

Day 5 Exercise 2

Parameter Optimization and Sensitivity Analysis: An Example Using a Physiologically Based Pharmacokinetic Model for Warfarin

A Course on Physiologically Based Pharmacokinetic (PBPK) Modeling in Drug Development and Evaluation

April 6-10, 2009

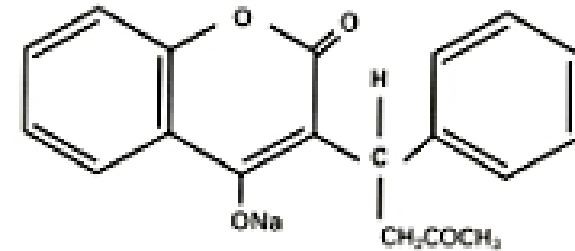
Center for Human Health Assessment
Center for Drug Safety Sciences



Outline

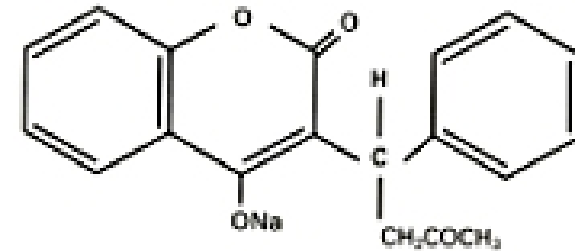
- Exercise #1: sensitivity analysis
- Introduction to optimization
- Exercise #2: optimizing metabolic constants using a single data set
- Exercise #3: optimizing metabolic constants using multiple doses

Warfarin



- An anticoagulant which acts by inhibiting vitamin K-dependent coagulation factors. Chemically, it is 3-(α -acetylbenzyl)-4-hydroxycoumarin and is a racemic mixture of the R and S enantiomers.
- Warfarin is used for the prophylaxis and/or treatment of venous thrombosis and pulmonary embolism.
- Dosage must be tailored to the individual, based on their sensitivity (standard clotting test) to the drug.
- The S enantiomer is ~3 times more active than the R enantiomer.

Warfarin



- Highly bound in plasma (~99%) and tissues (95%)
- Not particularly lipophilic (partition coefficients ~1)
- Metabolism stereo-specific
- The R and S enantiomers are competitive inhibitors of each others metabolism
- Polymorphisms in the P450's responsible for metabolism (and clearance) can affect warfarin pharmacokinetics

Warfarin metabolism

S-Warfarin

- Metabolized predominantly by CYP2C9.
- There are three principal alleles of CYP2C9, CYP2C9*1 , CYP2C9*2 , CYP2C9*3.
- The wild-type, CYP2C9*1 is the most active. Expression of CYP2C9*3 results in clinically significant reductions in metabolism.
- Metabolic constants, VMax and KM, are available for these three alleles.

R-Warfarin

- Metabolized by CYP2C19, CYP1A2, CYP3A4, and CYP2C9.
- Metabolic constants are available for CYP2C19, CYP3A4 and CYP2C9, but not CYP1A2.
- The relative contribution of these P450's to R-Warfarin metabolism is not known.

Warfarin PK data

- Andreassen and Vesell, 1974. Four male volunteers received 0.76 mg/kg warfarin either orally or by IV
- Benedek et al., 1992. Twelve male volunteers received a single oral dose of 25 mg sodium warfarin (5 tablets of 5mg)
- Black et al., 1996. Six male volunteers received a single oral dose of 0.75 mg/kg pseudoracemic warfarin (equal amounts of (S)-4'deuteriowarfarin and unlabeled (R) warfarin)
- Breckenridge and Orme, 1973. Four patients were given either an IV or an oral dose of 0.5 mg/kg ^{14}C warfarin
- Chan et al., 1994. Six male subjects were given a single oral dose of 1.5 mg/kg pseudoracemic warfarin (1:1 mixture of ^{12}C -R+ and ^{13}C -S- warfarin)
- Choonara et al., 1986. Eight volunteers received a single oral dose of 15 mg of either (S) warfarin or (R) warfarin
- O'Reilly et al., 1971. Six volunteers received IV doses of 50, 100, or 200 mg warfarin

Questions to address with the warfarin PBPK model

- Which model parameters have the greatest influence on the plasma time course (or AUC, CMax, etc.)? (The sensitivity analysis exercise).
- How well do the *in vitro* metabolic constants predict R and S warfarin clearance?
- If the *in vitro* metabolic constants are not sufficient, how do we fit the metabolic parameters to the PK data we have? (Parameter fitting exercise).
- What changes to the dosing regimen must be made to account for patient-specific polymorphisms in the metabolic clearance of S-warfarin, the most active enantiomer?

Sensitivity analysis

- Sensitivity analysis is the measurement of the change in one response/output with respect to the change in some parameter.
- Formally, it is the calculation of the partial derivatives of model responses with respect to model parameters.
- This is a measure of the importance of model parameters on model outcomes. For example, one could ask what is the impact of changing body fat (different species) on blood/plasma time course? Or what is the impact of changes in KM/V_{Max} ?

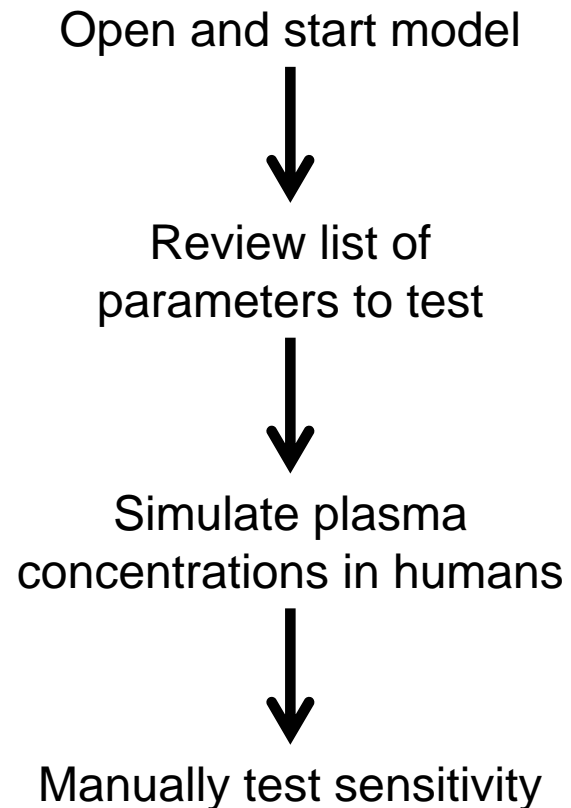
Sensitivity analysis (cont.)

- There are two methods of computing sensitivity coefficients, but because the focus here is on optimization, we will limit ourselves to the approach that allows a normalized approach, that is, it allows you to compare the impact of several parameters on outcomes on the same basis.
- The equation, in simplest terms, is:

$$\text{Sensitivity Coefficient} = \frac{\left(\frac{\text{Change in Response}}{\text{Initial Response}} \right)}{\text{Fractional Change in Parameter}}$$

$$\text{e.g., } \frac{\left(\frac{0.01 \text{ nM}}{10 \text{ nM}} \right)}{0.01} = \text{Sensitivity Coefficient} \quad t = 0.1$$

Outline for sensitivity analysis



Sensitivity analysis exercise #1

Manual sensitivity analysis

Open the Warfarin model.

Set: IVDose=0.0
PDrink=0.0
BW=70.0
PDose=0.214
Frac=0.0
Stoptime=240.0
Vmaxc_r=4.0
Km_r=123

Simulate the R-warfarin oral dosing in humans using the parameter values to the left.
(select overlay plots)

What is the final value for :

AUCPlas_R _____ (nM*h/L)
(Hint: final value in table view)

Sensitivity analysis exercise #1

Manual sensitivity analysis

Now we will vary one parameter. Choose one of the following parameters to vary:

PSlw: slowly perfused tissue:plasma partition coefficient

VMaxC_R: VMax for metabolism of the R enantiomer

kAS: rate constant for uptake from stomach.

Increase the value of a parameter by 1%

Run the simulation (effect on time-course of Cplas_R?)

AUCPlas_R _____

Sensitivity Coefficient _____

Sensitivity analysis exercise #1

Manual sensitivity analysis

Increase the parameter by 10% and run simulation

AUCPlas_R _____

Sensitivity Coefficient _____

Compare sensitivities.

	1%	10%
Sensitivity Coefficient		

Sensitivity analysis exercise #1

Manual sensitivity analysis

Now reset the parameter that you just evaluated and perform sensitivity analysis on the other two parameters

Parameter	Initial AUCPlas_R	AUCPlas_R (After 1% Change in Parameter)	Sensitivity Coefficient
PSlw			
VMaxC_R			
kAS			

Parameter optimization

“Fitting the model to the data”

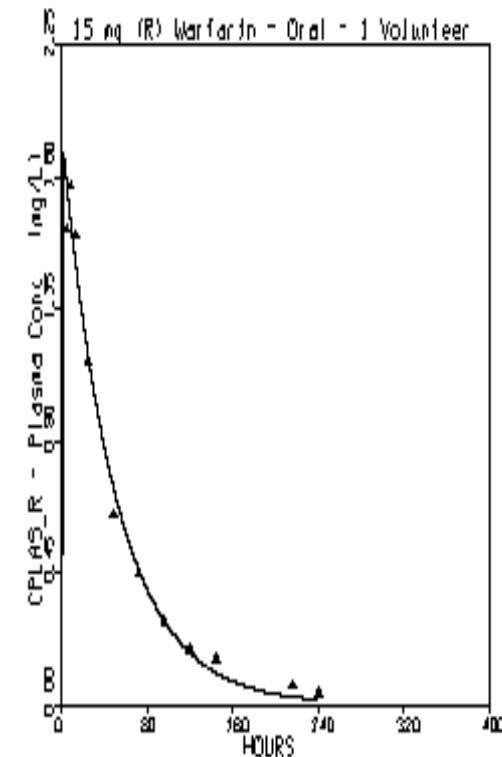
Objective

- Find the value of the parameter(s) that best predicts the observed data (repeatable, more formal than visual optimization).

Method

- Visual Fit for good starting point
- Curve Fit
- Goal is to minimize the difference between predicted and observed data using biologically relevant values for parameters

$$\frac{(\text{predicted} - \text{observed})}{\text{observed}}$$

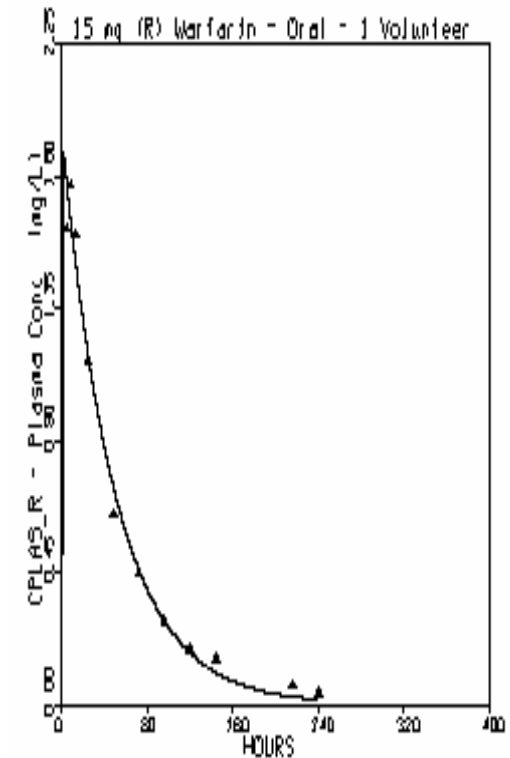


Parameter optimization

“Fitting the model to the data”

Approach in Berkeley Madonna:

- Visually estimate the constants (sliders are useful)
- Open the “Curve Fit” and:
 - Establish constants to be fit (VmaxC_R and KM_R)
 - Use values from visual fit as starting point
 - Establish Variables (Cplas_R)
 - Establish dataset(s) (#ChoonaraCPlas_R)
- Run parameter fitting
- Evaluate results



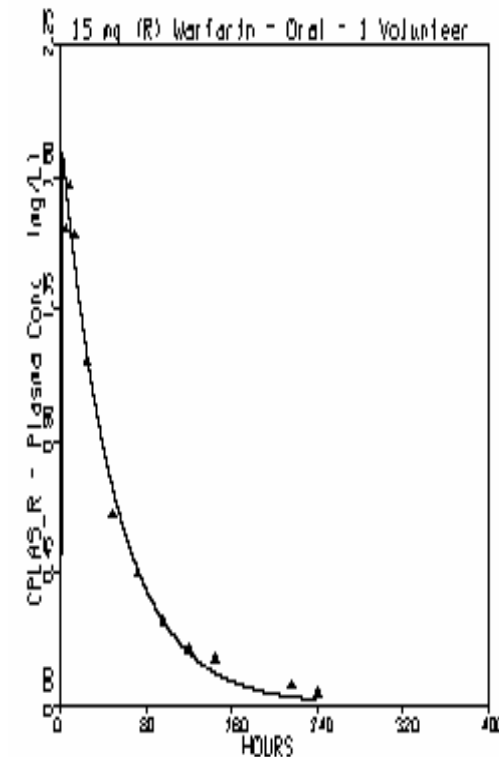
Parameter optimization

“Fitting the model to the data”

Specifying Initial Guesses:

- Guess #1 and 2 must be different
- Guesses must fall within established max and min
 - Default guesses are set to 0.5 and 1.5 of the current model value
- Want the fractional difference between the two guesses to be much greater than the specified tolerance

$$\frac{|g1 - g2|}{\frac{1}{2}(|g1| + |g2|)} \gg tol$$



Optimization exercise #2

Fitting R-Warfarin metabolic constants using plasma concentration time course data

Open the Warfarin model

In Parameters Window

set: Stoptime = 240.0
BW = 70
Pdose = 0.214
VMaxC_R = 4.0
KM_R = 12.0
Frac = 0.0

Create **Sliders** for **VMaxC_R** and **KM_R**

(hint: try to keep both values between 1.0 and 5.0, figure page 1)

VMaxC_R: _____ KM_R: _____

Optimization exercise #2

Fitting R-Warfarin metabolic constants using plasma concentration time course data

In Curve Fit window:

Add Parameters VMaxC_R and KM_R and change bounds

VMaxC_R lower bound = 0.5
upper value = 5.0
guess 1 and 2 = Use defaults if possible

KM_R lower bound = 0.5
upper value = 3.0
guess 1 and 2 = Use defaults if possible

Fit Variable: Cplas_R

Choose Dataset: #ChoonaraCPlas_R

Click Ok to run (view fit on Page 1 of figure window)

VmaxC_R:_____ KM_R:_____

Optimization exercise #2

Evaluating the fit

Try different guesses and bounds.

What happens to the results?

Difficult to fit V_{max} and K_m simultaneously with only one concentration dataset – there are many possible solutions

Optimization exercise #3

Fitting R-Warfarin metabolic constants using plasma concentration time course data: multiple concentrations

Data: O'Reilly et al., 1971. Six volunteers received IV doses of 50, 100, or 200 mg warfarin

* Visually optimize V_{maxC_R} and KM_R to each concentration
(hint: use previous values as starting point)

Set:

BW = 70.0 Frac = 0.0 Stoptime = 125.0

(Doses are 0.714, 1.429 and 2.857 mg/kg)

Dose (mg)	V_{maxC_R} (hr*mg/kg)	KM_R (mg/L)
50		
100		
200		

Optimization exercise #3

Fitting R-Warfarin metabolic constants using plasma concentration time course data: multiple concentrations

Now try to visually optimize one set of values to V_{maxC_R} and KM_R to fit all concentrations

V_{maxC_R} (hr*mg/kg)	KM_R (mg/L)

Additional uses for PBPK model based optimization of clinical doses for special patient populations

- Compensating for changes in cardiac output: surgery, cardiac arrest
- Adjusting for pharmacodynamic differences: intrinsic differences in clotting rate, the impact of co-administered drugs or disease state on vitamin K concentrations
- Compensating for reduced metabolic clearance resulting from liver disease
- Dose scaling for pediatric populations

Summary

- Understand your model. Develop an intuitive understanding of the principal parameters controlling model output and follow with a formalized sensitivity analysis to establish, quantitatively, the importance of the various parameters.
- Don't refrain from visual optimization of parameters. Take advantage of tools that allow formal, repeatable optimization for regulatory submissions and to support other important decisions.
- Think broadly about where optimization can aid in testing and development.
- Consider some of the advantages of using PBPK models in PK/PD analyses.