Simulation for the Analysis of Distorted Pharmacodynamic Data

Yukiya Hashimoto,[1] Junko Ozaki,[1] Toshiko Koue,[1] Atsuko Odani,[1] Masato Yasuhara,[1,3] and Ryohei Hori[1,2]

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A simulation study was conducted to compare the performance of alternative approaches for analyzing the distorted pharmacodynamic data. The pharmacodynamic data were assumed to be obtained from the natriurertic peptide-type drug, where the diuretic effect arises from the hyperbolic (E_{max}) dose–response model and is biased by the dose-dependent hypotensive effect. The nonlinear mixed effect model (NONMEM) method enabled assessment of the effects of hemodynamics on the diuretic effects and also quantification of intrinsic diuretic activities, but the standard two-stage (STS) and naive pooled data (NPD) methods did not give accurate estimates. Both the STS and the NONMEM methods performed well for unbiased data arising from a one-compartment model with saturable (Michaelis–Menten) elimination, whereas the NPD method resulted in inaccurate estimates. The findings suggest that nonlinearity and/or bias problems result in poor estimation by NPD and STS analyses and that the NONMEM method is useful for analyzing such nonlinear and distorted pharmacodynamic data.

KEY WORDS: Michaelis–Menten kinetics; nonlinear mixed effect model (NONMEM); pharmacodynamics; population pharmacokinetics; statistical simulation.

INTRODUCTION

Natriuretic peptides have not only natriuretic and diuretic but also hypotensive activities. The decreased renal perfusion caused by excessive hypotension attenuates the diuretic actions, which have been especially confounding to our understanding of net diuresis of the peptides. Both the diuretic and the hypotensive actions of natriuretic peptides are dependent on the dose administered. Therefore, how the diuretic action is caused by the dose administered and is influenced by the hemodynamics cannot be estimated easily from the pharmacological data in individuals. In addition, these arguments may not be confined to the hypotensive action of natriuretic peptides and may be extended to other complications such as the hemodynamic actions of antiarrhythmics and anesthetics, the chronotropic action of antihypertensives, and the additive or synergistic effect of active metabolites of certain drugs.

In our previous study (1), we analyzed the pharmacodynamics of natriuretic peptides and suggested the usefulness of the population analysis. In the present study, we simulated the distorted pharmacodynamic data to mimic those of natriuretic peptides and compared the performance of the nonlinear mixed effect model (NONMEM) method with that of two standard methods of population data analysis, the standard two-stage (STS) and naive pooled data (NPD) methods (2,3). We further characterized the analysis methods using the unbiased but highly nonlinear pharmacokinetic data, which arise from a one-compartment model with Michaelis–Menten elimination.

METHODS

Simulation Models

Pharmacodynamic Model. We assumed the existence of a hypothetical drug which has both diuretic and hypotensive activities (1). The jth diuretic effect (DE_{ij}) in the ith individual at an intravenous dosing rate (DR_{ij}) is assumed to arise from the E_{max} model (4) and to be influenced by the true blood pressure (BP_{ij}):

$$DE_{ij} = E_{\max} \cdot DR_{ij}/(D_{50_i} + DR_{ij}) \cdot \{1 - \theta_{BP} \cdot (1 - BP_{ij})\} \cdot (1 + \epsilon_{DE_{ij}}) \quad (1)$$

where $E_{\max_i}$ is the maximum drug-related diuretic effect, and D_{50_i} is the value of dosing rate causing 50% of the maximum effect in the ith individual. θ_{BP} is the coefficient decreasing (increasing) the diuresis below (above) blood pressure, 1. The quantities $E_{\max_i}$ and D_{50_i} are assumed not to vary within the ith individual but may differ between subjects. For this variation, we assumed that $E_{\max_i}$ and D_{50_i} are independently normally distributed with mean $E_{\max}$ and D_{50} and variances $\omega^2_{E_{\max}}$ and $\omega^2_{D_{50}}$, respectively. The observed diuretic effect (DE_{ij}) is assumed to be randomly and normally distributed from the predicted value, and $\epsilon_{DE_{ij}}$ is a random variable describing intraindividual variability with mean zero and variance σ^2_{DE}. We further assumed that BP_{ij} is also dependent on the dose administered and that BP_{ij} is modeled as a linear function of DR_{ij}. However, BP_{ij} may fluctuate by the true intraindividual variability, and the observed blood pressure (BPO_{ij}) may also fluctuate by the measurement error. Thus, we modeled BP_{ij} and BPO_{ij} as follows:

$$BP_{ij} = (\mathrm{BASE}_i - \mathrm{SLOPE}_i \cdot DR_{ij}) \cdot (1 + \epsilon_{BP_{ij}}) \quad (2)$$

$$BPO_{ij} = BP_{ij} \cdot (1 + \epsilon_{BPO_{ij}}) \quad (3)$$

where BASE_i is the baseline blood pressure before administration of the drug, and SLOPE_i is the constant representing drug-related hypotensive effects in the ith individual. BASE_i and SLOPE_i are independently normally distributed with mean BASE and SLOPE and variances ω^2_{BASE} and $\omega^2_{\mathrm{SLOPE}}$, respectively. $\epsilon_{BP_{ij}}$ is a random variable describing (true) intraindividual variability with mean zero and variance σ^2_{BP}, and $\epsilon_{BPO_{ij}}$ is a random variable describing measurement error with mean zero and variance σ^2_{BPO}.

Pharmacokinetic Model. The unbiased pharmacokinetic data are assumed to arise from a one-compartment model with Michaelis–Menten elimination. The Michaelis–Menten differential equation following intravenous administration (or rapid absorption from some other site) is described as follows:

[1] Department of Pharmacy, Kyoto University Hospital, Kyoto University, Sakyo-ku, Kyoto 606, Japan.
[2] Pharmaceutical Research and Technology Institute, Kinki University, Kowakae, Higashi-osaka 577, Japan.
[3] To whom correspondence should be addressed.

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$$dCp/dt = -V_{max_i} \cdot Cp/(K_{m_i} + Cp)/V_i \quad (4)$$

where Cp and t are the drug concentration and time, respectively. V_{max_i}, K_{m_i} and V_i are the maximal dosing rate (daily dose) to be cleared, the Michaelis–Menten constant, and the volume of distribution in the ith subject, respectively. We assumed that V_{max_i}, K_{m_i}, and V_i are independently normally distributed with mean V_{max}, K_m, and V and variances $\omega^2_{V_{max}}$, $\omega^2_{K_m}$, and ω^2_V, respectively. In addition, the jth observed concentration in the ith subject (Cp_{ij}) is assumed to be randomly and normally distributed from the true value (Cp^*_{ij}):

$$Cp_{ij} = Cp^*_{ij} \cdot (1 + \epsilon_{Cp_{ij}}) \quad (5)$$

where $\epsilon_{Cp_{ij}}$ is a random variable describing intraindividual variability with mean zero and variance σ^2_{Cp}.

Simulated Parameter Values and Study Designs

The simulated (true) pharmacodynamic parameters were as follows: $(E_{max}, \omega_{E_{max}}) = (1, 0.3)$, $(D_{50}, \omega_{D_{50}}) = (0.25, 0.125)$, $\theta_{BP} = 1$, $\sigma_{DE} = 0.15$, (BASE, ω_{BASE}) = (1, 0.15), (SLOPE, ω_{SLOPE}) = (0.2, 0.14), $\sigma_{BP} = 0.1$, and $\sigma_{BPO} = 0.05$. The design for the study was as follows: $DR_{ij} = 0.125$, 0.25, 0.5, and 1.0 were administered to each of 40 subjects, and the blood pressure and diuretic effect were measured once for each dosing rate. The total number of data was 160 for the blood pressure and diuretic effect.

The simulated pharmacokinetic parameters were as follows: $(V_{max}, \omega_{V_{max}}) = (2, 0.4)$, $(K_m, \omega_{K_m}) = (4, 0.4)$, $(V, \omega_V) = (1, 0.2)$, $\sigma_{CP} = 0.1$. We assumed that the drug was administered repetitively for each of 20 subjects, and two blood specimens were obtained at steady-state. This procedure is repeated until each subject receives four dose levels. The design parameters for the pharmacokinetic study were as follows: the interdose interval, $\tau = 1.0$; the sampling time after the preceding dose, $t_{ij} = 0.25$ and 1.0; and the dose, $D_{ij} = 0.25$, 0.5, 0.75, and 1.0. The total number of data was 160.

All random variables in the pharmacokinetic and pharmacodynamic models were realized as pseudonormal variates, using the Box–Muller algorithm (5). In addition, Eq. (4) was solved numerically (6). Figures 1 and 2 show typical sets of simulated pharmacodynamic and pharmacokinetic data, respectively.

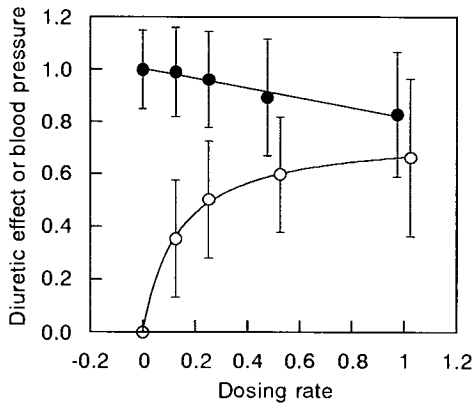

Fig. 1. Typical course of mean (±SD) diuretic effect (open circles) and blood pressure (filled circles) following intravenous infusion of a hypothetical diuretic drug.

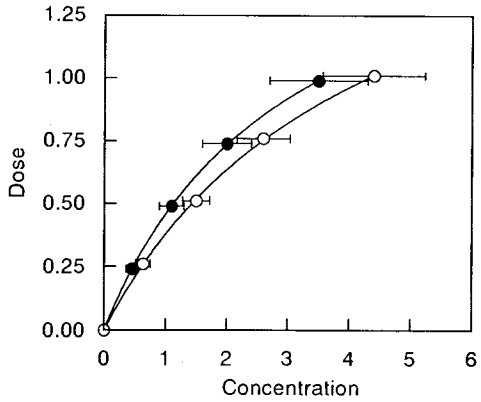

Fig. 2. Typical relationship between mean (±SD) plasma concentrations and doses of a hypothetical drug with Michaelis–Menten elimination. $t_{ij} = 0.25$ (open circles) and $t_{ij} = 1.0$ (filled circles).

Analysis Models

Pharmacodynamic Model. In the actual situation, BP_{ij} is not known and must be predicted from the pharmacodynamic data to analyze the diuretic effect. We simply used BPO_{ij} and modified Eq. (1) as follows:

$$DE_{ij} = E_{max_i} \cdot DR_{ij}/(D_{50_i} + DR_{ij}) \cdot \{1 - \theta_{BP} \cdot (1 - BPO_{ij})\} \cdot (1 + \epsilon_{DE_{ij}}) \quad (6)$$

Though there are some variants to analyze the diuretic effect, we did not try further in the present report. In addition, we focused on the diuretic effect and did not analyze the hypotensive effect.

Pharmacokinetic Model. The Michaelis–Menten differential equation gives analytical solutions for the peak and trough levels at steady-state following repetitive intravenous administration (6). The synthesized equation for the peak ($t_{ij} = 0$) and trough ($t_{ij} = \tau = 1.0$) levels is described as follows:

$$Cp_{ij} = D_{ij}/V_i/\{1 - e^{-(V_{max_i} - D_{ij}/\tau)/K_{m_i}/V_i \cdot \tau}\} \cdot e^{-(V_{max_i} - D_{ij}/\tau)/K_{m_i}/V_i \cdot t_{ij}} \cdot (1 + \epsilon_{Cp_{ij}}) \quad (7)$$

This equation is also an approximate analytical solution for the time course of drug concentration in the interdose interval and is used in this study. In addition, Table I shows the drug concentrations calculated by the simulation [Eqs. (4)

Table I. Comparison of Pharmacokinetic Data Calculated by the Simulation and Analysis Models for a Typical Subject with $(V_{max_i}, K_{m_i}, V_i, \epsilon_{CP_{ij}}) = (V_{max}, K_m, V, 0)$

Dose	Time	Concentration	
		Simulation model	Analysis model
0.25	0.25	0.634	0.632
	1.00	0.456	0.456
0.50	0.25	1.461	1.456
	1.00	1.099	1.099
0.75	0.25	2.593	2.584
	1.00	2.044	2.044
1.00	0.25	4.259	4.247
	1.00	3.521	3.521

and (5)] and analysis [Eq. (7)] models for a typical subject with $(V_{max_i}, K_{m_i}, V_i, \epsilon_{CP_{ij}}) = (V_{max}, K_m, V, 0)$. The analysis model is suggested to be a very precise approximation of a simulation model for the pharmacokinetic parameter–design parameter combination.

Analysis Methods

STS Method. The method proceeds in two stages. At stage 1, the pharmacodynamic/kinetic parameters in individuals were estimated with nonlinear least squares. At stage 2, these estimates were combined across individual subjects to obtain the population mean parameters. The parameter estimation of individual subjects was performed by the Nelder–Mead algorithm (7).

NPD Method. All pharmacodynamic/kinetic data from all subjects were pooled, and the parameters were estimated using the nonlinear least-squares method as though all the data had come from one individual. This is accomplished by ignoring the "i" subscript in Eq. (6) and Eq. (7), using these equations as the regression function.

NONMEM Method. This method uses an extension of nonlinear least squares and resembles the NPD method in its approach. However, it explicitly models and handles the error structure arising from proper accounting of the random effects. NONMEM and also NPD analyses were performed with the NONMEM software (double-precision NONMEM Version IV Level 1.1 and NM-TRAN Version II Level 1.1) (8).

Comparison of Analysis Methods

The simulation was performed on a FACOM M-1800 computer running under a MXP/M UNIX clone at the Kyoto University Data Processing Center, and all three estimation methods were used on each replication of simulation. Forty replications of the data set for both the pharmacodynamic and the pharmacokinetic models were used for the comparison of analysis methods. The primary interest is in the population mean dynamics/kinetics, and the additional interest may be in their variability. However, the NPD method gives only the population mean structural parameters, and does not provide estimates of the interindividual variability. Moreover, we used "semiexperimental" designs for the dynamic/kinetic studies in the present report, and it may be difficult for the STS and NONMEM methods to give a precise estimation of the interindividual variability from such a "small" population (3,4,9–11). We, therefore, focused on the population mean parameters to compare the performance of analysis methods. Both degree of bias and precision of point estimates relative to true (simulated) values are of interest. To express bias and precision for all parameters on the same scale, percentage error (% error) of estimates was computed as follows: % error = (estimated value − true value) ÷ true value × 100. The accuracy of the estimated parameters was judged by the mean (over the 40 simulated data sets) of percentage error, and the precision by the standard deviation of the percentage error.

RESULTS AND DISCUSSION

Sheiner and Beal have initiated a series of simulation studies comparing the performance of population approaches to the analysis of fragmentary data arising from a steady-state Michaelis–Menten model (3), experimental data arising from a single-dose biexponential model (9), and fragmentary data arising from a multiple-dose monoexponential model (10). In all cases, a NONMEM approach has been superior to the NPD method in estimating the population mean (structural) parameters and superior to the STS method in estimating the interindividual variability of the mean parameters. They also analyzed the dose-ranging pharmacodynamic data arising from an E_{max} model (4,11) and demonstrated that the NONMEM method is robust for imbalance/bias in data, arising from study-design problems and/or certain complications in study execution ("placebo" effect, "carryover" effect, "toxic dropout" of subject, and so on). In the present study, the pharmacodynamic data were assumed to be obtained from the natriuretic peptide-type drug (1), where the diuretic effect arises from the hyperbolic (E_{max}) dose–response model and is attenuated by the dose-dependent hypotensive effect. We focused on the pharmacodynamic parameters for the diuretic effect and examined the performance of the NONMEM method for analyzing such distorted/biased pharmacodynamic data, compared with the standard STS and NPD methods.

Figure 3 shows the mean and standard deviation of percentage error of the pharmacodynamic parameter estimates in the STS, NPD, and NONMEM analyses. The STS method gave poor parameter estimates, especially in D_{50} and θ_{BP}. We assumed that a hypothetical diuretic drug has both diuretic and hypotensive activities and that the diuretic action of the drug is highly correlated not only with the dose administered but also with the hypotensive action. Therefore, the intrinsic diuretic activity (E_{max} and D_{50}) and the influence of hemodynamics on diuresis (θ_{BP}) cannot be estimated separately from the individual analysis. In addition, we used the observed blood pressure (BPO_{ij}) instead of the true value (BP_{ij}) to obtain the pharmacodynamic parameters for diuretic effects. This may also be partly responsible for the poor estimation of θ_{BP} in the STS analysis. In the NPD analysis as well as the NONMEM analysis, all pharmacodynamic data from all subjects were pooled, and the information about effect of blood pressure on diuresis at each dosing rate was accumulated from all subjects. Thus, the NPD method gave accurate estimates for θ_{BP}. However, the pre-

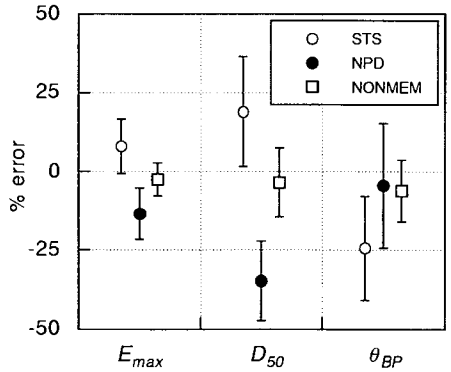

Fig. 3. Mean percentage error (±SD) of the pharmacodynamic parameter estimates from STS, NPD, and NONMEM analyses.

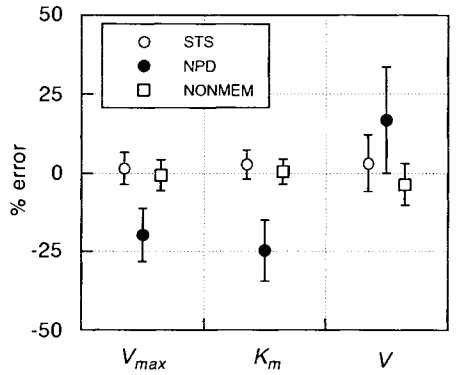

Fig. 4. Mean percentage error (±SD) of the pharmacokinetic parameter estimates from STS, NPD, and NONMEM analyses.

cision of the estimation of θ_{BP} was poor, and the estimation of E_{max} and D_{50} in the NPD analysis was inaccurate. The NONMEM method enabled accurate and precise estimation of the effects of hemodynamics on the diuretic effects (θ_{BP}), probably because the analysis was keeping track of which data arose from which individuals. That is, the inference of the greater (lesser) diuretic response in the sensitive (insensitive) subjects may serve to prevent the estimation error of θ_{BP}. Quantification of intrinsic diuretic activities (E_{max} and D_{50}) by the NONMEM analysis was also much more accurate than those by the STS and NPD methods.

We further characterized three analysis methods using the unbiased but highly nonlinear pharmacokinetic data, which arise from a one-compartment model with Michaelis–Menten elimination. Figure 4 shows the mean and standard deviation of percentage error for the pharmacokinetic parameter estimates. The STS method as well as the NONMEM method gave accurate estimates for all the pharmacokinetic parameters, V_{max}, K_m, and V. However, the NPD method resulted in inaccurate estimation of the pharmacokinetic parameters. These findings suggest that the poor estimation by the NPD method for the pharmacodynamic/kinetic parameters was due partly to the nonlinearity of the structural model.

The simplicity and rapidity of the NPD analysis are attractive if one is interested only in the population mean kinetics/dynamics, and not in their variability. However, the faults of the NPD approach have been noted repeatedly (3,9) and are also shown in the present study. The NPD method should be used only where the structural model is known to be linear in its parameters, but it may be difficult to identify the exact model for distorted data prior to data analysis. The STS method seems to present accurate structural parameters for the unbiased data if a sufficient number of data is obtained from each subject (3,9,10). The estimates of the STS analysis for the present pharmacodynamic model might also be improved by obtaining much more hypotensive and diuretic data from individual subjects. However, this inefficiency of the STS method is a major drawback. We have demonstrated experimental evidence of the usefulness of the NONMEM method for analyzing distorted pharmacodynamic data for which the STS and NPD analyses resulted in poor parameter estimation.

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