Modeling a time-dependent absorption constant: a trick and some considerations

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Introduction

Simple first-order absorption models are often inadequate to describe the processes that rule the absorption of a drug. In particular, the inclusion of a lag-time parameter in the model may result in difficulties in the parameter estimation, due to discontinuity issues. To overcome the latter problems, sometimes we found beneficial to "turn on" the absorption rate constant using a time-varying function. Many continuous functions have been proposed in the literature for modeling absorption processes, such as the single or double Weibull distributions [1, 2].

Objectives

In general, all models described above can be implemented in NONMEM using differential equations (ADVAN6) [3]. Interestingly, we observed that they could also be directly implemented using the corresponding built-in PK models (e.g., ADVAN2/ADVAN4).
In this communication we present the results obtained using these two different approaches, describe and report some considerations on their implementation in NONMEM.

Methods

Models

Two different empirical models were used to describe the time-dependency of an absorption rate constant:

1. Sigmoidal Emax model:

$$k_a(t) = \frac{t^{\gamma}}{t_{50}^{\gamma} + t^{\gamma}} \cdot k_{a,fin}$$

where $k_{a,fin}$ is the asymptotic value of k_a, t_{50} is the time at which k_a assumes 50% value of $k_{a,fin}$ and γ a shape factor that modulates the onset of $k_{a,fin}$

2. Weibull-like model:

$$k_a(t) = k_{a,fin} \cdot (1 - e^{-(k \cdot t)^{\gamma}})$$

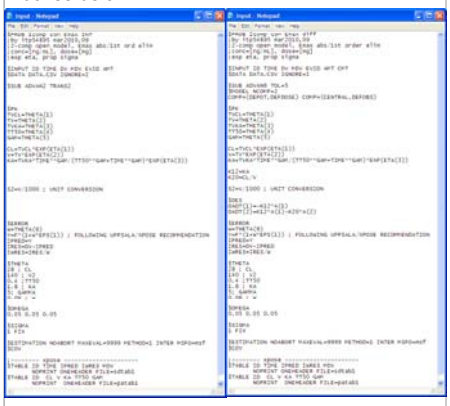
where $k_{a,fin}$ is the asymptotic value of k_a, k a time constant and γ a shape factor.

Data

•Three datasets (n=500) were simulated using 1- or 2-compartment open models and atypical absorption (Emax-type). Simulations were performed either using ADVAN2 or ADVAN4 (1- or 2-compartment pharmacokinetic model built in NONMEM) or ADVAN 6 (user-defined 1- or 2-compartment pharmacokinetic model using differential equations). Twenty-five subjects extracted from these datasets were analysed using the same models (ADVAN2, ADVAN4 or ADVAN6) including either the sigmoidal Emax model or the Weibull-like absorption.
•A real dataset, obtained in a phase I trial (N=56, six dose levels, placebo-controlled, double blind, randomized study for investigation of pharmacokinetics of increasing multiple doses for up to 28 days), was analysed using a 3-compartment open model with Weibull-type absorption, implemented either as ADVAN12 or ADVAN6.

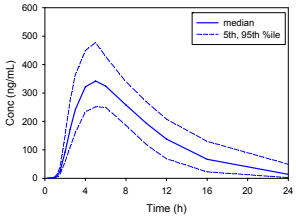
Implementation

The implementations for the 1-compartment model with sigmoidal Emax absorption using ADVAN2 and ADVAN6 are reported in the boxes below:

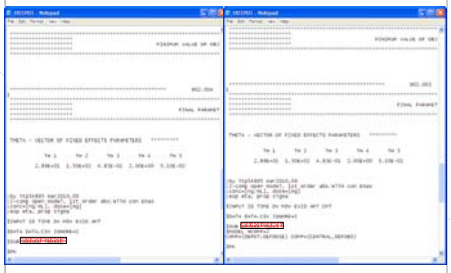


Results – simulated data

1-compartment open model, sigmoidal Emax absorption
Simulation: simulations were identical with ADVAN2 and ADVAN6



Fitting: model parameters and OBJ were identical with ADVAN2 and ADVAN6



For:
a) 2-compartment open model with sigmoidal Emax absorption and
b) 1-compartment open model with Weibull-like absorption model.

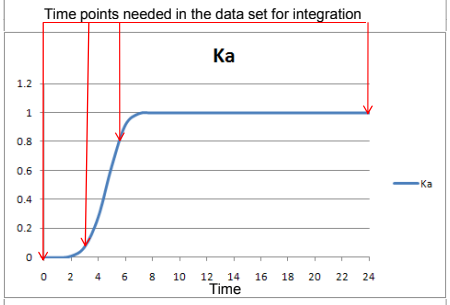
analogous results were obtained:
•Simulations performed with ADVAN4 and ADVAN6 were identical .
•Fitting: the model parameters obtained using the implementations with ADVAN4 and ADVAN6 were identical.

Results-experimental data

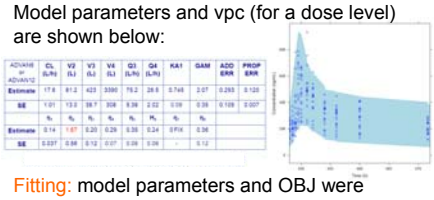
With both ADVAN12 and ADVAN6 it was immediately clear that the program was not appropriately handling the multiple dosing events, when the data file included only actual timings of dosing and concentrations: plasma concentrations were lower than expected.

Results-exp data (cont'd)

Dummy time points were needed to correctly characterize the amounts handled with the dosing events: these dummy time points are depicted on the ka vs. time plot shown below:



Model parameters and vpc (for a dose level) are shown below:



Fitting: model parameters and OBJ were identical with ADVAN12 and ADVAN6

Conclusions

•Some atypical absorption processes can be implemented in NONMEM either using differential equations or the corresponding built-in pharmacokinetic models.
•The simulated datasets obtained using either ADVAN6 or ADVAN2/4 models were identical.
•Model parameters were identical when the models were fitted to real or synthetic datasets using the different implementations. The implementation with built-in models resulted in considerably shorter run-times: the example with ADVAN12 had run times <3 min vs. 20 min using the implementation with ADVAN6.
•The adopted implementations are both approximate (Gibiansky L, personal communication): they refer to an input function defined based on the time points of the data file. Thus, for both implementations, caution should be made to provide an appropriate number of datapoints over time (i.e. few time points with missing observations for each dosing event) to allow NONMEM to correctly handle the input function. This is particularly important for repeated dose regimens.
•The empirical model used here had the form of a cumulative Weibull distribution. Please refer to [4] and reference therein for a more formal implementation of Weibull absorption: although "the Weibull is a mathematical figment of the imagination", you may be willing to correlate in vivo data with dissolution data for IVIVC....

References

[1]Piotrovsky V. JPP 1987, 15:681-6.
[2]Zhou H. J Clin Pharmacol. 2003, 43: 211-27.
[3]Petricoul O, Cosson V, Fuseau E, Marchand M. Pharmacometrics: the science of quantitative pharmacology, 2007, Ette EI, Williams PJ (eds). John Wiley&Sons Inc.
[4]Gibiansky L. NMUSERS, Weibull Absorption http://www.cognigencorp.com/nonmem/current/2010-April/2476.html