Simulation for Population Pharmacodynamic Analysis of Dose-Ranging Trials: Usefulness of the Mixture Model Analysis for Detecting Nonresponders

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KEY WORDS: dose-ranging trial; mixture model; NONMEM; nonresponder; population pharmacodynamics.

INTRODUCTION

Knowledge of dose-response relationships is important for the safe and effective use of drugs in individual patients. This information can help to identify an appropriate starting dose, the best way to adjust the dosage to the needs of a particular patient, and the dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects. In addition, dose-ranging trials to evaluate dose-response relationships are helpful in the clinical development of new drugs, to judge whether a drug is not effective enough for a disease, or whether the dosage is too low to exhibit any efficacy. Therefore, the assessment of dose-response relationships is becoming an integral component of drug development.

Recent progress in molecular biology has shown that genetic polymorphisms of receptors (1–3), enzymes (4–6), or transporters (7,8) play important roles in the pharmacokinetics or pharmacodynamics of several drugs. These polymorphisms are deeply involved in the pharmacokinetic/pharmacodynamic variability of drugs and may be the cause for the occurrence of nonresponders (NRs), that is, patients who do not respond to a certain drug (7,9,10). However, the molecular mechanisms of the polymorphisms have not been completely revealed at present. If NRs were included in the dose-ranging trials, accurate population parameters with which to describe dose-response relationships could not be obtained from current statistical analyses, which ignore the existence of NRs. Therefore, we determined that a new analysis method that discriminates between responders (RPs) and NRs is necessary for the estimation of the dose-response relationships. A mixture model was developed by Beal and Sheiner (11), and has been implemented in the computer software NONMEM. The mixture model assumes that the population consists of two or more subpopulations where each subpopulation may have its own model and estimates the population parameters for each subpopulation and the corresponding ratio of these subpopulations. We applied this analysis method to the identification of RPs and NRs. It also has been reported that the design of a dose-ranging trial is important in determining the dose-response relationship (12,13). In this study, we evaluated different data analysis methods and trial designs to estimate the population pharmacodynamic parameters from the dose-ranging trials, which include NRs.

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ABBREVIATIONS: DE, dose-escalation; NR, nonresponder; PD, parallel dose; RP, responder; XO, crossover.

METHODS

Pharmacodynamic Models

The patient population was assumed to include RPs and NRs. In the actual situation, the pharmacologic response may have baseline values. However, we simply assumed that the drug effects could be calculated by subtracting the pharmacologic response after administering a placebo from the response to the active drug (14). The dose-response relationship for RPs was assumed to arise from the E_{max} model, which is represented by the following equation:

$$E_{ij} = \frac{E_{max_i} \times D_{ij}}{D_{50i} + D_{ij}} (1 + \varepsilon_{E_{ij}}) \quad (1)$$

where E_{ij} is the observed pharmacodynamic effect at the jth dose in the ith individual (D_{ij}). E_{max_i} is the maximum drug-related effect of RPs, and D_{50_i} is the dose causing 50% of the maximum effect in the ith individual. The values of E_{max_i} and D_{50_i} were assumed not to vary within the ith individual but may differ between subjects. For this variation, E_{max_i} and D_{50_i} were assumed to distribute independently and normally, with the mean E_{max} and D_{50} varying by $\omega^2_{E_{max}}$ and $\omega^2_{D_{50}}$, respectively. E_{ij} was assumed to be randomly and normally distributed from the predicted value. $\varepsilon_{E_{ij}}$ is a random variable describing intraindividual variability with a mean of zero and a variance of σ^2_E.

The dose-response relationship for NRs was assumed to arise from two kinds of dose-response models, the E_{max} model or the linear model. The E_{max} model for NRs has small E_{max} values and represents patients who experience a decreasing maximum pharmacologic effect, which is represented by the following equation:

$$E_{ij} = \frac{E_{max,\,NR_i} \times D_{ij}}{D_{50i} + D_{ij}} (1 + \varepsilon_{E_{ij}}) \quad (2)$$

where E_{max,NR_i} is the maximum drug-related effect of NRs in the ith individual. The value of E_{max,NR_i} was assumed not to vary within the ith individual but may differ between subjects. For this variation, E_{max,NR_i} was assumed to distribute independently and normally, with mean $E_{max,NR}$ varying by $\omega^2_{E_{max,NR}}$.

The linear model for NR is an approximate E_{max} model with a large D_{50} value and represents patients with decreasing

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sensitivity to the drugs, which is represented by the following equation:

$$E_{ij} = SLOPE_i \times D_{ij}(1 + \varepsilon_{E_{ij}}) \quad (3)$$

where $SLOPE_i$ is the constant representing the drug-related pharmacodynamic effect in the ith individual. The value of $SLOPE_i$ was assumed not to vary within the ith individual but may differ between subjects. For this variation, $SLOPE_i$ was assumed to distribute independently and normally, with mean $SLOPE$ varying by ω^2_{SLOPE}.

Dose-Ranging Trial Designs

The parallel-dose (PD), crossover (XO), and dose-escalation (DE) designs were considered for the dose-ranging trials (12,13). In the PD design, each subject receives just one of m doses. The assignment of each dose to patients was determined randomly. If n patients are studied for each dose, the total number of subjects studied is $N = nm$. All dose levels were studied in parallel, so the total study lasted one period. In the XO design, each of the n subjects received all the m doses of the drug. The doses were administered to different subjects in different orders so that period effects were not confounded with the dose effects. The assignment of the dose orders was determined randomly. The DE design resembles the XO design. The essential points of difference are that not all subjects receive all doses, and the dose order is fixed for all subjects. In the DE design, each of the n subjects was given the lowest dose. If the response failed to satisfy a certain clinical end point, the dose was escalated to the next higher dose. This process was repeated for each dose level until either the clinical end point was reached or the highest dose was attained. If the response was adequate, the dose was maintained at that level for the duration of the trial. In the present study, we were not concerned with the complicated biases arising from the study design such as the carryover effect or subject dropout due to toxicity.

Simulations

The simulated (true) pharmacodynamic parameters were as follows: (E_{max}, $\omega_{E_{max}}$) = (1, 0.3), ($E_{max,NR}$, $\omega_{Emax,NR}$) = (0.2, 0.06), (D_{50}, $\omega_{D_{50}}$) = (0.5, 0.15), ($SLOPE$, ω_{SLOPE}) = (0.1, 0.03), σ_E = 0.15. $E_{max,NR}$ was adjusted to 20% of the E_{max} value for RPs, and the $SLOPE$ was adjusted to 20% of the E_{max} value for RPs at the dose of 2.0. The probability of NR, p_{NR}, was set at 0.2. Thus, the patient population was assumed to be made of 80% RPs and 20% NRs. All random variables in the pharmacodynamic models were considered as pseudonormal variates and were calculated using the Box-Muller algorithm (15).

One hundred twenty subjects were assumed for the PD trial, and 30 subjects each were assumed for the XO and DE trials. The active doses selected were as follows: D_{ij} = 0.25, 0.5, 1.0, and 2.0, respectively. Each subject received one dose in the PD trial and four doses in the XO and DE trials. Therefore, the total number of data in each trial was 120. Figure 1 shows typical data sets of simulated pharmacodynamic data for RPs and for two types of NRs in the XO trial, which were generated using a computer simulation method. The clinical end point of the pharmacodynamic effect in the DE design was assumed to be 0.75, which is the expected response attained at a dose 3-fold of D_{50}. Ten percent and 30% of RPs reached the desired pharmacologic response in the DE trial at doses of 0.5 and 1.0, respectively, and those doses were maintained for the duration of the trial. There were no NR patients who satisfied the criteria even when the maximum dose was administered.

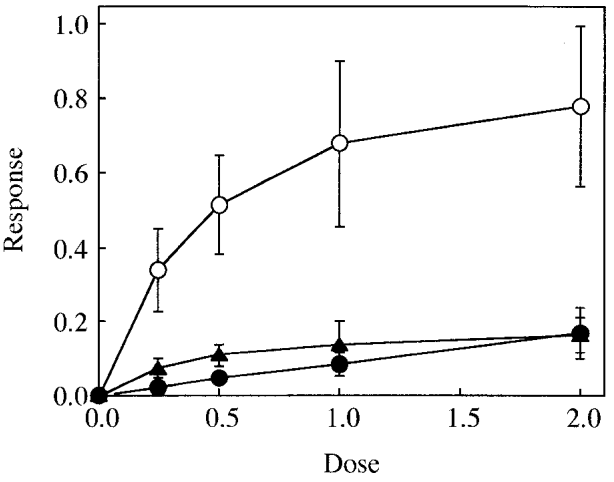

Fig. 1. Typical dose-response relationships of RPs (open circles), E_{max} (closed circles), and linear-type NRs (closed triangles) in the XO trial. Data are given as the mean ± SD (bars) of values determined from 30 patients.

Data Analysis Methods

Population analysis was performed using the nonlinear mixed-effects model of the NONMEM software (double-precision NONMEM, version IV Level 1.1 and NM-TRAN, version II Level 1.1) (11). We used the ordinary least-squares method for analysis of the PD data, and the first-order conditional estimation with interaction method for the XO and DE data. The boundaries of each parameter were set from 0 to 5-fold the true value. Two kinds of analysis methods, which use a nonmixture (conventional) or mixture model, were evaluated in this study (16). The nonmixture model analysis does not take into account the existence of NRs, and it estimates the pharmacodynamic parameters of RPs and NRs as belonging to the same population. On the other hand, the mixture model analysis estimates the probability of NR (p_{NR}) and the pharmacodynamic parameters for both RPs and NRs. The mixture model analysis is enabled by using the MIX subroutine in NONMEM. The MIX subroutine allows mixture modeling to be carried out within the context of mixed-effects modeling. A mixture model assumes that the population consists of two or more subpopulations, each approximating a normal distribution, where each subpopulation may have its own model. For example, with two subpopulations it might be assumed that one fraction of the population has one set of typical values of the parameters and that the remaining fraction has another set of typical values. The ratio of each fraction and the corresponding sets of typical values can be estimated, and NONMEM computes an estimate of the subpopulation to which an individual belongs. The simulation and analysis were performed on a Indigo^2 computer (Silicon Graphics, Mountain View, California) running under an IRIS 6.0 operating system.

Comparison of Analysis Methods and Dose-Ranging Trial Designs

Forty simulation data sets were generated from each pharmacodynamic model and dose-ranging trial design, and either the nonmixture or the mixture model analysis of the pharmacodynamic data was carried out for the estimation of the population parameters. Estimation performance was quantified by accuracy and precision estimates of the structural mean parameters and the interindividual and intraindividual variabilities in the XO and DE trials. However, population analysis in the PD trial gave only the structural mean parameters and the residual error, and did not provide estimates of inter individual and intraindividual variability. Therefore, the accuracy and precision of the structural mean parameters were evaluated to assess the performance of the PD design. To express all parameter estimates with the same scale, the percentage of the error (% error) of the estimates was computed as follows:

$$\%\ \text{error} = \frac{\text{estimated value} - \text{true value}}{\text{true value}} \times 100 \qquad (4)$$

The accuracy and precision of the parameter estimates were obtained based on the mean and SD of the percentage of the error, respectively.

RESULTS AND DISCUSSION

In the conventional nonmixture model analysis, all trials did not always provide accurate estimates (Fig. 2). Figure 2A shows the accuracy and precision of the estimated population parameters in the nonmixture model analysis when the E_{max}-type dose-response relationship was assumed for NR. In the PD design, considerable estimation errors were observed for E_{max} and D_{50}. Almost all the estimations of E_{max} were negatively biased and were consistent with the mean of the true E_{max} value of all patients including NRs, whereas 2 of 40 simulations diverged and the estimates of E_{max} and D_{50} were near the upper limit of the boundary. The estimate of E_{max} obtained from the XO and DE trials was slightly lower than the true value. This value was consistent with the mean of the true E_{max} value of all patients, including NRs. As expected, the variation of the population parameters, $\omega_{E_{max}}$, was biased in the XO and DE trials. Figure 2B shows the accuracy and precision of the estimated population parameters and their variations in the nonmixture model analysis when a linear dose-response model was assumed for NRs. The linear model can be considered as an approximate E_{max} model with a large D_{50}. As expected, estimates of D_{50} and $\omega_{D_{50}}$ were much greater than their true values and largely were biased in the XO and DE trials. Interestingly, no serious bias was observed in the PD trial when a linear dose-response relationship was assumed for NRs.

In the mixture model analysis, the PD trial did not always provide accurate estimates when the E_{max}-type dose-response was assumed for NR. On the other hand, accurate population pharmacodynamic parameters were obtained from the XO and DE trials (Fig. 3). Figure 3A shows the accuracy and precision of the estimated population parameters in the mixture model analysis when the E_{max}-type dose-response relationship was assumed for NRs. Considerable extent of estimation errors was observed in p_{NR} and $E_{max,NR}$, and $E_{max,NR}$

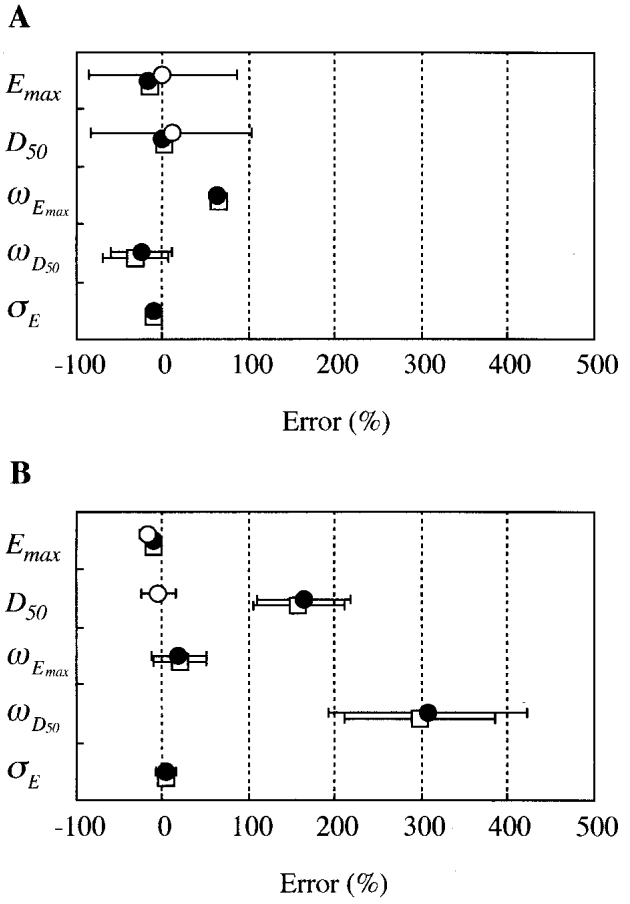

Fig. 2. Accuracy and precision of estimated population parameters and their variations in the nonmixture model analysis obtained from the PD (open circles), XO (closed circles), and DE trials (open squares) when an E_{max}-type (A) or a linear (B) dose-response relationship was assumed for NRs.

was overestimated in the PD trial. In addition, p_{NR} was estimated to be 0 in 10 of the 40 simulations. This implies that $E_{max,NR}$ was estimated as having the same value as that of E_{max} for RPs in these simulations. This result suggests that RPs and NRs are not always distinguished even with the mixture model analysis in the PD trial. On the other hand, accurate population parameters were obtained from the XO and DE trials. The estimations of the structural mean parameters were estimated accurately, and only slightly negative biases were observed for $\omega_{D_{50}}$ and $\omega_{E_{max,NR}}$. Figure 3B shows the accuracy and precision of the estimated population parameters in the mixture model analysis when a linear dose-response relationship was assumed for NRs. Biases in the estimated population parameters in the PD trial when a linear dose-response was assumed for NRs were not more serious than those when the E_{max}-type dose-response relationship was assumed for NRs. The precision of D_{50} and the accuracy and precision of p_{NR} were slightly incorrect in the PD trial compared with those in the XO and DE trials. p_{NR} was estimated to be 0 in 7 of the 40 simulations in the PD trial. The estimates of the *SLOPE* could not be obtained from these simulations. Therefore, the bias arising from identification errors of RPs and NRs affected only p_{NR}, and the *SLOPE* was apparently not biased, as shown in Fig. 3B. These results indicate that RPs and NRs are not always identified, even with use of the

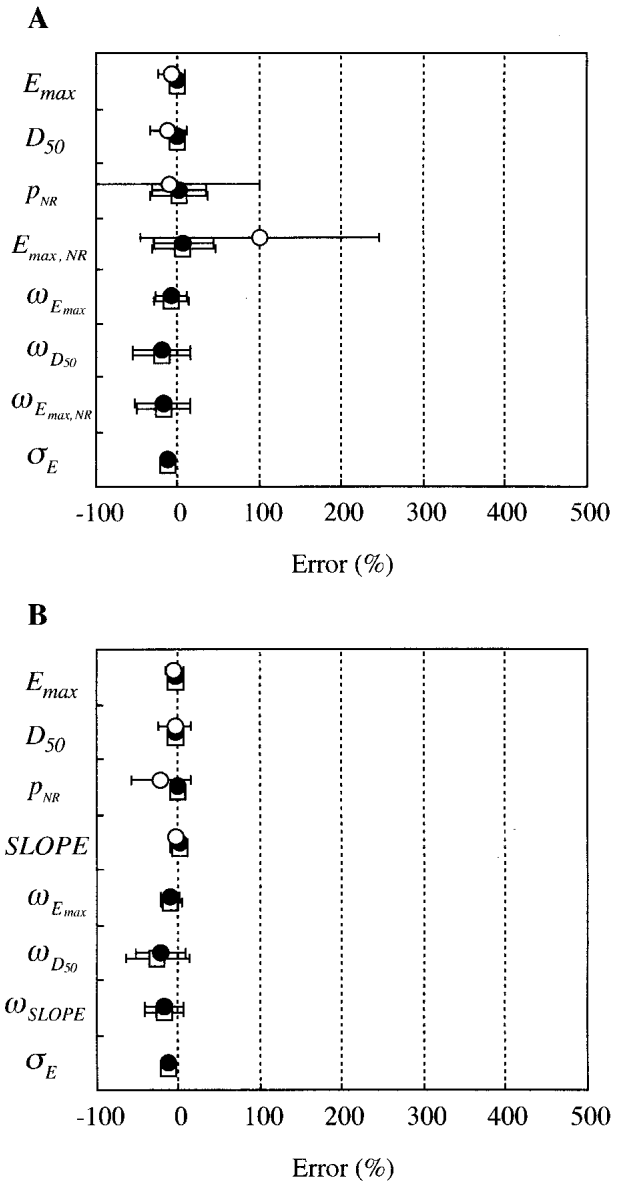

Fig. 3. Accuracy and precision of estimated population parameters and their variations in the mixture model analysis obtained from the PD (open circles), XO (closed circles), and DE trials (open squares) when an E_{max}-type (A) or a linear (B) dose-response relationship was assumed for NRs.

mixture model analysis in the PD trial, when either the E_{max} or linear model was assumed for NRs. On the other hand, accurate population parameters were obtained from the XO and DE trials. The estimations of the structural mean parameters were estimated accurately, and only slightly negative biases were observed for $\omega_{D_{50}}$ and ω_{SLOPE}.

A mixture model, which was recently implemented in NONMEM, has been developed for the analysis of a subpopulation (11). The mixture model analysis was utilized for identifying the normal and low-clearance patients, and its usefulness was shown in a simulation study of population pharmacokinetics (16). In consideration of the multiplicity of pharmacodynamics in real patients, we applied this analysis method to identify RPs and NRs in a simulation study of dose-ranging trials in cases in which the molecular mechanisms of the polymorphism are unknown and the classification from the genotype cannot be carried out. The current analysis method, which ignores the existence of NRs, cannot always provide accurate analyses. On the other hand, RPs and NRs were discriminated in the XO or DE trial by the mixture model analysis, which can identify RPs and NRs, and their population parameters were estimated accurately. The usefulness of the mixture model analysis also was shown from our pharmacodynamic simulation. In the selection of analysis models, whether to use the nonmixture or mixture model should be determined based on how the objective function decreases. This point, which was not considered in this study, remains to be investigated by further studies.

The PD trial does not always provide accurate estimates of population parameters even when using the correct analysis method (i.e., the mixture model analysis) when NRs were included in the dose-ranging trials. The mixture model analysis did not work well in the PD trial, and RPs and NRs were not always identified. It was reported that the estimates of the mean population parameters obtained from PD trials can be considerably biased even when NRs were not included in the dose-ranging trials (12,13). Moreover, PD trials give only the structural mean parameters and residual error, and they do not provide the estimates of interindividual and intraindividual variability, ω and σ, respectively. The importance of the dose-ranging trial design was reconfirmed from our results.

In conclusion, we evaluated different data analysis methods and trial designs to estimate the population pharmacodynamic parameters from dose-ranging trials, which included NRs. The pharmacodynamic analyses, which ignore the existence of NRs, did not always provide accurate estimates. In the mixture model analysis, the accurate population parameters were obtained from the XO and DE trials. On the other hand, the PD trial design did not always provide accurate population parameters, even when the correct analysis method was used. Therefore, we conclude that the mixture model analysis is useful for data analysis of dose-ranging trials, which may include NRs to estimate accurate population parameters, and should be considered as a possible analysis method for dose-ranging trials. In addition, the accuracy of the estimated pharmacodynamic parameters was found to depend heavily on the trial design. Based on our results, one should use the XO or DE trial design for the estimation of a dose-response relationship.

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