Population pharmacokinetic-pharmacodynamic modeling of moxonidine using 24-hour ambulatory blood pressure measurements

Objectives: To develop a model for 24-hour ambulatory blood pressure measurements (ABPM) that can be applied in a pharmacokinetic-pharmacodynamic model.
Methods: Four different data sets were prepared from 2 studies to accommodate different modeling strategies. In study A, a double-blind placebo-controlled study in 47 patients, 24-hour ABPM profiles (74 to 99 measurements per profile) were obtained during the placebo run-in phase and after 3, 5, and 11 weeks during the treatment. Three to 5 plasma samples were taken. Cosine and polynomial models were evaluated to describe the circadian rhythm in blood pressure based on 3 data sets (1: only run-in data; 2: only placebo data; 3: all data). In study B, a double-blind placebo-controlled study in 94 patients, two 24-hour ABPM profiles per patient (during placebo run-in and after 8 weeks) were recorded and randomly reduced to 15 measurements per profile to evaluate the robustness of the baseline model.
Results: The mean moxonidine clearance was 35 L/h, and the volume of distribution was 132 L. The final baseline model consisted of 2 cosine terms with fixed-effect parameters for rhythm-adjusted 24-hour mean blood pressure, amplitude, phase, and period; random-effect parameters for interindividual variability in rhythm-adjusted 24-hour mean, amplitude, and clock time; and interoccasion variability in rhythm-adjusted 24-hour mean and clock time. The final baseline model was combined with an E_{max} model for the drug effect. An effect compartment was used (k_{eo} = 0.198 h^{-1}). The maximum decrease in diastolic blood pressure (E_{max}) was 16.7%, and EC_{50} was 0.945 μg/L.
Conclusion: The pharmacokinetic-pharmacodynamic model for 24-hour ABPM can be used to estimate the concentration-effect relationship of antihypertensive drugs. (Clin Pharmacol Ther 1998;64:622-35.)

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With the availability of automated devices to measure blood pressure noninvasively and continuously, most of the recent phase II and III clinical trials for antihypertensive drugs have used this method to evaluate the effect of the drug on the 24-hour blood pressure profile. Regulatory authorities require 24-hour ambulatory blood pressure measurements (ABPM) to be included in the New Drug Application submission. However, regulatory approval is still based on conventional cuff blood pressure measurements. This lack of acceptance of 24-hour ABPM for approval has several reasons, including (1) the lack of concordance between ABPM and office mercury sphygmomanometry, (2) the fact that a decrease in conventional cuff blood pressure measurements has been shown to be associated with a decrease in mortality, which has yet to be shown for 24-hour ABPM, and (3) the absence of harmonized statistical methods for its analysis. The Food and Drug Administration has therefore initiated a program to retrospectively evaluate its 24-hour ABPM database to

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Table I. Description of the data sets used and patient demographics

	Data set 1	*Data set 2*	*Data set 3*	*Data set 4*
Study	A	A	A	B
Treatment	Placebo	Placebo	Placebo + drug	Placebo
No. of patients	47	9	21 drug, 9 placebo	94
Sex				
Women	14	5	10	51
Men	33	4	20	43
Age (yr)*	59.2 ± 10.2	58.9 ± 10.0	59.4 ± 11.6	53.5 ± 8.7
Weight (kg)*	82.2 ± 12.9	82.1 ± 18.8	83.4 ± 14.2	76.8 ± 9.2
Height (cm)*	172 ± 8.7	170 ± 7.5	172 ± 8.6	171 ± 8.1
CL_{CR} (mL/min)*	96.9 ± 22.7	100.1 ± 18.5	98.2 ± 26.8	102.7 ± 27.9
No. of blood pressure measurements	3496 SBP, 3496 DBP	2928 SBP, 2928 DBP	7050 DBP	2984 SBP, 2984 DBP
Occasions per patient	1	2 to 4	2 to 4	2
No. of data points per occasion (mean)	74	89	99	15
No. of plasma concentration measurements	None	None	53	None

CL_{CR}, Creatinine clearance; SBP, Systolic blood pressure; DBP, diastolic blood pressure.
*Mean ± SD.

help define the role of 24-hour ABPM with respect to drug approval.*

However, in early drug development the major objective of the analysis of blood pressure data is to define the dose-concentration-effect relationship for the drug to guide dosage form development (eg, extended-release versus immediate-release) and to define the dosing regimen for the pivotal phase III trials. The use of 24-hour ABPM data instead of conventional cuff measurements is appealing because of its data richness. Up to now analyses techniques for 24-hour ABPM profiles tended to reduce the available information by calculating daily arithmetic mean values or average values for daytime and nighttime periods and ignoring different sources of variability.[1] Hourly or bihourly average values have also been used, but they lead to discontinuous blood pressure profiles.[2] Modeling with spline functions, cosine functions,[3] and Fourier analysis[4] has been applied. These methods require a great number of parameters, and each individual profile must be modeled separately. Population pharmacokinetic-pharmacodynamic modeling has been developed over the past 3 decades and has been shown to be particularly useful to characterize the dose-concentration-effect relationship of new chemical entities or established drugs.[5-7] Nonlinear mixed-effects modeling[8] is especially suited for 24-hour ABPM because it allows the simultaneous quantification of fixed effects and random effects (ie, interindividual, interoccasion, and residual or intraindividual variability) from all study data. Differences in the timing and number of observations between subjects can be easily handled. The baseline submodel of the pharmacodynamic model, which describes the blood pressure when no drug is present, is particularly challenging for 24-hour ABPM because of the circadian rhythm and different sources of variability, which are interindividual, interoccasional, and residual variability.

In this report the application of NONMEM for the modeling of 24-hour ABPM data is presented. In a first step, different models (including polynomials and cosine functions) have been applied to model blood pressure data from patients treated with placebo. At this stage the pharmacostatistical model for the baseline was defined, and then this baseline model was used in a full population pharmacokinetic-pharmacodynamic model that included the patients treated with drugs in the data set to describe the effect of the new I_1-receptor agonist moxonidine. To our knowledge this approach to model 24-hour ABPM has not yet been reported.

METHODS

Patients and data

Study A was a double-blind, placebo-controlled study to investigate the effects of moxonidine in patients with hypertension during early phase II development. After a run-in phase of at least 2 weeks, patients were randomized to receive either moxonidine or placebo once daily. Patients in the moxonidine group received 0.3 mg once daily for 1 week and 0.6 mg moxonidine for up to 11 weeks. We recorded 24-hour ABPM of up to 47 patients during the run-in phase and at 3, 5, and 11 weeks after

*FDA, Division of Cardio-Renal Drug Products, Medifacts Ltd, Cooperative Research and Development Agreement, ABPM Steering Committee. Contact: Dr Sandra Garett, Medifacts.

Table II. Summary of pharmacokinetic parameters

Parameter	*Parameter estimate*	*Standard error (%)*
Apparent clearance (L/h)*	35.0	5.71
Interindividual variability in apparent clearance (%)	13.5	42.9
Change in apparent clearance per 10 mL/min change in CL_{CR} (%)	6.71	12.6
Apparent volume of distribution (L)	132	4.33
Absorption rate constant (L/h)	2.30	17.9
Interindividual variability in absorption rate constant (%)	99	36.5
Residual variability		
Proportional, %CV	12.2	12.1
Additive, SD	1.12	55.4

CL_{CR}, Creatinine clearance.
*For a subject with a CL_{CR} of 90 mL/min.

randomization to moxonidine or placebo. Measurements were taken every 15 minutes from 8 AM to 10 PM and every 30 minutes during the night with a Space Labs Ambulatory Blood Pressure Monitor (Medifacts, Ltd., Rockville, Md). Three to 5 blood samples were taken from all patients between 0.5 and 24 hours after dosing. Blood samples were analyzed with a validated gas chromatography-mass spectrometry procedure with a limit of quantification of 0.05 mg/L. As expected, moxonidine plasma concentrations from the placebo group were all below the limit of quantification. The data sets 1, 2, and 3 described in Table I were extracted from the study data. Data set 1 includes all patients enrolled into the study who had a 24-hour ABPM profile during the placebo run-in phase (n = 47; one 24-hour ABPM profile per patient). Data set 2 includes all patients treated with placebo over the full study period (n = 9; two to four 24-hour ABPM profiles per patient), and data set 3 contains the data of all patients who completed the study (n = 21 for moxonidine and n = 9 for placebo; two to four 24-hour ABPM profiles per patient).

Study B was a placebo-controlled fixed-dose trial that compared the antihypertensive effect of moxonidine with that of placebo.[9] Patients received placebo during a 2-week placebo run-in phase and were then randomized to either placebo or moxonidine. The duration of treatment was 8 weeks. The 24-hour ABPM profiles were obtained at the end of the placebo run-in phase and after 8 weeks of treatment. No plasma samples were taken, and 24-hour ABPM were available from 94 patients in the placebo group on 2 different days. Before analysis was performed, the number of blood pressure measurements per patient was randomly reduced so that 1 measurement in a 1½-hour interval was maintained. On average, 15 data points per day and individual were used (data set 4).

For both studies written informed consent was obtained from all patients. The studies were approved by independent ethics committees and conducted in accordance with Good Clinical Practice and under required local regulations.

Data analysis

To develop a population pharmacokinetic-pharmacodynamic model, the following strategy was used.

Step 1: Model to describe the 24-hour ABPM profile without drug present (baseline). We used 24-hour ABPM during the placebo run-in period from 47 patients, with each patient contributing 1 profile (Table I, data set 1), to optimize and compare different structural and statistical models to describe the circadian rhythm, interindividual, and residual variability in blood pressure over a single 24-hour period.

The following cosine and polynomial models were evaluated. Individual-specific subscripts on the η variables are not presented. Random-effect parameters were assumed to be normally distributed with a mean of zero and a variance of ω^2.

Cosine models:

$$Bsl(t) = \theta_1 \cdot \exp(\eta_1) \cdot \left[1 + \sum_{i=1}^{n} \theta_{2i} \cdot (1 + \eta_2) \cdot \cos\left(\frac{i \cdot \pi \cdot (t + \eta_3)}{12} - \theta_{2i+1}\right)\right] \quad (1)$$

with n = 1, 2, or 3 and θ denoting fixed-effect parameters and η denoting random-effect parameters. In this equation, Bsl(t) is blood pressure as a function of t, t is clock time, θ_1 is rhythm-adjusted 24-hour mean, η_1 is interindividual variability on rhythm-adjusted 24-hour mean. θ_{2i} is amplitude of the cosine terms, η_2 is interindividual variability in the amplitudes, η_3 is interindividual variability

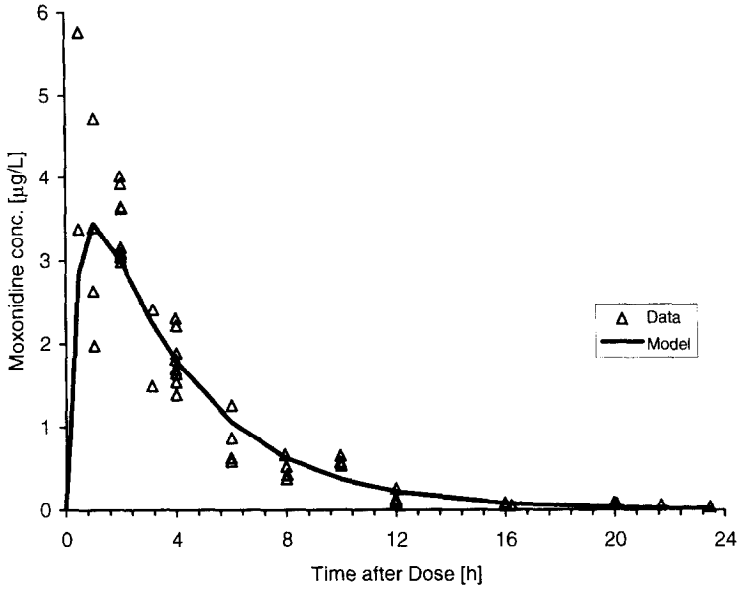

Figure 1. Moxonidine concentration measurements *(data points)* and predictions *(solid line)* based on typical parameter values of population pharmacokinetic model for creatinine clearance of 90 mL/min and dose of 0.6 mg moxonidine.

on clock time, and θ_{2i+1} is parameter for phase shifts of the cosine terms.

Polynomial models:

$$Bsl(t) = \theta_1 \cdot \exp(\eta_1) + \sum_{i=1}^{n} \theta_{i+1} \cdot \exp(\eta_{i+2}) \cdot (t + \eta_2)^i \qquad (2)$$

with n = 3, 4, 5, or 6 and θ denoting fixed-effect parameters and η denoting random-effect parameters. In equation 2, Bsl(t) is blood pressure as a function of t, t is clock time, θ_1 is average baseline value at midnight, η_1 is interindividual variability on baseline, θ_{i+1} is parameter of the polynomial function, η_2 is interindividual variability on clock time, and η_{i+2} is interindividual variability on the parameters of the polynomial function.

Step 2: Introducing interoccasion variability. The final baseline model from step 1 was extended to include interoccasion variability.[10] We used 24-hour ABPM from 9 patients receiving placebo, with each patient contributing between 2 to 4 profiles (data set 2), to find the optimal model to account for interoccasion variability in the baseline. Results were confirmed with a reduced (less observation per patient) data set of 94 patients, with each patient contributing 2 profiles (Table I; data set 4). Interoccasion variability was evaluated on all θ values; however, the best-fit model included interoccasion variability only on the rhythm-adjusted 24-hour mean and clock time.

Cosine model with interoccasion variability:

$$Bsl(t) = \kappa_{1d} + \theta_1 \cdot \exp(\eta_1) \cdot \left[1 + \sum_{i=1}^{n} \theta_{2i} \cdot (1 + \eta_2) \cdot \cos\left(\frac{i \cdot \pi \cdot (t + \eta_3 + \kappa_{2d})}{12} - \theta_{2i+1}\right)\right] \qquad (3)$$

with n = 2 and θ denoting fixed-effect parameters and κ and η denoting random-effect parameters. In equation 3, Bsl(t) is blood pressure as a function of t, t is clock time, θ_1 is rhythm-adjusted 24-hour mean, η_1 is interindividual variability on baseline, κ_{1d} is interoccasion variability in rhythm-adjusted 24-hour mean, d indicates different study days, θ_{2i} is amplitude of the cosine terms, η_2 is interindividual variability in the amplitudes, θ_{2i+1} is parameter for phase shift of the cosine terms, η_3 is interindividual variability on clock time, and κ_{2d} is interoccasion variability on clock time.

The following polynomial model was also explored.

Polynomial model with interoccasion variability:

$$Bsl(t) = \kappa_{1d} + \theta_1 \cdot \exp(\eta_1) + \theta_2 \cdot \exp(\eta_2) \cdot (t + \kappa_{2d} + \eta_3)^5 + \theta_3 \cdot (t + \kappa_{2d} + \eta_3)^4 + \theta_4 \cdot (t + \kappa_{2d} + \eta_3)^3 + \theta_5 \cdot (t + \kappa_{2d} + \eta_3)^2 + \theta_6 \cdot \exp(\eta_4) \cdot (t + \kappa_{2d} + \eta_3) \qquad (4)$$

with θ denoting fixed-effect parameters and κ and η denoting random-effect parameters. In equation 4,

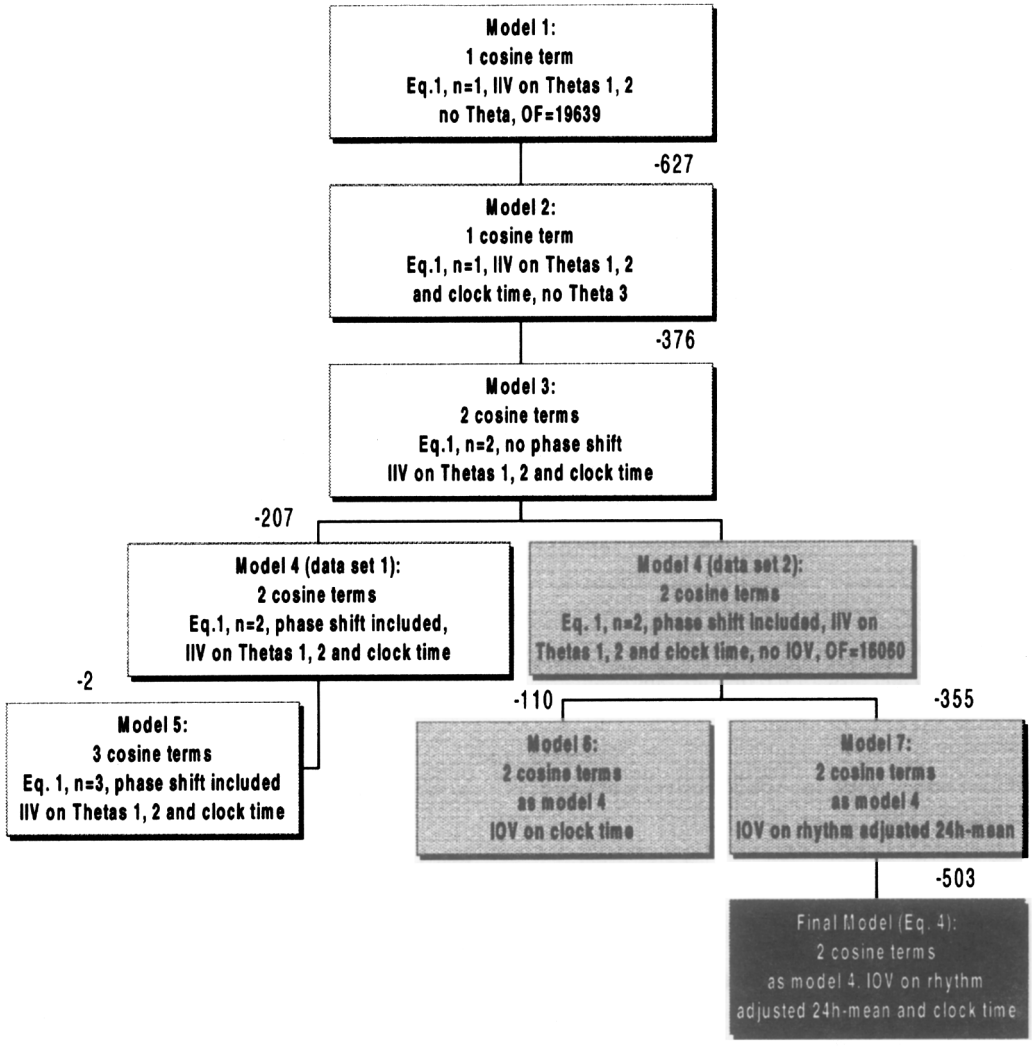

Figure 2. Model development scheme for baseline model for diastolic 24-hour ambulatory blood pressure measurements (ABPM). Data set 1 has been used to investigate models in *white boxes*. Models in *grey boxes* were evaluated with data sets 2 and 4. Model with *black box* has been used for pharmacokinetic-pharmacodynamic analysis. Numbers between boxes indicate difference in objective function for data sets 1 and 2. IIV, Interindividual variability; IOV, interoccasion variability.

Bsl(t) is blood pressure as a function of t, t is clock time, θ_1 is average baseline value at midnight (t = 0), η_1 is interindividual variability on baseline, κ_{1d} is interoccasion variability in baseline (d indicates different study days), θ_2, θ_3, θ_4, θ_5, and θ_6 are parameters of the polynomial function, η_2 and η_4 are interindividual variability on the parameters of the polynomial function, η_3 is interindividual variability on clock time, and κ_{2d} is interoccasion variability on clock time (d indicates different study days).

Step 3: Full population pharmacokinetic-pharmacodynamic model. A full population pharmacokinetic-pharmacodynamic model for the effect of moxonidine on diastolic blood pressure was developed with a data set with all patients who completed study A (data set 3). The pharmacokinetic model was developed first. Final pharmacokinetic parameters and their interindividual variability were fixed during the pharmacodynamic model development. Initial analysis showed a delay between the peak plasma concentrations of the drug and the maximum decrease in blood pressure. Therefore an effect compartment model[11] was introduced to account for this hysteresis. Different pharmacodynamic models were tested, and the best-fit model

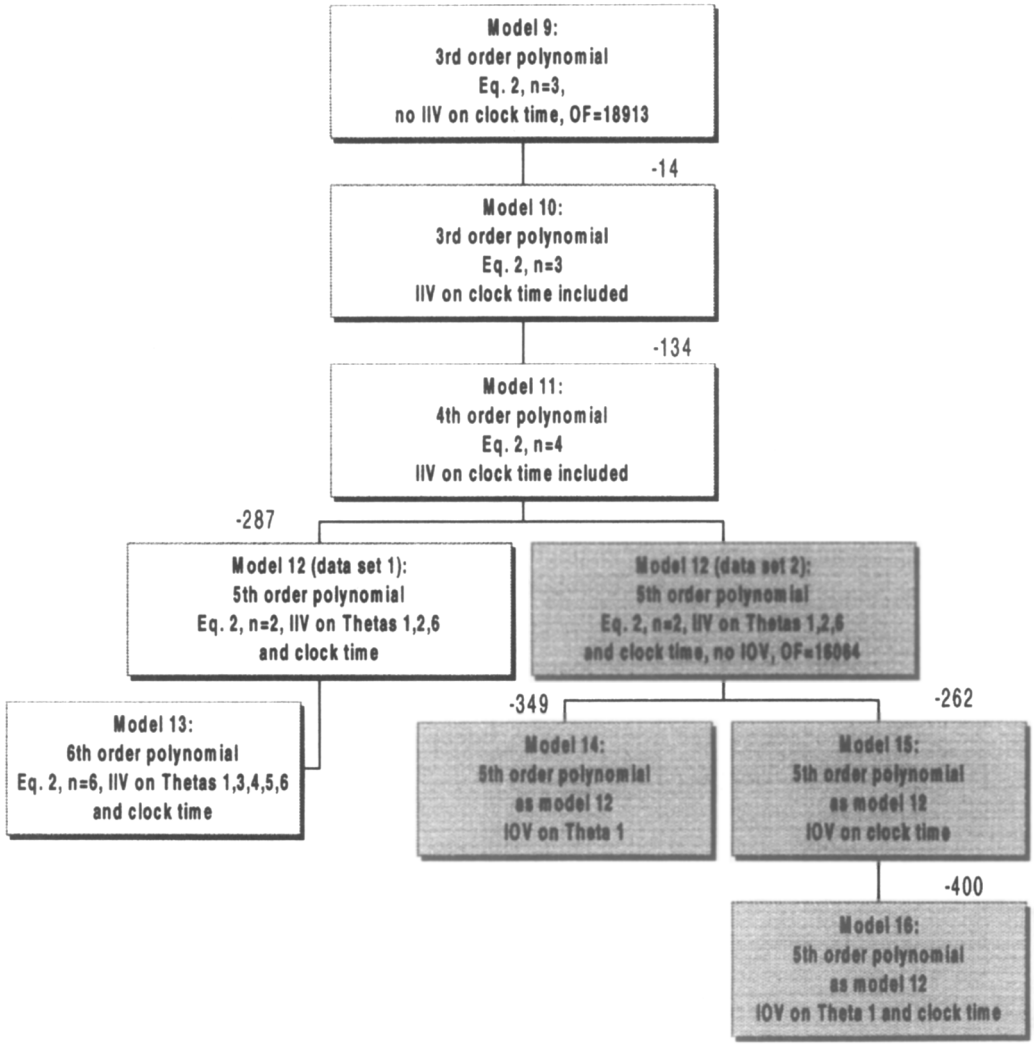

Figure 2. *Continued from page 626.*

was selected based on goodness-of-fit criteria and comparison of objective function values. The final pharmacodynamic model to describe the diastolic blood pressure as a function of moxonidine concentrations, study time, and clock time is given in equation 5:

$$BP(T) = Bsl(t) \cdot (1 - \theta_1 \cdot \exp(\eta_1) \cdot Ce(T)/[\theta_2 \cdot \exp(\eta_2) + Ce(T)]) \quad (5)$$

with θ denoting fixed-effect parameters and η denoting random-effect parameters. In equation 5, Bsl(t) is blood pressure as a function of clock time (as defined in equations 1 through 4), t is clock time, θ_1 is maximum effect (E_{max}; ie, decrease in blood pressure), η_1 is interindividual variability in θ_1, θ_2 is moxonidine steady-state concentration where 50% of the maximum effect is reached (EC_{50}), η_2 is interindividual variability in θ_2, and Ce(T) is moxonidine effect site concentration at study time T.

An additive residual error model for the pharmacodynamic model was chosen because it was superior to all other models tested. Equation 3 was used for Bsl(t). All pharmacodynamic model parameters including all baseline parameters were estimated simultaneously.

All analyses were carried out with NONMEM (version V)[11] with the use of the first-order method. Of all models tested, the key models are described in detail.

RESULTS

Pharmacokinetic analysis

Fifty-three moxonidine plasma concentrations from 13 patients were available (Table I). The number of

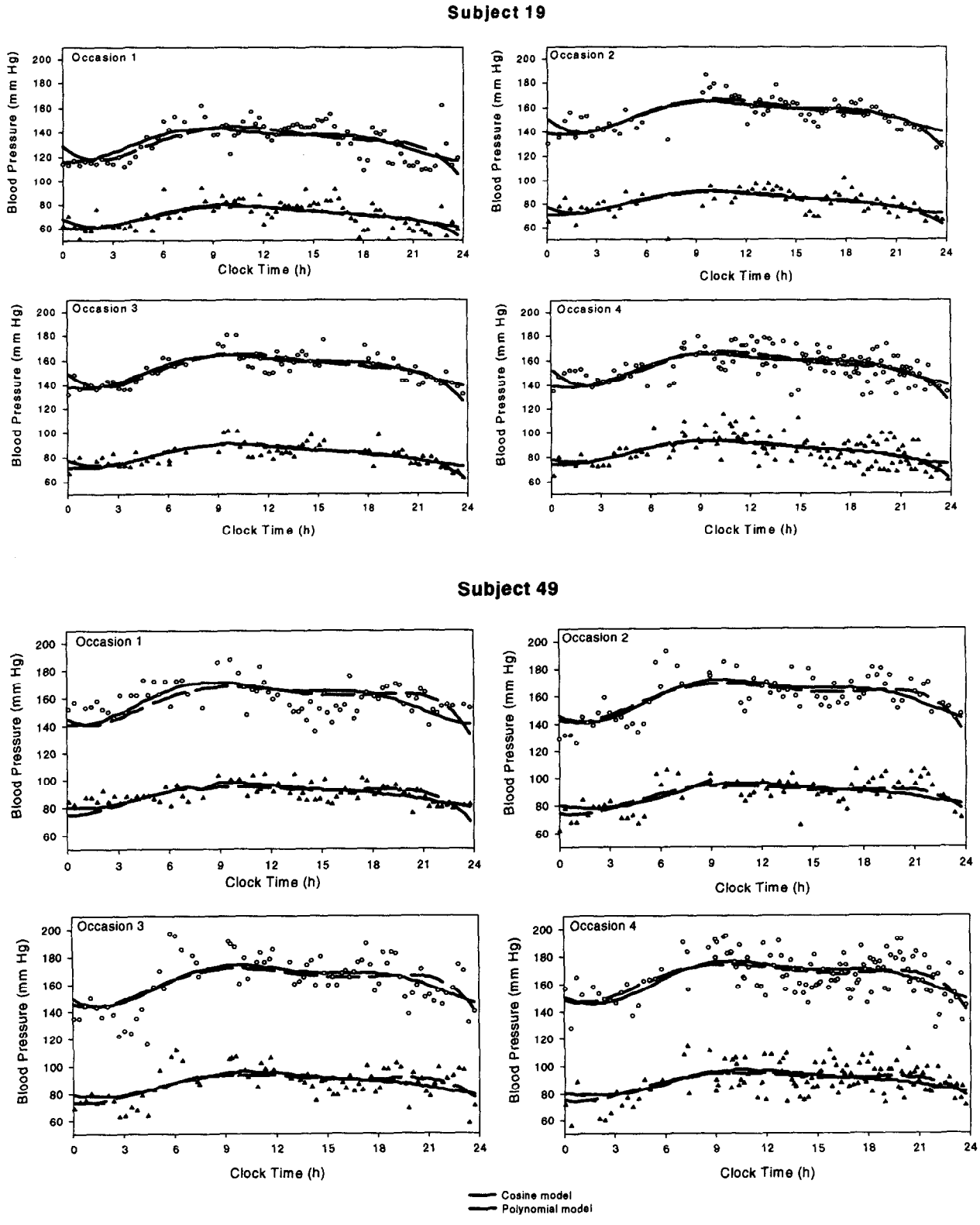

Figure 3. Individual predictions of systolic and diastolic 24-hour ABPM versus observations for 3 representative patients from placebo group (data set 2). *Solid line* represents predictions based on cosine model; *broken line* represents predictions based on polynomial model.

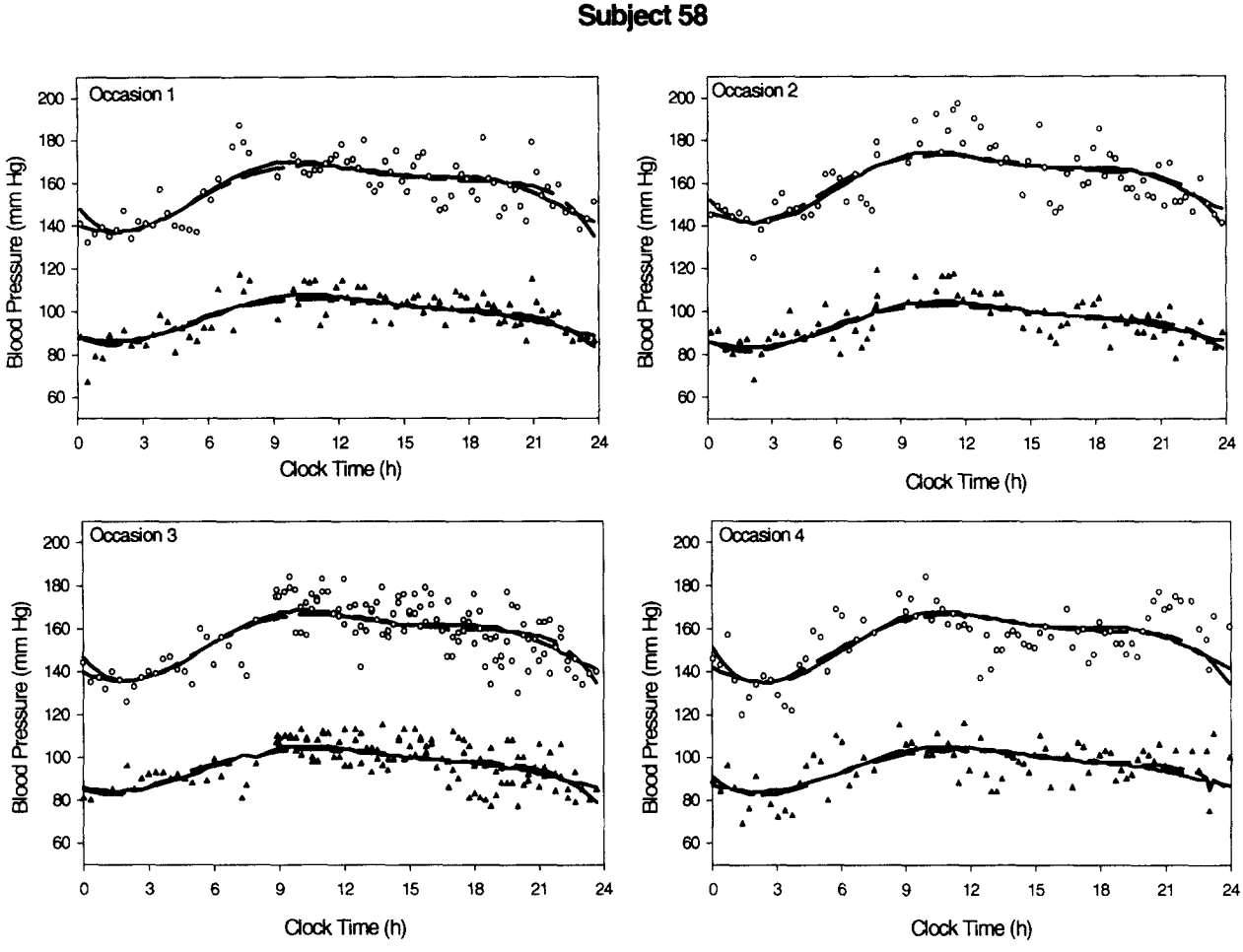

Figure 3. *Continued from page 628.*

plasma concentrations per patient ranged between 3 and 5. The results of the pharmacokinetic analysis are summarized in Table II. A proportional variance model for intersubject variability on clearance has been used. Moxonidine pharmacokinetics after oral administration could be described by a 1-compartment model with first-order absorption and elimination. Figure 1 shows the observed plasma concentrations and the population predictions for a dose of 0.6 mg moxonidine. Creatinine clearance was identified as a significant covariate, which is reasonable because moxonidine is primarily renally excreted.[12] A decrease in creatinine clearance of 10 mL/min resulted in a reduction of moxonidine clearance of 6.71% according to equation 6:

$$CL/F = \overline{CL}/F \cdot [1 + 0.00671 \cdot (CL_{CR} - 90)] \quad (6)$$

in which $\overline{CL}/F$ is the population mean apparent oral clearance, assuming a creatinine clearance (CL_{CR}) of 90 mL/min. This clearance was estimated to be 35 L/h, with an interindividual variability of 13.5%. The apparent volume of distribution was 132 L. Interindividual variability in this parameter could not be precisely estimated because of the limited number of patients. The typical value for the elimination rate constant was 0.265 h^{-1}, which corresponds to a terminal plasma half-life of 2.61 hours. This is in accordance with earlier studies in healthy volunteers.[13]

Pharmacodynamic analysis

Step 1: Model to describe the 24-hour ABPM profile without drug present (baseline).

Cosine functions. The model development procedure is shown in Figure 2. The principal components of the baseline model [Bsl(t)] are the rhythm-adjusted 24-hour mean (θ_1) and the cosine functions, which modify the mean blood pressure as a function of clock time. The cosine functions have fixed-effect parameters for

Table III. Parameter estimates and standard errors of the final baseline model with cosine terms for diastolic and systolic blood pressure for data sets 2 and 4

		Data set 2: diastolic blood pressure		*Data set 4: diastolic blood pressure*	
Parameter	*Symbol*	*Parameter estimate*	*Standard error (%)*	*Parameter estimate*	*Standard error (%)*
Rhythm-adjusted 24-hour mean blood pressure (mm Hg)	θ_1	90.8	2.84	90.2	0.78
Interindividual variability in mean blood pressure (%)	$\omega_{\theta 1}$	8.14	14.25	6.7	9.1
Interoccasion variability in baseline (mm Hg)	$\omega_{\kappa 1 d}$	4.03	16.53	7.06	10.5
Amplitude, first cosine term	θ_2	–0.0592	19.26	–0.0894	6.2
Interindividual variability on amplitude of first and second cosine term (%)	$\omega_{\theta 2/\theta 4}$	46.0	21.11	42.6	13.2
Phase shift, first cosine term	θ_3	5.82	2.73	0.369	13.7
Amplitude, second cosine term	θ_4	0.0185	17.35	–0.042	10.5
Phase shift, second cosine term	θ_5	–2.94	3.78	1.16	10.5
Interindividual variability on clock time (h)	$\omega_{Clocktime}$	5.06	26.68	1.03	24.1
Interoccasion variability on clock time (h)	$\omega_{\kappa 2 d}$	2.44	33.2	1.8	17.7
Residual variability (mm Hg)	σ	8.27	3.65	11.4	3.4
		Data set 2: systolic blood pressure		*Data set 4: systolic blood pressure*	
		Parameter estimate	*Standard error (%)*	*Parameter estimate*	*Standard error (%)*
Rhythm-adjusted 24-hour mean blood pressure (mm Hg)	θ_1	151	1.97	146	0.95
Interindividual variability in mean blood pressure (%)	$\omega_{\theta 1}$	5.38	27.1	8.77	6.81
Interoccasion variability in baseline (mm Hg)	$\omega_{\kappa 1 d}$	7.53	18.9	13.0	9.23
Amplitude, first cosine term	θ_2	–0.0668	15.3	–0.0587	7.12
Interindividual variability on amplitude of first and second cosine term (%)	$\omega_{\theta 2/\theta 4}$	42.9	25.4	48.2	13.6
Phase shift, first cosine term	θ_3	not used	—	0.480	14.7
Amplitude, second cosine term	θ_4	0.0292	30.3	–0.031	13.3
Phase shift, second cosine term	θ_5	–8.82	1.78	–1.91	7.28
Interindividual variability on clock time (h)	$\omega_{Clocktime}$	2.52	30.6	0.848	35.9
Interoccasion variability on clock time (h)	$\omega_{\kappa 2 d}$	1.26	56.3	1.33	28.0
Residual variability (mm Hg)	σ	11.0	4.26	14.2	3.2

$$Bsl(t) = \kappa_{1d} + \theta_1 \cdot \exp(\eta_1) \cdot \left[1 + \sum_{i=1}^{n} \theta_{2i} \cdot (1 + \eta_2) \cdot \cos\left(\frac{i \cdot \pi \cdot (t + \eta_3 + \kappa_{2d})}{12} - \theta_{2i+1}\right)\right]$$

the amplitude (θ_{2i}), phase shift (θ_{2i+1}), and period (fixed to 24 hours, 12 hours, 8 hours, or 6 hours). Interindividual variability was introduced on various of these fixed-effect parameters during the modeling process. The baseline model was developed for both diastolic and systolic blood pressure measurements based on data set 1 (Table I). Because the modeling process for both response variables was very similar, only results for diastolic blood pressure are reported in detail.

The starting point was 1 cosine function with a 24-hour cycle (equation 1 with n = 1, without η_3 and θ_{2i+1}). Adding interindividual variability in the clock time (η_3 in equation 1) resulted in a highly improved fit with a decrease in the objective function of 627 for data set 1. The interindividual variability in clock time can be interpreted as differences in wake-up times between subjects.

The introduction of a second cosine function with a 12-hour rhythm (equation 1 with n = 2, without θ_{2i+1}) further improved the model with a reduction in objective function by 376. With 2 cosine functions both peaks in blood pressure (early morning and afternoon) could be described, whereas 1 cosine function with a 24-hour period could describe only 1 peak over the 24-hour period. In the next step, 2 parameters for a phase shift (θ_{2i+1}) of each cosine term were introduced to the model (equation 1 with n = 2; $\Delta_{OF} = -207$). The addition of a third cosine function (equation 1, with n = 3)

Table IV. Parameter estimates and standard errors of the full pharmacokinetic-pharmacodynamic model for diastolic blood pressure

Parameter	*Symbol*	*Data set 3: diastolic blood pressure*	
		Parameter estimate	*Standard error (%)*
Rhythm-adjusted 24-hour mean blood pressure (mm Hg)	θ_1	92.8	1.7
Interindividual variability in mean blood pressure (%)	$\omega_{\theta 1}$	7.56	17.6
Interoccasion variability in baseline (mm Hg)	$\omega_{\kappa 1 d}$	5.08	27.0
Amplitude, first cosine term	θ_2	-0.0797	12.3
Interindividual variability on amplitude of first and second cosine term (%)	$\omega_{\theta 2/\theta 4}$	44.6	24.0
Phase shift, first cosine term	θ_3	Not included	—
Amplitude, second cosine term	θ_4	-0.0274	13.8
Phase shift, second cosine term	θ_5	0.517	23.8
Interindividual variability on clock time (h)	$\omega_{Clocktime}$	2.94	20.3
Interoccasion variability on clock time (h)	$\omega_{\kappa 2 d}$	0.603	33.8
Rate constant of loss from the effect site, k_{eo} (1/h)	—	0.198	44.9
Interindividual variability in k_{eo} (%)	—	191	39.6
Maximum decrease in diastolic blood pressure (%)	E_{max} (θ_1 in equation 5)	16.7	47.7
Interindividual variability in E_{max} (%)	ω_{Emax}	50.2	46.2
Steady-state concentration resulting in 50% E_{max} (μg/L)	EC_{50} (θ_2 in equation 5)	0.945	111
Interindividual variability in EC_{50} (%)	ω_{EC50}	130	51.2
Residual variability (mm Hg)	σ	8.61	2.39

k_{eo}, Equilibration rate constant; E_{max}, maximum effect; EC_{50}, 50% of the maximum effect.

into the model with a shorter period of 6 hours or 8 hours only slightly improved the fit ($\Delta_{OF} = -2$). Therefore the baseline model with 2 cosine terms was chosen for step 2. This model consists of 5 structural parameters and 3 random-effect parameters (accounting for interindividual variability in mean blood pressure [θ_1], amplitude [θ_{2i}], and clock time [t]). For the systolic blood pressure measurements the decreases in objective function were approximately -684, -412, -178, and -15 for the previously mentioned models, respectively.

Polynomial functions. The model development procedure is shown in Figure 2. The baseline model was developed for both diastolic and systolic blood pressure measurements based on data set 1 (Table I). Because the modeling process for both response variables was very similar, only results for diastolic blood pressure are reported in detail. First, a third-order polynomial was tested (equation 2 with n = 3, without η_2). For every polynomial model interindividual variability was initially allowed on each parameter (η_{i+2} in equation 2) of the function. Subsequently, all the η terms that tended toward zero were omitted. The use of an additive instead of a proportional error model for the interindividual variability did not improve the model. Allowing interindividual variability in clock time (η_2 in equation 2) improved the model but only to a slight degree ($\Delta_{OF} = -14$ for data set 1). A better fit was achieved with a fourth-order polynomial (equation 2 with n = 4; $\Delta_{OF} = -134$), which was further improved with a fifth-order polynomial (equation 2 with n = 5; $\Delta_{OF} = -287$ compared with the fourth order function). A sixth-order polynomial did not improve the model, and for some of the data sets a successful minimization could not be achieved. Thus the final polynomial model chosen was a fifth-order function with 6 structural and 3 random-effect parameters accounting for interindividual variability in θ_1, θ_2, and θ_6.

Compared with the best cosine model, the objective function was between 20 and 60 points higher for all data sets investigated. In general, the parameter estimates were precise, with small standard errors. The same model was the best-fit model for systolic blood pressure.

Step 2: Introducing interoccasion variability. If more than 1 profile of 24-hour ABPM is obtained in a patient, interoccasion variability must be introduced in the baseline model to reflect day-to-day changes in mean blood pressure. Data set 2 was used for the analysis. The best-fit cosine and polynomial models from step 1 were selected to explore interoccasion variability. First, a parameter (κ_{1d}) allowing for differences in the mean blood pressure (θ_1) for different occasions was introduced (equation 3 and 4). The reduction in objective function was 355 and 349 for the cosine and the polynomial model, respectively. If interoccasion

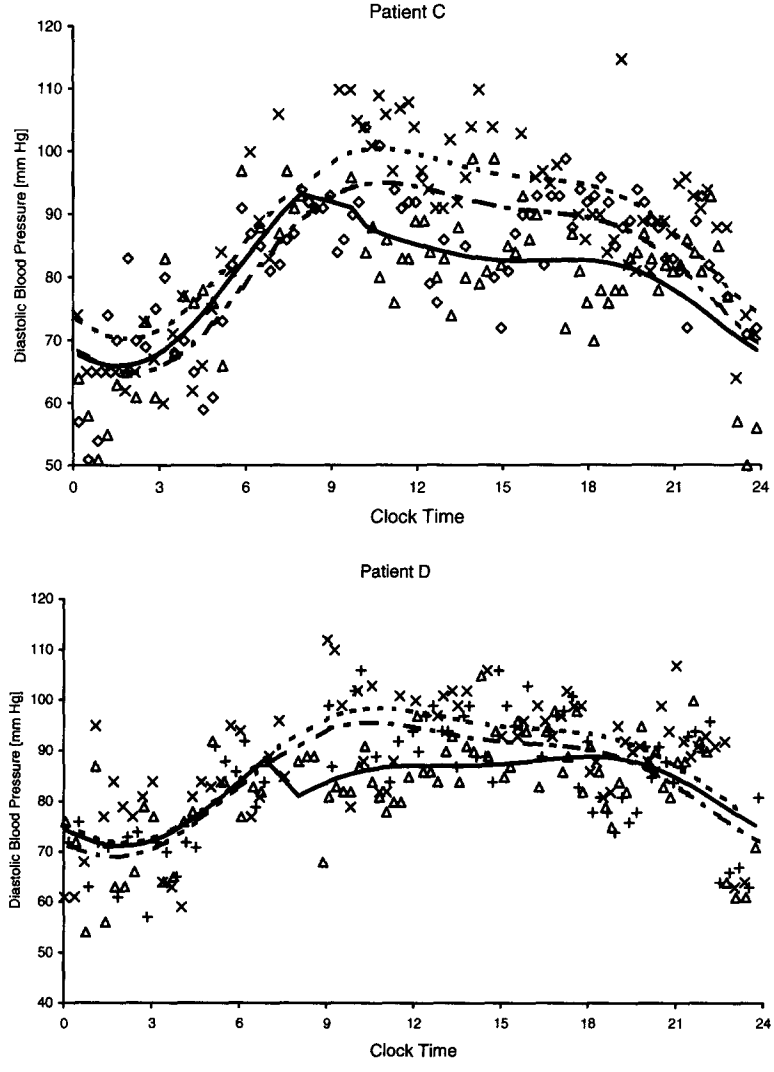

Figure 4. Individual predictions of diastolic 24-hour ABPM *(lines)* versus observations (*X symbols,* with placebo—occasions 1 and 2; *triangles and diamonds,* with moxonidine—occasions 1 and 2) for 4 representative patients on different occasions. *Solid lines* represent model predictions on treatment days; *broken lines* represent model predictions on placebo days.

variability on clock time (κ_{2d}) were introduced (equation 3 and 4), which enables the model to adjust for changes in wake-up times or activity from day to day, a clear improvement was observed ($\Delta_{OF} = -110$ and -262 for the cosine and polynomial model, respectively). The inclusion of both interoccasion variability parameters (κ_{1d}; κ_{2d}) resulted in the best models for both the cosine and polynomial functions, with a decrease in objective function by 503 and 400, respectively, compared with the model without interoccasion variability. A decrease occurred in objective function by 594 and 527 for cosine and polynomial models, respectively, by introducing interoccasion variability to the models for systolic blood pressure measurements. Figure 3 shows the individual observed diastolic and systolic 24-hour ABPM and the individual predictions from the final cosine and polynomial models for 3 representative patients in data set 2.

To confirm the results, the final models were applied to a data set (data set 4) from 94 patients (2 occasions per patient) but with a reduced number of observations per 24-hour profile (15 versus 89). As for data set 2, introducing a parameter to allow for interoccasion variability in the mean baseline value greatly improved the fit. Interoccasion variability on clock time only slightly improved the model. As for the other data sets, the best

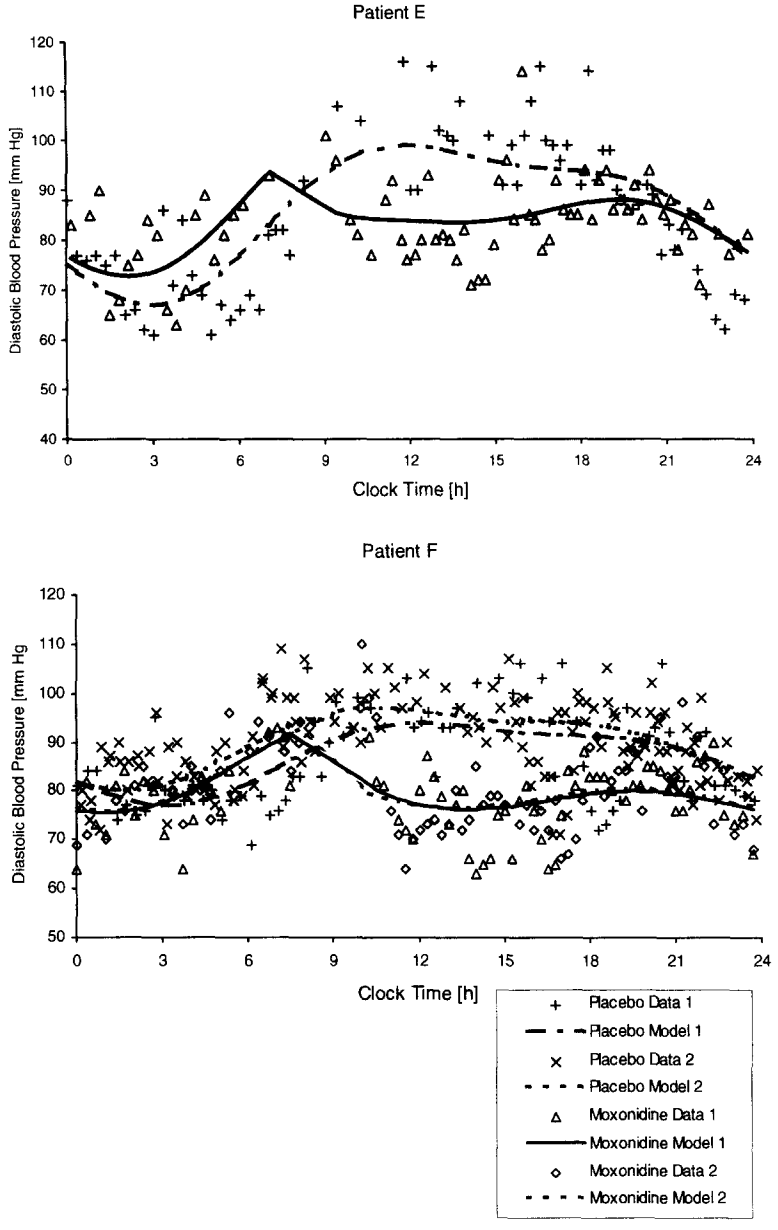

Figure 4. *Continued from page 632.*

results were obtained with the 2 cosine term model with interoccasion variability on baseline and clock time. With the use of the polynomial model, similar results were obtained regarding the improvement of fit by introducing the interoccasion variability terms. However, probably because of the higher number of parameters and the lower number of data points in this data set, standard errors could not be calculated for the polynomial model with interoccasion variability on baseline and clock time. The parameter estimates of the final cosine model are given in Table III.

Step 3: Full population pharmacokinetic-pharmacodynamic model. The final baseline model (2 cosine terms with interoccasion variability on baseline and clock time; equation 3; n = 2) was combined with different effect models including a linear model, an E_{max} model, and a sigmoid E_{max} model. The mean pharmacokinetic parameters and their interindividual variability were fixed to the final parameter estimates (Table II). Of all models tested, the E_{max} model performed best. The parameter estimates for the final pharmacodynamic model are summarized in Table IV.

The parameters describing the baseline [Bsl(t)] were very similar to those obtained from data set 2, where only the patients treated with placebo were included (Tables III and IV). The equilibration rate constant (k_{eo}) was 0.198 1/h, which corresponds to a half-life of approximately 3½ hours. Interindividual variability in this parameter was high (191%). The maximum effect (θ_1 in equation 5) was estimated as 16.7% (interindividual variability 50.2%; η_1 in equation 5) and EC_{50} (θ_2 in equation 5) as 0.945 μg/L (interindividual variability 130%, η_2 in equation 5). The diastolic blood pressure measurements and the individual predictions for 4 representative patients are shown in Figure 4.

DISCUSSION

The use of 24-hour ABPM data provides additional information to conventional cuff blood pressure measurements during the drug development process because more frequent blood pressure measurements are being obtained for a longer period and equally spaced over a 24-hour period. It can therefore be anticipated that 24-hour ABPM are extremely useful to characterize the dose-concentration-effect relationship for an antihypertensive compound. To do so, population pharmacokinetic-pharmacodynamic modeling techniques can be applied. However, it is difficult to find an appropriate baseline model for the circadian rhythm in blood pressure. The baseline model must include different sources of variability to reflect differences in the baseline profile between patients and differences in the baseline profile within 1 patient from 1 occasion to the other that are not attributable to a drug effect. Previously reported methods[14-16] did not incorporate these different factors, and thus their use was limited. The proposed method includes fixed- and random-effect parameters in the baseline model, whereas previous methods used only fixed-effect parameters. In addition, those methods did not distinguish between a model for the baseline and drug effect, and baseline parameters were used to describe both. However, the presented method resulted in very similar estimates of the baseline parameters, regardless of whether the analysis was performed on placebo data only or included data from treated patients. The drug effect is solely modeled with the use of the pharmacodynamic model. Cosine functions and polynomials have been used previously to describe circadian rhythms in response variables. So the structural models tested in detail were sums of cosine functions and up to sixth-order polynomials. Both models were equally able to describe the circadian rhythm (Figure 3). The major difference between these 2 types of equations is their periodicity. The cosine functions gave similar values for the clock times 11:59 PM and 0:01 AM, whereas the polynomial often had a difference greater than 10 mm Hg. Both functions provided precise parameter estimates with low standard errors. However, because the best-fit baseline model with cosine terms required fewer parameters and achieved a lower objective function value compared with the best-fit polynomial baseline model, the former model was used in the full pharmacokinetic-pharmacodynamic analysis. In addition, the cosine function was more stable during the fitting process compared with the polynomial. The final baseline model (equation 3) consisted of a parameter for the rhythm-adjusted 24-hour mean (θ_1) and 2 cosine terms, which modify the mean blood pressure as a function of clock time. The cosine terms have fixed-effect parameters for the amplitude (θ_2 in the first cosine term and θ_4 in the second cosine term), phase shift (θ_3 in the first cosine term and θ_5 in the second cosine term), and period (fixed to 24 hours and 12 hours for the 2 cosine terms, respectively). Interindividual variability was included on the rhythm-adjusted 24-hour mean, the parameters for amplitude, and on clock time. It was assumed that the interindividual variability was the same on θ_2 and θ_4. The interindividual variability on clock time allows a shift in the 24-hour profile to the left or right without changing the shape. Patients can have the same circadian rhythm (shape) but reach their peaks and trough blood pressure measurements at slightly different clock times. Therefore this parameter translates the "clock time" into the patient's "biologic time." The rhythm-adjusted 24-hour mean (θ_1) gives information regarding the average blood pressure during a 24-hour time interval. Interoccasion variability was allowed for the rhythm-adjusted 24-hour mean and for clock time (κ_{1d}; κ_{2d}). The distribution of individual post hoc estimates of κ_{1d} must be checked carefully because it can mask a systematic drug effect, especially if no placebo group or only a small placebo group is present in the data set. If, for example, only 2 profiles are obtained, 1 during run-in and 1 at the end of the treatment period, a bias in the frequency distribution of individual κ_{1d} values may indicate a drug effect, resulting in a decrease in average blood pressure without changing the shape of the 24-hour profile. The introduction of interoccasion variability should therefore be done on the placebo data set first and then extended to the full data set. Even a reduction in the number of measurements per patient from approximately 89 to 15 (1 measurement in a 1½-hour time interval) resulted in a reliable estimation of all parameters (Table III). The use of this baseline model during the pharmacokinetic-pharmacodynamic model-

ing process allowed estimation of the pharmacodynamic parameters for the antihypertensive effect on diastolic blood pressure for moxonidine, a new I_1-receptor agonist. The advantage of the presented approach is the clear separation between a model describing the baseline 24-hour blood pressure profile and the pharmacodynamic model for the drug effect. This model is being used to evaluate several phase II and III studies of moxonidine to describe the dose-concentration-effect relationship and to identify patient covariates (ie, demographics and disease state) that might influence this relationship.

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