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Impact of dose selection on parameter estimation using a rapid binding approximation model of target-mediated drug disposition

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Abstract

The purpose of this study was to examine the role of dose selection on population pharmacokinetic (PK) parameter estimation using a rapid binding approximation of a target-mediated drug disposition (TMDD) model previously developed for interferon- β (IFN- β). A total of 50 replicate datasets each containing 100 subjects were created using NONMEM[®]. The study design included IV injection of IFN- β followed by the SC route in a crossover manner, with each dose and route of administration separated by a 1,000 h washout period. Serial plasma PK samples were simulated up to 48 h for all subjects following each dose. Population mean PK parameters were re-estimated in NONMEM[®] for each simulated dataset using the same TMDD model after including the following doses (MIU/kg): (A) 1, 3 and 10 (original study); (B) 1, 3 and 7; (C) 1, 3 and 5; (D) 1, 3 and 4; (E) 1 and 3; (F) 3 and 10; or (G) 10 MIU/kg only. Bias in the model fit was assessed by calculating the percent prediction error (PE%) for each of the population mean PK parameters relative to the estimates obtained from the fit to the 1, 3, and 10 MIU/kg doses (Case A).

Relatively unbiased population mean PK parameter estimates (median PE% <8%) were obtained only when the study design included 1, 3 and a minimum higher dose of 7 MIU/kg. Bias increased for various parameters when the highest dose was less than 7 MIU/kg along with 1 and 3 MIU/kg being the low and intermediate dose levels. An increase in the bias for binding capacity, R_{tot} , and the equilibrium dissociation constant, K_D , was observed as the highest dose included in the dataset was reduced from 5 to 3 MIU/kg (median PE% ranged from -4.71 to -23.9% and -4.76 to -34.6%). Similar increases in the range of median PE% were also observed for other model parameters as the highest dose was reduced from 5 to 3 MIU/kg. Severely biased results were obtained from the study design that included only the 10 MIU/kg dose (Case G) suggesting that it is not sufficient to study just a high dose group. This bias was greatly reduced (median PE% <14%) for all parameters except K_D when the 3 and 10 MIU/kg doses were co-modeled (Case F). Plots of the PE% for R_{tot} and K_D versus the molar ratio of maximum dose to R_{tot} suggest that study designs should evaluate at least one IFN- β dose 3.5- to 4-fold higher than R_{tot} along with the 1 and 3 MIU/kg dose levels to obtain unbiased population PK parameter estimates. In summary, for the IFN- β model and study design, dose selection influences the ability to generate relatively unbiased population mean TMDD parameter estimates, which is based on maximum dose levels relative to R_{tot} . This simulation study highlights the role of dose selection in optimal study design strategies for drugs such as IFN- β that exhibit TMDD properties.

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Keywords

Target-mediated drug disposition; Rapid binding approximation; NONMEM; Pharmacokinetics; Simulation; Interferon- β

Introduction

Target-mediated drug disposition (TMDD), a phenomenon where the pharmacokinetic properties of a drug is significantly influenced by its high affinity binding to a biological target, has become increasingly important with the development of a large number of proteins, peptides and monoclonal antibodies as therapeutics [1, 2]. A general pharmacokinetic model of TMDD has been developed [3], along with several approximations of the full model that improve on parameter identifiability from routine datasets and speed of computation [4, 5]. Experimental designs can potentially influence the estimation of mean population parameters and their variance for drugs that exhibit TMDD. As is the case with any capacity-limited system, the dose range studied can potentially influence parameter estimation. In the sigmoidal $E_{\max}$ pharmacodynamic model for example, bias in the estimates of $E_{\max}$ and EC_{50} were reported when the highest measured PD outcome was less than 95% of the true $E_{\max}$ [6]. Similarly, during the evaluation of a TMDD model for the anti-platelet drug abciximab, the equilibrium dissociation constant (K_D) was estimated with low precision and the maximum receptor density (R_{tot}) was determined to be unidentifiable (which required fixing R_{tot} to literature values) when the dose administered was comparable to R_{tot} [7]. A sensitivity analysis performed using a rapid binding approximation of the TMDD model also demonstrated that perturbations in K_D can influence the terminal elimination phase [8], suggesting that uninformative study designs may introduce bias into the estimates of one or more of the model parameters. The purpose of this simulation study was to investigate the impact of dose selection on population mean PK parameter estimation using a rapid binding approximation of the TMDD model previously developed to describe the disposition of recombinant IFN- β following IV or subcutaneous (SC) administration to monkeys [9]. In this assessment, the bias and precision for the TMDD model parameters were compared using data simulated from study designs that included various combinations of IV and SC doses of IFN- β ranging from 1 to 10 MIU/kg to determine the impact of dose selection on TMDD parameter estimation.

Methods

Structural pharmacokinetic model

A rapid binding approximation of the full TMDD model originally utilized to describe the plasma concentration–time profile for IFN- β following IV or SC administration [9] was used as the structural PK model for this study. The model for IFN- β disposition is illustrated in Fig. 1, and the previously estimated parameter values are listed in Table 1. Two sequential first-order absorption rate constants were utilized to account for the transfer of drug from the SC injection site into the lymphatic compartment (k_a), and then from the lymphatic compartment to the central plasma compartment (k_{a2}). Drug in the plasma (A_P , V_C) distributes between the central and non-specific peripheral tissue compartment (A_T) according to two separate first-order transfer rate constants (k_{pt} and k_{tp}) and undergoes first-order elimination from the central compartment (k_{el}). Drug in the plasma compartment can also reversibly bind to free target receptors to form a drug–receptor complex (AR) which can be internalized (k_{int}), representing another elimination pathway for IFN- β . The model assumes that the drug–receptor binding is rapid. The total receptor pool, which at any given point in time was comprised of the sum of the free receptors and the drug–receptor complex

($R_{\text{tot}} = R + AR$), was considered to be constant and set equal to the maximum receptor quantity (R_{tot}). The structural PK model equations for IFN- β are as follows:

$$\frac{dA_{\text{sc}}}{dt} = -k_a \cdot A_{\text{sc}}; \quad A_{\text{sc}}(0) = \text{Dose}_{\text{sc}} \quad (1)$$

$$\frac{dA_L}{dt} = k_a \cdot A_{\text{sc}} - k_{a2} \cdot A_L; \quad A_L(0) = 0 \quad (2)$$

$$\frac{dA_{\text{tot}}}{dt} = k_{a2} \cdot A_L - k_{\text{int}} \cdot A_{\text{tot}} - (k_{\text{el}} + k_{\text{pt}} - k_{\text{int}}) \cdot C_p \cdot V_c + k_{\text{tp}} \cdot A_T; \quad A_{\text{tot}}(0) = A_{\text{tot}}^0 \quad (3)$$

$$\frac{dA_T}{dt} = k_{\text{pt}} \cdot C_p \cdot V_c - k_{\text{tp}} \cdot A_T; \quad A_T(0) = 0 \quad (4)$$

where A_{sc} , A_L , A_T are the amounts of drug in the SC injection site, lymphatic, and tissue compartments. The quantity A_{tot} is the total drug in the plasma and represents the sum of free drug and the drug–receptor complex at any given point in time. The initial condition for Eq. 3 was set to 0 for SC dosing and the IV dose level for IV administration. The bioavailability of IFN- β following SC administration (F) was found to be dose-dependent in monkeys and thus separate bioavailability terms were included for the 1, 3 and 10 MIU/kg doses (represented as F_1 , F_3 and F_{10} , respectively). The total IFN- β concentration was defined as $C_{\text{tot}} = A_{\text{tot}}/V_c$, and the free IFN- β concentration in plasma (C_p) was described by an explicit equation:

$$C_p = \frac{1}{2} \left[(C_{\text{tot}} - R_{\text{tot}}/V_c - K_D) + \sqrt{(C_{\text{tot}} - R_{\text{tot}}/V_c - K_D)^2 + 4 \cdot K_D \cdot C_{\text{tot}}} \right] \quad (5)$$

Data simulation

A total of 50 replicate data sets each containing 100 subjects were created using different random seeds within NONMEM[®] Version 6 [10]. In the original study design, each subject was given IFN- β (1, 3 and 10 MIU/kg) as a single IV bolus followed by a SC injection after a one-week washout period [9]. For the current simulation study, six IV or SC dose levels of IFN- β were evaluated (1, 3, 4, 5, 7, and 10 MIU/kg) with complete washout between doses. Serial plasma IFN- β concentrations were simulated at 0.25, 0.5, 1, 1.5, 2, 3, 6, 9, 12, 18, 24, 36 and 48 h after each dose administered. As in the original study, the same three different SC bioavailability parameters were utilized assuming that the bioavailability values for the 4, 5 and 7 MIU/kg doses were equivalent to the 10 MIU/kg dose. Inter-individual variability (ω^2) was assumed to be log-normally distributed and was set to 30% CV for each of the structural PK model parameters except the SC bioavailability terms. The off-diagonal elements of the variance–covariance matrix were assumed to be negligible and fixed to 0. Residual variability (σ^2) was incorporated using a proportional or constant coefficient of variation error model with a magnitude of 10% CV.

Data analysis

All 50 replicate data sets were analyzed using the first-order (FO) estimation method in NONMEM® with the identical TMDD model utilized to simulate the data. The first-order conditional estimation (FOCE) method with η - ε interaction was initially evaluated for use in this simulation study but was later replaced with the FO method after a pilot study indicated excessively long computation times (i.e., 3–7 days per run). Most runs were unstable and did not result in successful convergence, both of which were likely due to the large number of estimated random effect parameters in the model. Although the FO method is not the most robust method available within NONMEM®, all model runs did minimize successfully using the FO estimation method in this simulation study, whereas runs utilizing FOCE generally terminated earlier in the minimization process. Given that all parameters were simulated from a log-normal distribution using an exponential error model (e.g., η terms for each parameter are known a priori to be normally distributed) coupled with modest residual variability (10%), the FO approximation was considered an acceptably valid compromise for use in this simulation study [11].

To assess the impact of dose selection on TMDD parameter estimation, the 50 replicate datasets were analyzed after including only selected IV and SC dose combinations (MIU/kg) as follows: (A) 1, 3 and 10; (B) 1, 3 and 7; (C) 1, 3 and 5; (D) 1, 3 and 4; (E) 1 and 3; (F) 3 and 10; or (G) 10 MIU/kg only. The 1, 3 and 10 MIU/kg IFN- β doses used in the original study (Case A) were evaluated as a control group to help mitigate any potential bias which may have been introduced due to use of the FO estimation procedure. Cases E–G included only a subset of the original three dose levels in order to assess the relative importance of the highest and lowest dose levels studied. Cases B–D were evaluated to determine the lowest sufficient dose to pair with the 1 and 3 MIU/kg doses that provides unbiased and reasonably precise estimates of the TMDD model parameters.

Model performance for each series was assessed relative to the control case (A) consisting of the original three IFN- β dose levels. Bias in the TMDD model parameter estimates was assessed by calculating the percent prediction error for each parameter as [12]:

$$PE\% = \frac{P_{\text{estimated}} - P_{\text{control}}}{P_{\text{control}}} \times 100 \quad (6)$$

where $P_{\text{estimated}}$ is the population mean parameter estimate for each of the 50 replicate datasets in each series, and P_{control} is the population mean parameter estimate obtained from the fit of the model to each of the 50 replicate datasets containing the original IFN- β doses of 1, 3, and 10 MIU/kg (Case A). Model performance was also reported after calculation of the percent prediction error using the true simulated parameter values as the reference group, as opposed to the estimates from the control group, to provide an indication of how well the model was able to recapture the true parameter values after including residual error and despite computational difficulties and potential numerical instabilities associated with nonlinear mixed effects modeling.

Results

The simulated plasma IFN- β concentration–time data from a single replicate data set showing the data from only the 1, 3 and 10 MIU/kg dose levels are shown in Fig. 2. Boxplots of the PE% for each dose combination, evaluated using the estimates from the control group as the reference values during the calculation of PE%, are shown for selected target-mediated and linear parameters of the population PK model for IFN- β in Figs. 3 and 4, respectively. The same plots are also provided in Figs. S3 and S4 when alternatively the

true simulated parameter values were utilized as the reference group in the PE% calculation. Boxplots of the PE% for each dose combination are shown for the inter-subject variability terms of selected target-mediated and linear parameters of the population PK model for IFN- β in Figs. S1 and S2 (or Figs. S5 and S6 when using the true simulated parameters as the reference group in the %PE calculation). The percent prediction errors for the population mean PK parameters associated with both the linear (V_C , k_{el} , k_{pt} , k_{tp} , k_a , k_{a2} , F_1 , F_3 and F_{10}) and target-mediated (R_{tot} , K_D and k_{int}) components of the population PK model for IFN- β model are provided in Table S1 (using the control group as the reference) and in Table S2 (using the true simulated value as the reference) for each of the dose combinations studied.

For the parameters associated with the target-mediated component of the PK model, unbiased estimates, relative to the control design, were obtained only when the study design included the 1, 3 and 7 MIU/kg dose levels as evidenced by a median PE% of $\pm 2\%$ for R_{tot} , K_D and k_{int} (Fig. 3). The inter-subject variability on these parameters ($\omega_{R_{tot}}$, ω_{K_D} , $\omega_{k_{int}}$) also had negligible bias (median PE% $\pm 3\%$) when the 1, 3 and 7 MIU/kg doses were included. However, the bias increased progressively for R_{tot} , K_D and k_{int} (Fig. 3) and estimates of their inter-subject variability (Fig. S1) as the highest IFN- β dose included in the dataset was reduced below 7 MIU/kg while keeping 1 and 3 MIU/kg as the lower and intermediate doses. The median PE% ranged from -4.71 to -23.9% for R_{tot} , -4.76 to -34.6% for K_D , -1.04 to -5.79% for k_{int} , 6.97 to 8.41% for $\omega_{R_{tot}}$ and 3.87 to 16.6% for $\omega_{k_{int}}$ while negligible changes were observed for ω_{K_D} with the highest IFN- β dose of 5 to 3 MIU/kg. Thus, the inclusion of at least one high IFN- β dose was necessary for adequate estimation of the TMDD binding parameters R_{tot} and K_D . However, it was not sufficient to study only a very high IFN- β dose as R_{tot} and K_D were under-predicted and k_{int} was slightly under-predicted when the study design included only the 10 MIU/kg dose (median PE% was -53.2 , -54.5 and -14.4% , respectively). Significant bias was also observed in the inter-subject variability estimates for R_{tot} , K_D and k_{int} when only the 10 MIU/kg dose was studied (median PE% was 97.7 , 23.3 and 81.6%). Modeling the 3 and 10 MIU/kg doses together served to reduce the magnitude of this bias for these terms and their respective values of inter-subject variability. The low dose of 1 MIU/kg was not important for the estimation of R_{tot} (median PE% = -1.73%) but was shown to influence the estimation of K_D , which was under-predicted (median PE% = -20.7%) when the study design included only the 3 and 10 MIU/kg IFN- β dose levels.

Bias in the estimation of the linear PK component parameters and their respective inter-subject variability terms was also lowest for the case that included the 1, 3 and 7 MIU/kg dose levels (median PE% $< 8\%$). However, the bias increased progressively for V_C (median PE% ranged from 8.71 to 43.2%), k_{pt} (median PE% ranged from -5.94 to -12.6%) and k_{el} (median PE% ranged from 23.4 to 59.5%) when the highest dose evaluated was reduced below 7 MIU/kg while retaining 1 and 3 MIU/kg as the lower and intermediate doses. Bias in the inter-subject variability for the linear PK parameters increased when the highest IFN- β dose studied was reduced from 7 to 3 MIU/kg, with the largest increase observed for ω_{kel} (median PE% ranged from 3.23 to 28.1%). As was observed for the target-mediated parameters, a study design utilizing only the 10 MIU/kg dose increased the bias in the parameters for the linear PK terms with the largest bias observed for k_{el} , k_{pt} , and k_{a2} . Evaluation of both the 3 and 10 MIU/kg dose levels served to reduce this bias, relative to the control/reference design, and the median PE% was $\pm 10\%$ for all parameters except F_3 (median PE% of 13.9). In particular, the median PE% for k_{a2} , k_{pt} and k_{el} decreased from 52.6 to 9.48 , -37.2 to 1.30 and 85.4 to 4.63% when simultaneously fitting the data from both the 3 and 10 MIU/kg doses.

Discussion

Target-mediated drug disposition models have been used to describe the PK disposition of several proteins, peptides and monoclonal antibodies in both pre-clinical and clinical studies. Proper experimental design, with respect to selection of both a PK sampling strategy and the dose range to be studied, is critical to ensure that informative data is generated from the study to provide reliable and unbiased estimates of the parameters associated with the TMDD model during population PK analysis. Although bias in the population mean TMDD model parameter estimates may not appear to adversely impact the fit to the data, it may limit use of the model for predictive purposes. Allometric principles have been successfully applied to mechanism based models to predict response in humans for erythropoietin [13] and for 5-HT_{1A} receptor agonists [14]. Bias in model parameters might impair the ability to scale-up pre-clinical PK and/or PK-PD models to guide first-in-man doses in humans or to plan future dose-ranging studies for Phase 2/3 trials in much the same way failure to adequately capture the true $E_{\max}$ and EC_{50} using a Hill function can hinder characterization of PD responses beyond the range of doses studied.

This simulation study was conducted using a rapid binding approximation of a TMDD model based upon the PK component of a previously developed PK–PD model for IFN- β developed in monkeys following IV and SC dosing [9]. The original crossover study design was retained with respect to the dose range (single IV and SC doses ranging from 1 to 10 MIU/kg). Although the inclusion of data for both routes of administration inevitably added further complexity to the model and extended the computational run times, this provided a wider range of plasma drug concentrations, especially during the terminal elimination phase.

The results of this simulation study demonstrate that unbiased parameter estimates, relative to the control design, could be obtained for both the linear and target-mediated components of the population PK model for IFN- β when the study design included the 1, 3 and 7 MIU/kg IV and SC doses. However, the magnitude of the bias progressively increased when the highest dose included in the analysis was reduced to less than 7 MIU/kg. Conceptually, the maximum dose determines the highest IFN- β concentration (Dose/V_C) in the plasma achieved following an IV bolus dose. Scatterplots of the PE% for both R_{tot} and K_D versus the molar ratio of the maximum IFN- β dose administered to the true R_{tot} is shown in Fig. 5. Increasing the molar ratio of the maximum administered dose to R_{tot} improves model performance and reduces the bias in the estimation of both R_{tot} and K_D . For IFN- β , it appears that unbiased estimates of both R_{tot} and K_D can be obtained only when the study design includes at least one dose level 3.5- to 4-fold higher than R_{tot} along with a low and intermediate dose level. While the analysis presented here pertains directly to the TMDD model for IFN- β , it would be worthwhile to explore this further for other drugs that exhibit such behavior.

In summary, this simulation study investigated the role of dose selection on population mean PK parameter estimation using a rapid binding approximation of a TMDD model for IFN- β . The ability to generate relatively unbiased population mean parameter estimates using the TMDD model for IFN- β was affected by dose selection. Study designs which included a dose level 3.5- to 4-fold higher than the receptor density, R_{tot} , in addition to a low and intermediate dose, were shown to provide unbiased TMDD model parameter estimates as compared to the reference or control design. This simulation approach thus provides one possible strategy for assessing optimal study design for drugs such as IFN- β which exhibit target-mediated disposition. Although the findings reported here may not necessarily be generalized to other drugs displaying TMDD, it is likely that they have certain common characteristics and thus may benefit from performing a similar type of assessment to help guide dose selection for use in clinical trials.

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Fig. 1. Structural PK model for IFN- β disposition. *Symbols* are defined in “Structural pharmacokinetic model” section

Fig. 2. Simulated IFN- β plasma concentration-time data for **a** single replicate dataset following a IV or **b** SC administration of 1, 3 or 10 MIU/kg. *Lines* represent the median IFN- β plasma concentrations at each sample collection time, and the *symbols* represent the simulated concentrations

Fig. 3. Boxplots of the prediction error percents (PE%) for **a** R_{tot} , **b** K_D , and **c** k_{int} for each scenario relative to the fit of the TMDD model to all simulated data from the 1, 3 and 10 MIU/kg dose levels using the control group as the reference value when determining PE%. The box represents the 25th–75th percentiles, the line represents the 50th percentile, and the whiskers extend from the 5th–95th percentiles

Fig. 4.

Boxplots of the prediction error percents (PE%) for **a** V_c , **b** k_{pt} , and **c** k_{el} for each scenario relative to the fit of the TMDD model to all simulated data from the 1, 3 and 10 MIU/kg dose levels using the control group as the reference value when determining PE%. The *box* represents the 25th–75th percentiles, the *line* represents the 50th percentile, and the *whiskers* extend from the 5th–95th percentiles

Fig. 5.

Scatterplot of the prediction error percents (PE%) for **a** R_{tot} , **b** K_D , for selected dose scenarios, versus the molar ratio of the maximum dose and R_{tot} obtained from the fit of the TMDD model to all simulated data from the 1, 3 and 10 MIU/kg dose levels, using the control group as the reference value when determining PE%

Table 1Pharmacokinetic parameter values used for simulation of IFN- β profiles

Parameter	Abbreviation	Units	Value ^a
First-order absorption rate constant from the SC injection site	k_a	h^{-1}	0.104
First-order absorption rate constant from the lymph compartment	k_{a2}	h^{-1}	1.85
Volume of the central compartment	V_C	l/kg	0.0511
First-order distribution rate constant from plasma to tissue	k_{pt}	h^{-1}	0.213
First-order distribution rate constant from tissue to plasma	k_{tp}	h^{-1}	0.131
First-order elimination rate constant from the central compartment	k_{el}	h^{-1}	0.481
Equilibrium dissociation constant	K_D	nM	0.403
First-order receptor-complex internalization rate constant	k_{int}	h^{-1}	0.998
Maximum receptor amount	R_{tot}	nmol/kg	0.305
Bioavailability for 1 MIU/kg dose	F_1	–	0.272
Bioavailability for 3 MIU/kg dose	F_3	–	0.317
Bioavailability for the 4–10 MIU/kg doses	F_{10}	–	0.710

^aValues obtained from [9]. Molecular weight of IFN- β is 20,000 Da, and specific activity was 3.0×10^8 IU/mg