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Original Article

An experience on the model-based evaluation of pharmacokinetic drug-drug interaction for a long half-life drug

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ABSTRACT Fixed-dose combinations development requires pharmacokinetic drug-drug interaction (DDI) studies between active ingredients. For some drugs, pharmacokinetic properties such as long half-life or delayed distribution, make it difficult to conduct such clinical trials and to estimate the exact magnitude of DDI. In this study, the conventional (non-compartmental analysis and bioequivalence [BE]) and model-based analyses were compared for their performance to evaluate DDI using amlodipine as an example. Raw data without DDI or simulated data using pharmacokinetic models were compared to the data obtained after concomitant administration. Regardless of the methodology, all the results fell within the classical BE limit. It was shown that the model-based approach may be valid as the conventional approach and reduce the possibility of DDI overestimation. Several advantages (i.e., quantitative changes in parameters and precision of confidence interval) of the model-based approach were demonstrated, and possible application methods were proposed. Therefore, it is expected that the model-based analysis is appropriately utilized according to the situation and purpose.

INTRODUCTION

Fixed-dose combinations (FDC) contribute to a better clinical outcome with increased compliance over monotherapy [1-3]. In this context, many pharmaceutical companies are interested in the development of FDC. Drug-drug interaction (DDI) studies between active ingredients are required in FDC development, which generally encompasses multiple-dose studies. However, such clinical trials may encounter difficulties due to some pharmacokinetic (PK) properties, e.g., long half-life and delayed distribution. Drugs with such properties may cause carry-over between dosing, resulting in long sampling periods and wash-out periods, or steady-state achievement may be questioned in studies designed to avoid prolonged clinical trials, e.g., one-sequence cross-over design.

A typical example is amlodipine. Amlodipine is a frequently prescribed drug for managing hypertension and coronary artery disease in people suffering from angina [4]. Various medications such as statins for hyperlipidemia and cardiovascular disease treatment, or angiotensin receptor blockers and thiazide-like diuretics for hypertension treatment are used concomitantly as combination therapy with amlodipine to enhance the efficacy in patients. Conventional non-compartmental analysis (NCA) for DDI evaluation for this kind of drug may not be suitable due to the possibility of incomplete attainment of full-PK concentration-time profiles where AUC_{inf} and terminal half-life ($t_{1/2}$) are misestimated, producing inaccurate interpretations as a consequence. Therefore, several suggestions have been proposed to overcome NCA limitations regarding drugs with a long half-life [5-8].

Among these, model-based analysis has been recommended

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as an alternative method to NCA. Model-based analysis can comprehend the full concentration-time profiles even with sparse or incomplete data, allowing various scenarios to be simulated and can integrate prior information from the literature [6]. Also, Svensson *et al*. [7] reported that the NCA approach underpredicted DDI impact and showed bias in the bedaquiline (half-life more than five months) simulation study. Conversely, model-based analysis was unbiased and showed an increased precision in DDI predictions. The terminal half-life was estimated ten times lower in NCA than the actual value, caused by invalid extrapolation from insufficient sampling. The discrepancy between the two methods highlighted the accuracy of the model-based analysis compared to NCA [7]. Yet, the knowledge toward a comparison between strategies is incomplete and challenges should be clarified [9]. Further evaluation and research are needed for the utilization of the method.

The study's objective was to compare NCA and model-based analysis for DDI evaluation using amlodipine data from a human pharmacology study. The clinical trial was adequately designed according to the applicable regulations with sufficient sampling periods for steady-state achievement. We expect to contribute and accumulate our experiences by establishing a standard PK comparison method for drugs with a long half-life.

METHODS

Subjects and dataset

The PK data were obtained from a DDI study for FDC development, designed as an open-label, multiple-dose, single-sequence cross-over, comparative PK study. This study was conducted at Seoul St. Mary's Hospital under all applicable regulations and ethical principles (Institutional Review Board control number: KC20MDSF0055).

The included subjects were Korean male volunteers whose mean values for age, weight, and height were 30 years (range: 23–46 years), 72.0 kg (range: 56.2–83.9 kg), and 175.3 cm (range: 164–191 cm), respectively. No subjects had any evidence of underlying disease or history that could affect the study, including abnormal aspartate transaminase, alanine transaminase, total bilirubin and total cholesterol, allergic history reaction to the investigational drugs (amlodipine and potential interacting medications), excessive caffeine, alcohol consumption, and smoking, or any criteria that were considered ineligible by the investigator. The demographics and laboratory test results are summarized in Table 1.

Since it was a single-sequence cross-over study, amlodipine PK data without DDI were obtained during Period 1 (day 0–day 8), and that with possible DDI were obtained during Period 2 (day 9–day 13). A daily 5 mg dose of amlodipine was administered to each subject over the whole study period. Period 1 PK data was generated by a single sample on day 7 (pre-dose) and serial samples on day 8 (at pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, and 24 h after dosing). For Period 2, the same samplings were performed on days 12 and 13. Although the population PK modeling can handle sparse or incomplete full-PK data, only data from subjects who completed the PK sampling schedule (n = 14, 392 observations) were used to minimize the magnitude of possible selection bias.

Overall scheme for DDI evaluation

DDI evaluation was performed in three methods.

1. Conventional approach: NCA and bioequivalence (BE) approach

The maximum plasma concentration observed (C_{max}), the time to reach C_{max} from the last dosing (t_{max}), the area under the plasma concentration-time curve during a dosing interval (AUC_{τ}), and the half-life ($t_{1/2}$) were assessed for each period. *NonCompart* package (version 0.4.7, by Kyun-Seop Bae, 2020) in R (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria) was utilized in this procedure. The AUC_{τ} was calculated according to the linear trapezoidal rule [10]. The $t_{1/2}$ was estimated as the value of $0.693/\lambda_z$, where λ_z is the terminal elimination slope with the best determination coefficient from the linear regression of the last ≥ three observations. An average BE assessment between two periods was performed using the *nlme* package (version 3.1-152, by José Pinheiro *et al.*, 2021) in R. The log-transformed geometric mean ratios of C_{max} and AUC_{τ} with 90% confidence intervals (CI) were estimated. The DDI presence was assessed by whether the geometric mean ratios of the parameters and their 90% CI fell within the conventional BE range (0.8–1.25) [11].

2. Partial Model-based approach (MB1)

A simulated PK profile (for the planned time of Period 2) using the PK model built from Period 1 data was compared to the observed PK profiles of Period 2 under the same schema as the NCA and BE approach. For the simulations, the individual PK param-

Table 1. Subject demographics

Variables	Mean (range)
Age (yr)	30 (23–46)
Weight (kg)	72.0 (56.2–83.9)
Height (cm)	175.3 (164–191)
Albumin (g/dl)	4.6 (4.2–5.0)
Body mass index (kg/m^2)	23.4 (19.2–26.5)
Alanine transaminase (IU/L)	29.7 (9.0–54.0)
Aspartate transaminase (IU/L)	23.5 (15.0–36.0)
Serum creatinine (mg/dl)	0.9 (0.7–1.1)
Creatinine clearance (mL/min)	122.2 (90.5–175.6)
Glomerular filtration rate (GFR)* (ml/min/1.73m^2)	99.5 (77.3–131.1)

*GFR was calculated using Modification of Diet in Renal Disease equation.

eter values were fixed to reflect each subject's PK characteristics. This procedure was repeated 1,000 times, and the proportion of negative results for DDI was obtained.

3. Full Model-based approach (MB2)

Population PK model was developed using both Period 1 and 2 data, and possible DDI was investigated as the change of each PK parameter as follows:

$$P_{i,2} = P_{i,1} + \text{PRD} \cdot DP_i$$

where $P_{i,1}$ is the value of i^{th} PK parameter in Period 1, $P_{i,2}$ is the value of i^{th} PK parameter in Period 2, DP_i is the quantitative difference between i^{th} PK parameter according to the Period, and PRD is the indicator for Period (0 for Period 1 and 1 for Period 2). No period effect other than DDI was assumed since the actual period effect cannot be assessed in a single-sequence cross-over study.

For comparison, a similar NCA and BE approach was also utilized, and simulated steady-state PK profiles (on day 13) without DDI and with DDI (if it exists) were compared. The simulation was repeated 1,000 times, and the average BE results were summarized.

General procedures for model development

Nonlinear mixed-effects modeling was conducted using NONMEM version 7.4 (Icon Development Solutions, Ellicott City, MD, USA). The model was developed by evaluating different absorption models, adopting a two-compartment model with first-order absorption and first-order elimination initially [12]. The first-order conditional estimation with interaction (FOCE-I) was employed throughout the process. The most appropriate model selection was based on objective function values (OFV) evaluation, diagnostic plots (goodness-of-fit and individual plot) visual inspection, percent relative standard errors (%RSE), and parameter estimates of population fixed- and random- effects. The model was considered more appropriate if a decrease in the OFV was more than 3.84 (p-value < 0.05, $df = 1$) using the likelihood-ratio test. R was used for graphical analysis and model diagnostics.

Inter-individual variability of each parameter was described exponentially as:

$$P_{ij} = \theta_i \cdot \exp(\eta_{ij})$$

Where P_{ij} is the estimated parameter value for the j^{th} individual, θ_i is the typical value of the i^{th} PK parameter, and η is the between-subject variability (BSV), following a normal distribution η~N(0, ω^2). Covariance between inter-individual variability was evalu-

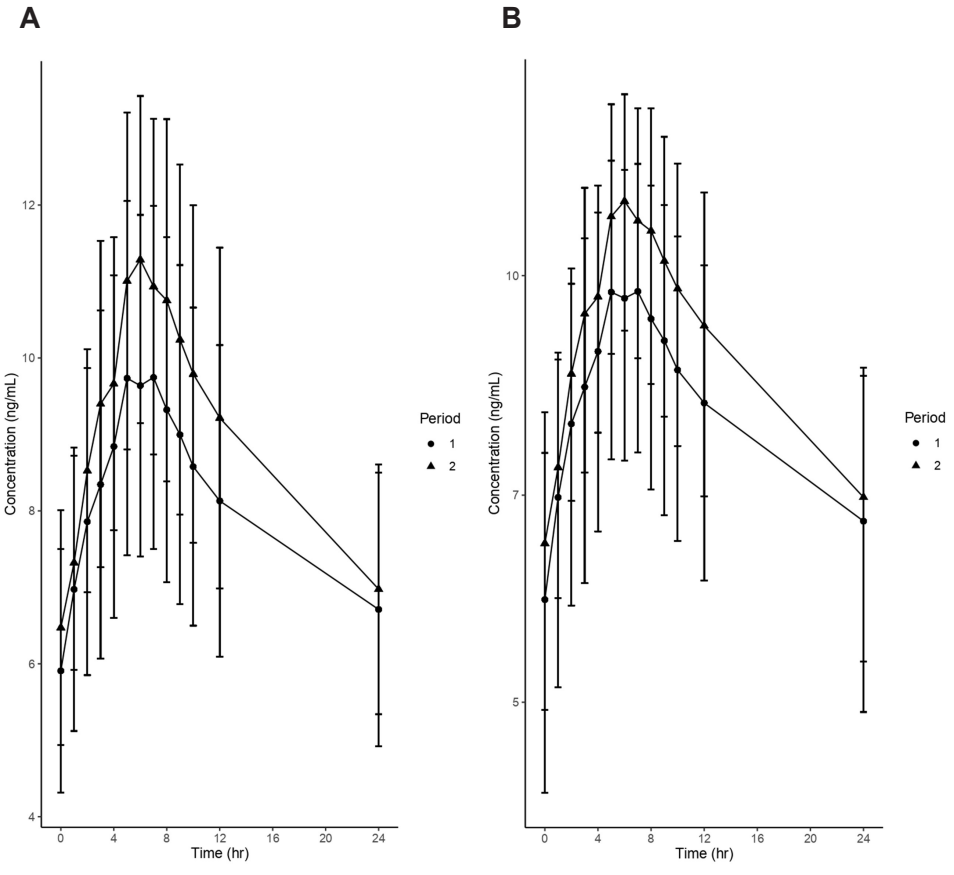

Fig. 1. Average plasma concentration versus time plots of amlodipine. (A) Linear scale, (B) Semilogarithmic scale.

ated for possible correlations. Intra-individual variability (residual error) was tested with either additive, proportional, and combined structures.

General procedures for model evaluation

Visual predictive checks (VPCs) were conducted to support model adequacy. The 5th, 50th, and 95th percentiles of the simulated data (n = 1,000 replicates) were plotted, and the observed data were superimposed for visual comparison using R.

Wings for NONMEM (version 741, by Nick Holford, 2017) was used for bootstrap analysis to examine model robustness. One thousand replicates of the original dataset were generated by resampling with replacement, and median values with 95% CIs of parameters were determined to compare with their respective final parameter values.

RESULTS

Conventional approach (NCA & BE)

The C_{max} and AUC_{τ} values for Period 1 and 2 were 10.00 ± 2.3 ng/ml and 11.69 ± 2.38 hr·ng/ml, and 192.46 ± 47.35 ng/ml and 213.41 ± 45.2 hr·ng/ml, respectively. The observed average concentration-time profile is illustrated in Fig. 1 ([Fig. 1A] linear and [Fig. 1B] semilogarithmic), and PK parameters are summarized in Table 2. The point estimate for log-transformed geometric mean ratio of C_{max} was 1.177 (1.127–1.229), and that of AUC_{τ} was 1.119 (1.068–1.174). The results fell within the BE limits of 0.8 to 1.25, indicating there was no significant DDI.

MB1

A two-compartment, dual (rapid zero-order and slow first-order) absorption followed by first-order elimination was chosen as the final structural model (Fig. 2). The estimated oral PK parameters and their values were as follows; clearance (CL/F) = 25.6 L/h, central volume (V_2/F) = 884 L, peripheral volume (V_3/F) = 446 L, intercompartmental clearance (Q/F) = 63.6 L/h, absorption rate constant (K_a) = 0.874, lag time for first-order absorption ($ALAG_1$) = 3.75 h, duration of zero-order absorption (D_2) = 3.31 h, and fraction absorbed through first-order absorption (F_1) = 0.458. BSVs for CL, V_2, and F_1 and a correlation between CL and V_2 were identified. Details for parameter estimates are shown in Table 3 with the bootstrap results and the goodness-of-fit plots illustrated in Fig. 3A. The model's predictive performance was judged by the VPC plot for Period 1 (Fig. 3B).

Table 2. Pharmacokinetic parameters using non-compartmental analysis

Parameter	Period 1	Period 2
C_{max} (ng/ml)	10.00 ± 2.3	11.69 ± 2.38
$AUC\tau$ (ng·hr/ml)	192.46 ± 47.35	213.41 ± 45.2
$t_{1/2}$ (hr)	46.67 ± 31.6	41.92 ± 46.65
t_{max} (hr)	5.5 (5–8)	6 (5–9)

Data presented as mean ± SD except for t_{max} values as median (range).

The point estimate for log-transformed geometric mean ratios of C_{max} and AUC_{τ} were 1.149 (1.097–1.203) and 1.105 (1.048–1.166), respectively. The results also proved that there was no significant DDI.

MB2

The model was best described by the same structure as the final model of MB1 (Fig. 2). DDI effect was explored for each PK parameter using the period as a covariate. Total bioavailability (BIO) was introduced as a relative bioavailability for Period 1. BIO showed a 30% increase compared to non-interacting situations, and $F1$ and CL showed approximately 16% and 15% increase, respectively. Estimated PK parameters and their values were as follows; clearance (CL/F) = 25.5 L/h, change in CL = 3.90 L/h, central volume (V_2/F) = 943 L, peripheral volume (V_3/F) = 403 L, intercompartmental clearance (Q/F) = 47.6 L/h, absorption rate constant (K_a) = 0.991, lag time for first-order absorption ($ALAG_1$) = 3.86 h, duration of zero-order absorption (D_2) = 3.42 h, fraction absorbed through first-order absorption during Period 1 (F_1 (PRD1)) = 0.405, fraction absorbed through first-order absorption during Period 2 (F_1 (PRD2)) = 0.468, and total bioavailability for Period 2 (BIO) = 1.30. BSVs of CL, V_2, F, and BIO were incorporated in the final model with a correlation between CL and V_2. The final PK parameter estimates and bootstrap results are also presented in Table 3. The goodness-of-fit plots and VPC plots presented in Fig. 4A and 4B demonstrated that the model provided a sufficient description of the observed data.

The point estimate for log-transformed geometric mean ratios of C_{max} and AUC_{τ} were 1.139 (1.092–1.188) and 1.116 (1.064–1.170),

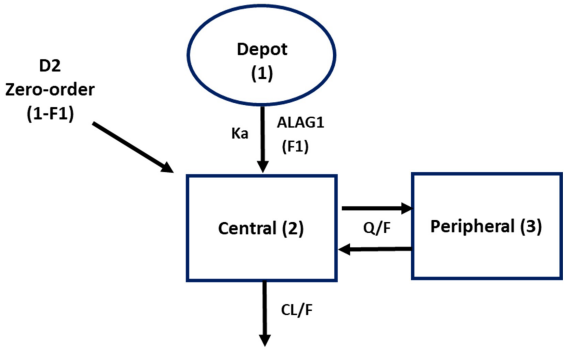

Fig. 2. PK Model structure. D_2, duration of zero-order absorption; F_1, fraction absorbed through first-order absorption; K_a, absorption rate constant; $ALAG_1$, lag time for first-order absorption; CL/F, apparent oral clearance; V_2/F, central volume; V_3/F, peripheral volume; Q/F, intercompartmental clearance.

Table 3. Summary of final population PK parameters

Parameter	MB1			MB2		
	Estimates	RSE (%)	Bootstrap median (95% CI)	Estimates	RSE (%)	Bootstrap median (95% CI)
Structural model						
CL/F (Period 1*)	25.6	6.10	25.3 (22.4–28.7)	25.5	6.00	25.2 (22.7–28.6)
CL change	-	-	-	3.90	23.4	4.16 (2.20–6.55)
V_2/F	884	7.50	864 (622–1,050)	943	8.60	921 (748–1,080)
V_3/F	446	27.6	533 (124–1,360)	403	37.0	462 (203–982)
Q/F	63.6	21.2	70.4 (22.6–122)	47.6	34.2	51.4 (22.2–92.5)
K_a	0.874	16.1	0.835 (0.453–1.55)	0.991	17.6	0.959 (0.588–1.44)
$ALAG_1$	3.75	3.00	3.77 (3.56–4.05)	3.86	1.70	3.87 (3.73–4.08)
D_2	3.31	9.10	3.35 (2.91–4.56)	3.42	5.10	3.44 (3.03–3.94)
F_1 (Period 1*)	0.458	10.7	0.461 (0.333–0.597)	0.405	14.3	0.410 (0.313–0.530)
F_1 (Period 2)	-	-	-	0.468	9.80	0.474 (0.391–0.563)
BIO	-	-	-	1.30	3.50	1.30 (1.20–1.41)
Between-subject variability (CV%, covariance for ρ)						
ω_{CL}	29.9	30.4	29.3 (20.4–39.2)	29.8	28.8	28.6 (20.5–37.2)
ω_{V2}	24.8	36.2	24.1 (15.6–33.1)	25.6	41.4	24.2 (14.6–35.8)
ω_{F1}	32.1	44.0	30.4 (18.5–51.6)	33.4	55.3	30.7 (17.6–52.1)
ω_{BIO}	-	-	-	8.80	43.5	8.30 (4.20–12.3)
$\rho_{CL\text{-}V2}$	0.857	-	0.872 (0.581–0.999)	0.802	-	0.800 (0.464–0.946)
Intra-individual variability (residual error)						
σ_{Add}	0.408	5.20	0.401 (0.357–0.442)	0.456	5.60	0.451 (0.397–0.499)

MB1, partial Model-based approach; MB2, full Model-based approach. RSE, relative standard errors; PK, pharmacokinetic; CI, confidence interval; *CL/F*, clearance; V_2/F, central volume; V_3/F, peripheral volume; *Q/F*, inter-compartmental clearance; K_a, absorption rate constant; $ALAG_1$, lag time for first-order absorption; D_2, duration of zero-order absorption; F_1, fraction absorbed through first-order absorption; *BIO*, total bioavailability of Period 2; ω_{CL}, between-subject variability of *CL*; ω_{V2}, between-subject variability of V_2; ω_{F1}, between-subject variability of F_1; ω_{BIO}, between-subject variability of *BIO*; $\rho_{CL\text{-}V2}$, correlation coefficient of *CL* and V_2; σ_{Add}, additive error. *Results were rounded to 3 significant digits; Period 1 applies to MB2 only.

respectively, indicating DDI is not significant. The average BE results for all DDI evaluation methods are summarized in Table 4.

DISCUSSION

In this study, two types of model-based approach methods were assessed for DDI evaluation. Overall, both approaches with simulated data showed similar results using raw data. In all cases, including the conventional approach (NCA & BE), C_{max} increased by about 13.9%–17.7%, and AUC_τ increased by 10.5%–11.9% between periods. However, due to the small intra-subject variability of amlodipine [13], the PK parameter ratio's CI was very narrow, satisfying the classical BE limit. There may be some differences in the actual numbers depending on the method used, but such differences do not significantly change the likelihood of clinical DDI occurrence. Therefore, confidently all approaches properly evaluated the degree of DDI occurrence.

A model-based approach can have several advantages over the conventional method, which uses raw data only. For drugs with a long half-life, the possibility of DDI overestimation due to changes in concentration associated with reaching steady-state may be reduced; this was confirmed by comparing the results of the conventional approach and MB1. The conventional approach showed a larger ratio of PK parameters (C_{max} and AUC_τ) than MB1 because the simulated data corresponding to Period 2 in MB1 reflected the steady-state concentration. At the time of study design, repeated administration is performed for a predicted period of steady-state achievement based on a known half-life. However, there is an uncertainty that the half-life may be longer than known in the subject population, and a long-term administration may be difficult to overcome this uncertainty for drugs with a long half-life [14]. Therefore, when evaluating clinical DDI with these drugs, using MB1 in addition to the conventional method may be sufficient to determine whether or not the DDI is overestimated in situations where steady-state is not achieved.

In the case of MB2, information on the change of each parameter was obtained from estimating model parameters that optimally described each period by using data from both periods. Although the role of the conventional approach and MB2 may be similar in that the overall C_{max} and AUC_τ show an increased pattern, the conventional approach has a limitation where it cannot be ascertained what mechanism is responsible for the change in the PK parameter [5,9]. According to the modeling results, it is highly likely that the increase in C_{max} was based on the increase in bioavailability (*BIO*), indicating that the absorption of the drug in Period 2 increased by 30.0% compared to Period 1. However, the actual increase in C_{max} and AUC_τ was not more significant than

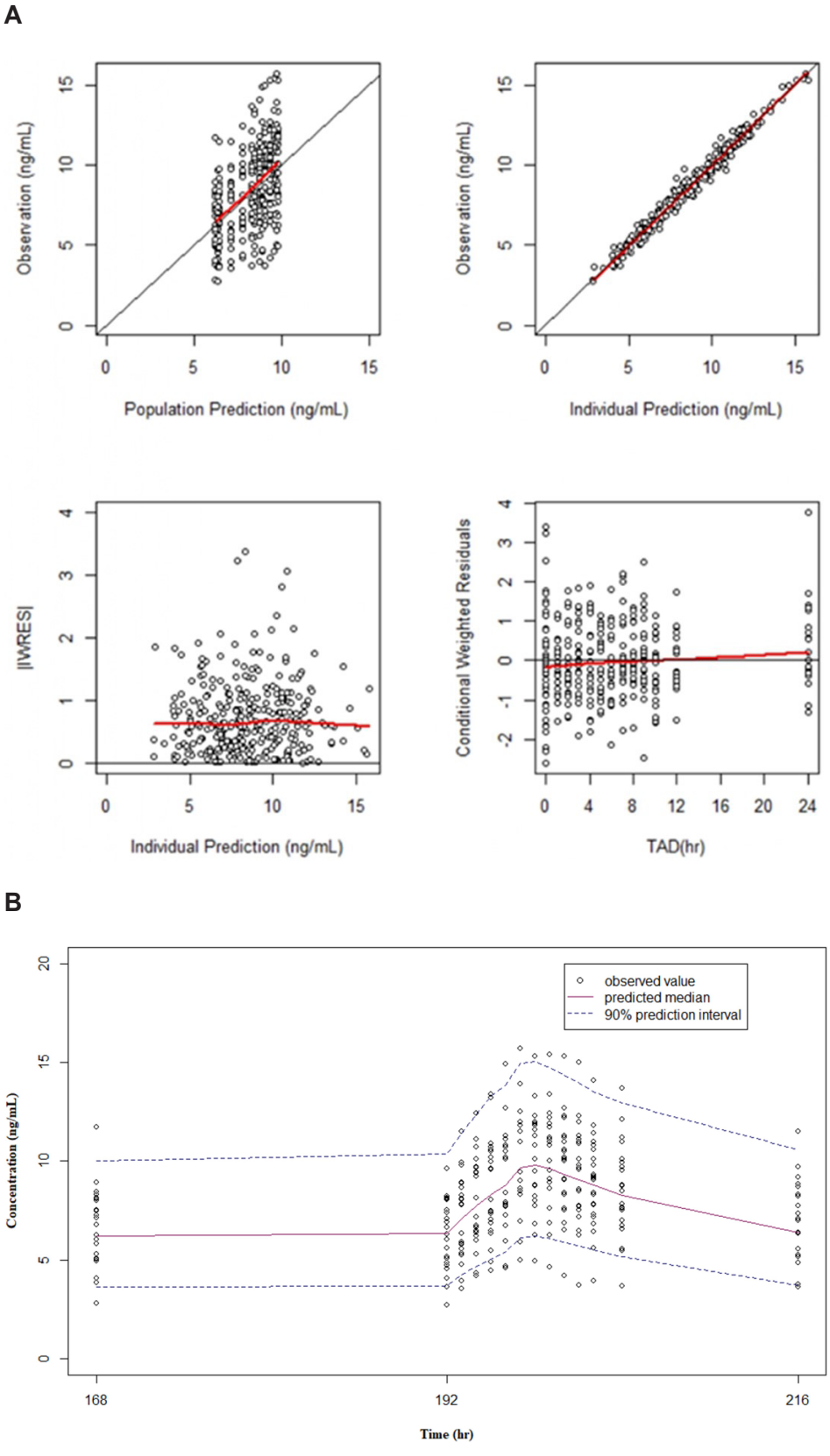

Fig. 3. Model outcomes of MB1. (A) Goodness-of-fit plots. (B) Visual predictive check. MB1, partial Model-based approach; TAD, time after dose; IWRES, individual weighted residuals.

this because the increase in bioavailability was offset to some extent by 15.3% increased clearance (*CL* change); this is illustrated in Fig. 1, where Period 2's terminal slope of elimination is larger than that of Period 1.

The model-based approach is valuable because it provides additional information while helping to overcome limitations in

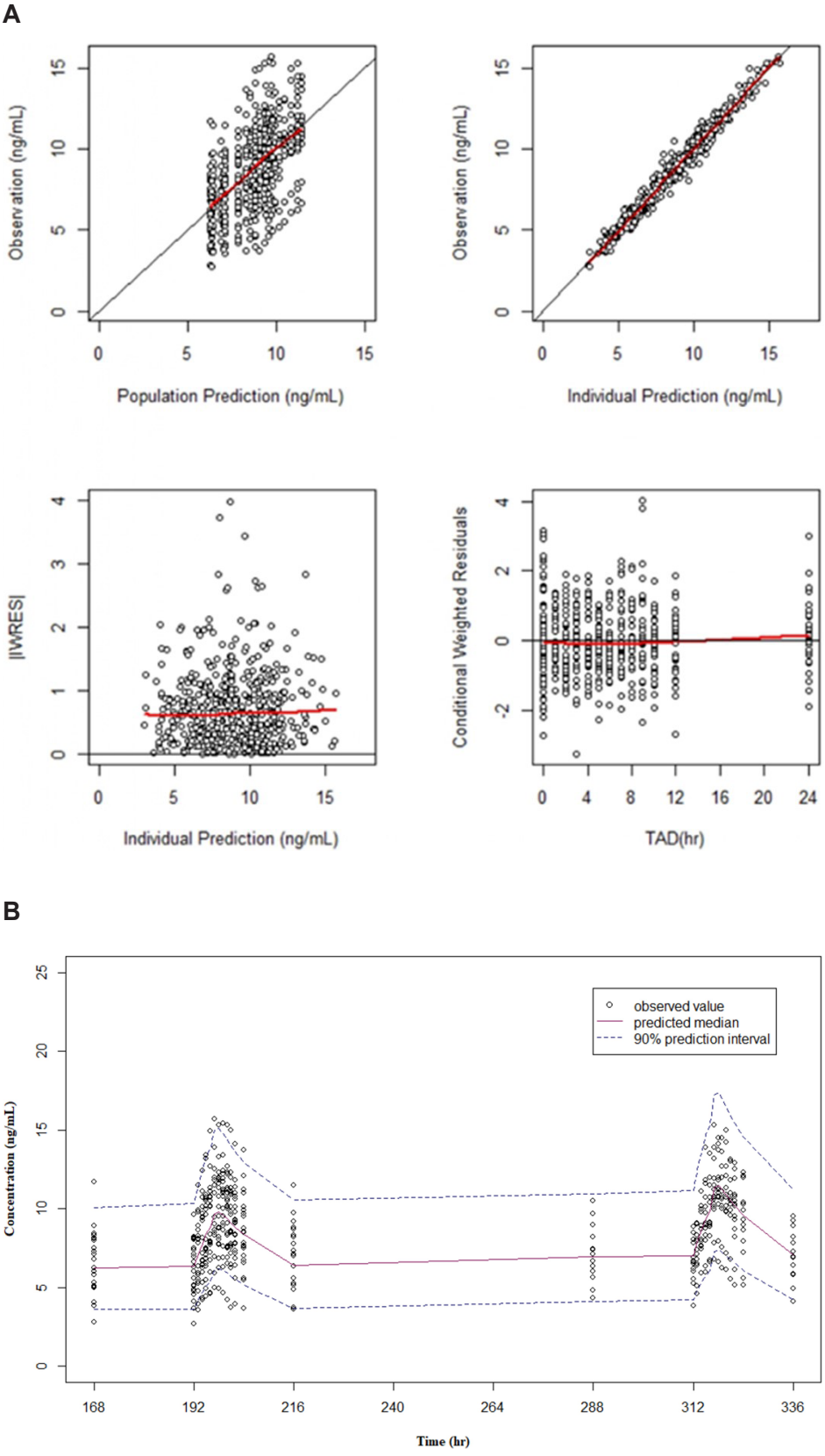

Fig. 4. Model outcomes of MB2. (A) Goodness-of-fit plots. (B) Visual predictive checks. MB2, full Model-based approach. TAD, time after dose; IWRES, individual weighted residuals.

clinical trial design. First, it is possible to predict C_{max} and AUC_{τ} without simulation through model parameter changes in two periods. Using AUC_{τ} as an example, the following calculation can be performed. Using the parameter estimates of *BIO* and *CL* from the model, *AUC* was calculated by the equations below:

Table 4. Summary table for BE limit with average geometric mean ratios and 90% confidence intervals (lower and upper) of DDI evaluation methods (n = 1,000)

Estimates	C_{max}			AUC_T		
	NCA & BE	MB1	MB2	NCA & BE	MB1	MB2
Lower	1.127	1.097 (1.079–1.114)	1.092 (1.088–1.095)	1.068	1.048 (1.036–1.059)	1.064 (1.063–1.066)
Point estimate	1.177	1.149 (1.130–1.167)	1.139 (1.134–1.143)	1.119	1.105 (1.092–1.118)	1.116 (1.113–1.118)
Upper	1.229	1.203 (1.179–1.227)	1.188 (1.181–1.195)	1.174	1.166 (1.147–1.186)	1.170 (1.165–1.175)
Percentage satisfied (%)	-	100	100	-	100	100

MB1, partial Model-based approach; MB2, full Model-based approach. BE, bioequivalence; DDI, drug-drug interaction; NCA, noncompartmental analysis.

$$AUC = F \cdot DOSE/CL$$

Assuming the same dose (*DOSE*) was given, the relative exposure was described by:

$$AUC_{period2}/AUC_{period1}$$

The point estimate was 1.124, and the 90% confidence interval was 1.089–1.154, similar to the results above. Second, precise changes in parameters provide an opportunity to assess whether such trends in DDI can be explained by the known effects of concomitant drugs on drug transporters or metabolic enzymes [15]. Finally, this approach provides a confidence limit in addition to the point estimate; this can be used as an indicator of the likelihood that the same results can be derived during repeated simulations [9]. The result confirmed that the 90% CI remained within 0.8–1.25, and accordingly, all met the classical BE limit.

Model-based comparative PK evaluations are not yet widely used, and results have not been published in many cases. In this study, several advantages of the model-based approach were demonstrated, and possible application methods were proposed.

With similar experiences accumulated from comparative PK studies on drugs of various characteristics, it is expected that the advantages of the model-based approach compared to the classical method can be appropriately utilized according to the situation and purpose.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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