Interactive Code for Guiding Dose Selection

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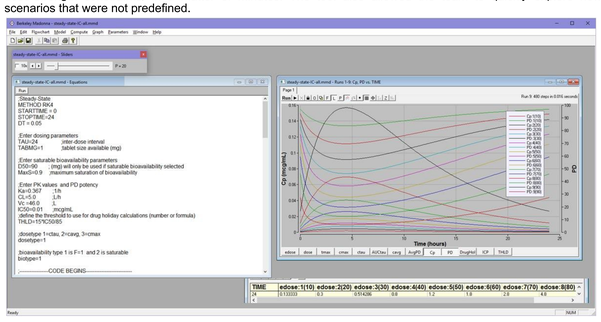
ABSTRACT

Objective: Assuming a linear one-compartment model for the pharmacokinetics (PK) with and without dose-dependent saturable bioavailability, and a direct inhibitory Emax model for bio-marker effect (PD), develop an interactive PK/PD response simulation tool to guide dose selection for a first-in-human study of an orally administered medication. The tool will simulate various scenarios of target plasma concentration and PD time profiles with and without consideration of discrete dose strength constraints.

Methods: Predicted human PK parameters allometrically scaled from an animal study and concentration required to achieve 50% suppression (IC50) from an in vitro experiment of the bio-marker were provided. Berkeley Madonna® was selected to implement the coding to allow use of interactive sliders for parameter values (PK, absorption type, and IC50) and 'batch run' mode to cycle through suppression values of IC10 to IC90. Equations were derived to calculate the exact dose needed to achieve steady-state trough, maximum, and average concentrations equivalent to ICx (x = 10 to 90% suppression). For each exact dose the following information was calculated: discrete dose to be administered, concentration/effect-time profiles, area under the curve (AUC) for concentration/effect-time, average effect, drug holiday (time effect is < 20% suppressed), and doses expected to achieve drug holidays of specific length.

Results: The interactive simulation tool allowed the drug development team to explore numerous scenarios allowing for uncertainty in predicted potency and PK, as well as various scenarios of target PK/PD profiles and dose-strength constraints, in a matter of minutes. The tool also allowed the team to quickly explore new scenarios that were not predefined.



Conclusions: Solving for dose instead of simulating to find the dose needed to achieve specific PD goals and front-loading other design choices into a simple interactive tool significantly increased the speed and confidence in dose selection for first-in-human studies.

INTRODUCTION

- As the development of drugs transition from the laboratory and pre-clinical setting, a dose range for the first-in-human study is needed. This is frequently done based upon simulations of an assumed PK and PD model with PK parameters obtained from animal-to-human allometric scaling and PD parameters from in vitro potency measures.
- Interactive tools are needed that will allow users to vary the PK and PD parameters and quickly obtain the predicted dose range needed to achieve target goals with a minimal number of simulations.

OBJECTIVE

- Develop an interactive PK/PD response simulation tool to guide dose selection for a first-in-human study of an orally administered medication.
  - Assume linear one-compartment PK model with and without dose-dependent saturable bioavailability.
  - Assume a direct inhibitory Emax model for bio-marker of PD effect.
- Interactive tool will have the following capabilities:
  - Accept PK and PD parameters as input and allow user to vary values.
  - Determine the dose of drug (exact and based on discrete dose strengths) expected to achieve specified maximum (Cmax), minimum (Cmin), and average concentration (Cavg) levels related to the anticipated potency of the drug (IC50).
  - Calculate PK and PD exposure measures and the drug holiday (DHOL) defined as the amount of time that the concentration is below a specified threshold (THLD).
  - Graph the predicted concentration and PD-time curves.

METHODS

Selection of Software

- Tool should allow user to change input parameters easily.
- Tool should be able to loop through multiple cases easily (ICp values).
- Tool should interactively generate basic graphs and tables of computed values.
- Selected software: Berkeley Madonna.[1]

Approach to Simulations

- Closed form solutions available for selected PK model.[2]
- Equation for Cp(t) can be solved for dose with or without saturable bioavailability.
- Instead of simulating a range of doses to find which dose meets the target criteria, the dose that meets the target criteria can be directly calculated.

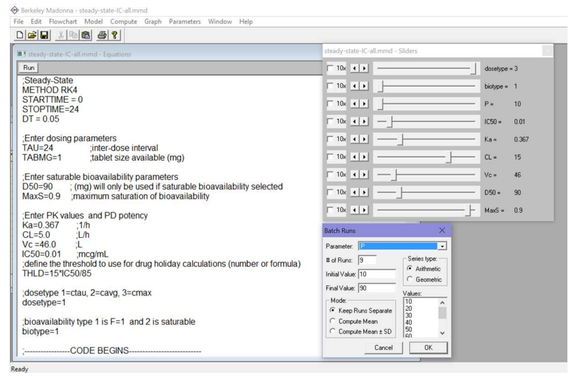
Program Flow

- Input parameters:
  - Dosing: inter-dose interval (TAU), minimum tablet strength (TABMG)
  - Saturable bioavailability parameters: maximum saturation (MaxS) and the dose at which 50% of MaxS (D50) occurs
  - PK: clearance (CL), volume of distribution (Vc), and absorption rate (Ka)
  - PD: inhibitory potency measure (IC50)
  - Select simulation type:
    - Bioavailability of 1 or saturable
    - Cmin, Cavg, or Cmax should have the specified value of ICp
  - Range of values allowed for all input parameters (except TAU and TABMG) using the slider feature
- Calculate ICp where p = 10 to 90 by 10
  - Performed using the batch runs feature
- Calculate exact dose needed for the selected concentration parameter to achieve IC10 to IC90 by 10
- Calculate the associated discrete dose using TABMG
- Compute Cp(t) and PD(t) as a function of time
- Compute the average PD response (PDavg)
  - (area under the PD response curve 0 to tau)/tau
- Compute the drug holiday
  - If Cp(t) > THLD then assign HOL = 1; else assign HOL = 0
  - Integration of HOL from time 0 to tau calculates duration of time Cp(t) > threshold
  - DHOL = tau - integrated value of HOL

RESULTS

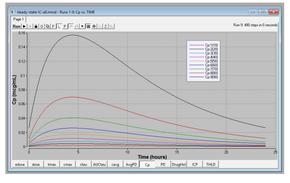
Code, Sliders, and Batch Run

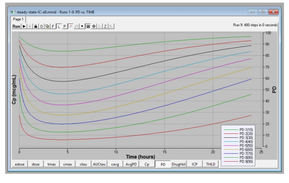
- Full code and equations provided upon request or download from the Cognigen Corporation web site (search: posters)

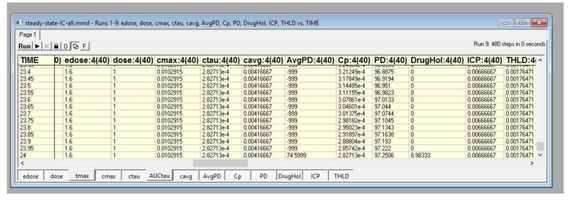


On-the-Fly Graphs and Tables

- Toggle on/off the endpoints to be shown in the graph and table
- Toggle between graph and table of computations
- Final parameter values displayed at 24 hours in the table
- File - Save As allows export of the table to a csv file
- File - Save As allows export of graphs as bmp or emf file

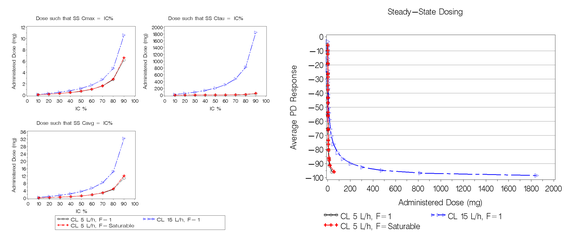


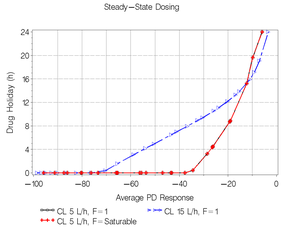




Quick Answers for the Clinical Team

- Which dose achieves the specific ICp targets?
- What is the average PD response relative to dose?
- How does drug holiday correspond to the average PD response?





CONCLUSIONS

- The interactive simulation tool allowed the drug development team to explore numerous scenarios allowing for uncertainty in predicted potency and PK, as well as various scenarios of target PK/PD profiles and dose-strength constraints, in a matter of minutes. The tool also allowed the team to quickly explore new scenarios that were not predefined.
- Solving for dose instead of simulating to find the dose needed to achieve specific PD goals and front-loading other design choices into a simple interactive tool significantly increased the speed and confidence in dose selection for first-in-human studies.

REFERENCES

1. Berkeley Madonna Version 8.3.18. 1996-2010. Robert I Macey and George F Oster. The Regents of the University of California.
2. Applied Biopharmaceutics and Pharmacokinetics. 3rd Edition. Leon Shargel and Andrew BC Yu. Appleton & Lange; Norwalk, Connecticut. 1993;363-364.

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