Application of Identifiability Analysis Algorithm to Population PK of the Drug with Target-Mediated Drug Disposition

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Background: The pharmacokinetic model for drugs exhibiting target-mediated disposition (TMDD) was suggested in [1]. Several simpler approximations of the TMDD model were proposed in [2,3]. The Quasi-Equilibrium (QE) [2] and the Quasi-Steady-State (QSS) [3] approximations apply when the drug-target-complex system rapidly riches quasi-equilibrium or quasi-steady-state, respectively. The Michaelis-Menten (MM) [3] approximation applies when concentrations of the free drug significantly exceed concentrations of the target and/or target occupancy is very high [3]. In cases when one of the approximations provides a good description of the data, the more complicated models are over-parameterized, especially when only the free or total (but not both) drug concentration measurements are available. An algorithm to test identifiability of the TMDD model parameters for a particular data set and to choose the correct (not-over-parameterized) approximation was suggested in [3].

Objectives: To test the proposed Identifiability Analysis Algorithm on an example dataset simulated from a TMDD model based on clinical data.

Methods: The simulated dataset included 150 densely sampled patients who received IV or SC doses ranging from 200 to 7000 units. Study design, sampling scheme, and the parameters of the TMDD model used for simulations were chosen to reflect the actual clinical data. Only free drug concentration was measured. First, the Identifiability Analysis Algorithm was implemented as following. The TMDD model was fitted to the data, and the obtained parameter estimates were used to simulate the concentration-time profiles for the TMDD and corresponding QE, QSS and MM models. The results of the simulations were used to identify: i) the simplest model equivalent to the TMDD model; ii) the identifiable combination of the TMDD model parameters; iii) the dosing regimens and the concentration levels that can be described by the MM model. Then, the QE/QSS and MM models were directly fitted to the data. The individual and population predictions of these models were compared with the predictions of the TMDD model. Precision of the parameter estimates was investigated using the bootstrap procedure. Conclusions of the Identifiability Analysis were compared with the results of the direct investigation of the TMDD, QE/QSS and MM models.

Results: QE, QSS and MM approximations were shown to be identical to the corresponding full TMDD model for all dosing regimens of interest. When fitted independently to the same data, all models provided nearly identical population and individual predictions. The TMDD and QE/QSS model parameters were strongly correlated. Significant correlation was observed even for the MM model parameters (V_{MAX} and K_M).

Conclusions: For the investigated dataset, the TMDD model parameters cannot be determined based on the available data. The MM approximation provides an adequate description of the data. No improvement can be obtained using more complicated QE and QSS approximations, or the TMDD model. The Identifiability Analysis Algorithm allows selection of the parsimonious model that describes the available data.

References

1.Mager DE, Jusko WJ. General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. J. Pharmacokinetic and Pharmacodynamic 28: 507-532 (2001).

2. Mager DE, Krzyzanski W. Quasi-equilibrium pharmacokinetic model for drugs exhibiting target-mediated drug disposition. Pharmaceutical Research, 22 (10): 1589-1596 (2005).

3. Gibiansky L, Gibiansky E, Kakkar T, Ma P, Approximations of the Target-Mediated Disposition Model and Identifiability of Model Parameters, Abstract 1269, PAGE 2008 .

METHODS

- The analysis data set was simulated from the clinical data with the dosing, concentration and model parameters scaled to mask the actual PK properties but to preserve the characteristic features of the model;
- Similar to the real data, the simulated dataset reflected the degenerate TMDD model which was similar to the MM model for dosing regimens of interest. Predictions of the TMDD model used for simulations, and the corresponding QE, QSS and MM approximations are illustrated in Figure 1 (top row) for two typical dosing regimens (200 and 2000 dose units);
- TMDD, QE/QSS and MM pharmacokinetic models were fitted to the simulated data (using FOI and FOCEI methods, Table 1);
- Model performance, parameter estimates and concentration predictions of the full TMDD and the parsimonious (MM) model were compared.

Table 1. Run time and convergence of TMDD, QE/QSS and MM Models

Run	Model	Method	Run Time	Conv.	$COV	OF	Condition Number
101	TMDD	FOI	1 hr	Yes	Yes	-3572	815
102	QE/QSS		1 min	Yes	Yes	-3407	5778
103	MM		1 min	Yes	Yes	-3336	218
111	TMDD	FOCEI	20 hrs	Yes	No	-3981	NA
112	QE/QSS		35 min	Yes	No	-3800	NA
113	MM		45 min	Yes	Yes	-4368	24

RESULTS

For the investigated dataset:

- TMDD and the corresponding QSS and MM models provided nearly identical predictions;
- Covariance step of TMDD and QE/QSS models was aborted when FOCEI method was used;
- TMDD and QE/QSS models were over-parameterized as evidenced by large condition number (ratio of the largest to the smallest eigenvalue) or aborted covariance step ;
- The MM model provided an excellent description of the data that was simulated using TMDD model (Figure 2, bottom row). The model converged (for both FOI and FOCEI), and the estimated VMAX and Km parameters were unbiased estimates of the corresponding combinations of the TMDD model parameters;
- Application of MM rather than QE/QSS and TMDD models allowed establishing a stable base model suitable for covariate investigation.
- Comparison of concentration-time profiles simulated from TMDD, and corresponding QE, QSS and MM models (Figure 2, middle row) offered a direct proof that MM approximation was adequate.

Table 2. Parameter Estimates of TMDD, QE/QSS and MM Models.

Parameter	True Value	TMDD (# 111)	QE/QSS (# 112)	MM (# 113)
K_{ON}	0.5	0.295		
K_{OFF}	0.1	0.094		
K_{Int}	1.0	0.937	3.49	
R_{Total}	20	21.6	6.16	
$K_D=K_{OFF}/K_{ON}$	0.2	0.32	4.86	
$K_{SS}=(K_{Int}+K_{OFF})/K_{ON}$	2.2	3.5		
$V_{MAX}= K_{Int}R_{Total}$	20	20	21.5	18.8
$K_m=(K_{Int}+K_{OFF})/K_{ON}$	2.2	3.5	4.86	2.23

Parameter values of the linear part of the model [K_{EL}=0.05 (CV_K=20%), V_C=1 (CV_K=20%), $K_{PlasmaTissue}$= $K_{TissuePlasma}$=0.1, K_A=0.2, CVE_{RROR}=20%] were well-estimated by all models

Figure 1. Comparison of Population and Individual Predictions for TMDD (# 111), MM (# 113), and True (simulated) TMDD Model.

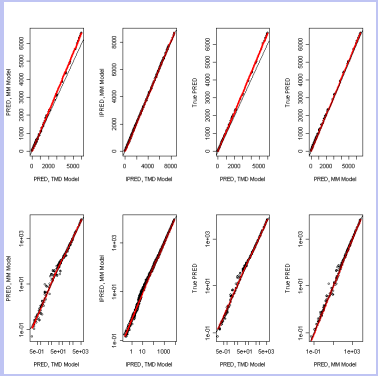
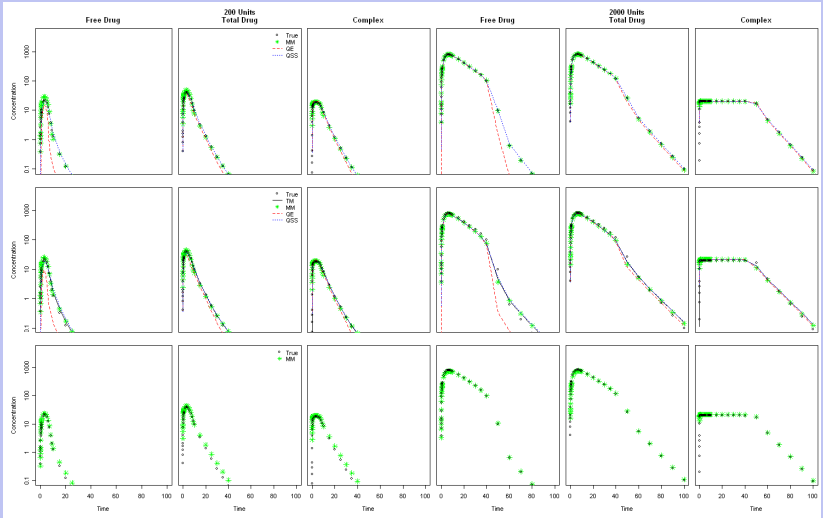


Figure 2. Free and total drug, and drug-receptor complex concentration-time profiles for two dosing regimens predicted by TMDD, and corresponding QE, QSS and MM models with the following parameters: **Top row**: True (simulation), **Middle row**: TMDD (# 111), **Bottom row**: MM (# 113). Points are true values (same in all rows).



CONCLUSIONS

- For the analysis data set, no improvement of the model fit or predictive power can be obtained using the full TMDD model when compared with the simpler MM model.
- The MM model was more stable than the corresponding TMDD model. It provided the parameter estimates as well as their precision.
- The MM model required much less time and resources for the population PK analysis while providing an excellent description of the data simulated from the full TMDD model.
- Application of Identifiability Analysis Algorithm allowed selection of the parsimonious model that described the available data.

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