. However, equilibrium half-life based on the estimated $k_0$ was 8.8 days (i.e. approximately 4 weeks to 90% of equilibrium), which was comparable with the previously reported time to maximum antihypertensive response to olmesartan medoxomil. As for azelnidipine, it was reported that its antihypertensive response took 4 weeks to reach its steady state. However, in the current study the introduction of an effect compartment could not improve the model. Instead, the baseline blood pressure reduction term, $E_o$, was significant, indicating that along with the immediate depressor effect, a long-delayed response which could not be explained from the direct link model might exist. The dose-dependent difference in $E_o$ was anticipated but was not statistically significant, possibly due to the dose titration design. The CCB lowers blood pressure not only by reducing the intracellular calcium levels but also by its natriuretic effect, which might contribute to the observed phenomenon. Another possibility is the paucity of the PK samplings, especially around its time to maximum concentration ($\sim 2.2$ hour). They might not have been sufficient to sensitively detect the putative hysteresis due to the high lipophilicity characteristics of azelnidipine.

In conclusion, the present study shows PK/PD relationships of the ARB olmesartan medoxomil and the CCB azelnidipine in Japanese hypertensive patients using 24-hour ABPM data and gives important clinical implications for the predictive performance of pre-treatment PRA for antihypertensive response to these agents through the covariate analyses. Our findings further support the concept regarding classification of hypertension contrasting renin activity-dependent and volume-dependent forms, and help physicians to optimize treatment, especially in the choice of an ARB or CCB.

References


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