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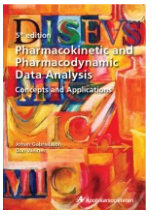
PML School: PD22 Effect Compartment II – Intravenous Infusion



Note: The exercise is based on exercise PD22 in the text: Gabrielsson, J. & Weiner, D.L. (5th ed., 2016). *Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications.* Swedish Pharmaceutical Press, Stockholm.

PD22: Effect Compartment – Link Model

Analysis and Comparison of Link, Turnover and Receptor Binding Models
Fit a link-, turnover- and receptor binding model to data
March 16, 2017 | 10am EST
Presenter: Dan Weiner

- Support Questions:
  - How to add an effect compartment to an existing PK model
  - How to combine Infusion PK model with link model
  - How to setup multiple doses for link model

PD22: Objective

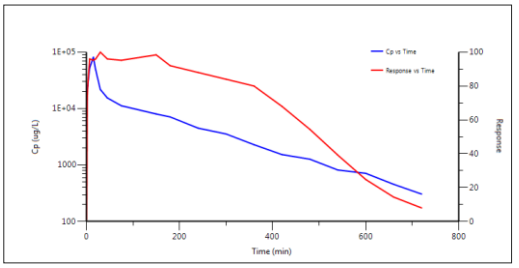
- Model response-time data with a link-model after iv infusion
- Find estimates for
  - PK:
    - V – Volume of central compartment
    - V_2 – Volume of peripheral compartment
    - Cl – Plasma clearance
    - Cl_2 – intercompartmental clearance
  - PD:
    - E_{max} – Maximum response
    - EC_{50} – Concentration at half-maximum response
    - gamma – Hill-coefficient
  - Link
    - k_{e0} – rate constant for effect compartment
- Simulate repeated infusion regimen with target responses

PK32: Problem specification

- A volunteer was given intravenous infusion dose of 69,000 units over 15 minutes.
- Plasma concentrations were sampled over 720 minutes
- Responses were measured at the same time points

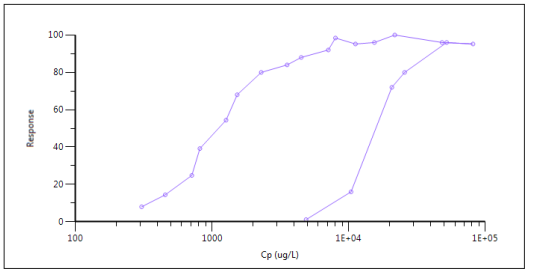
PD22: Exploratory Data Analysis

- Plot of concentration and response versus time

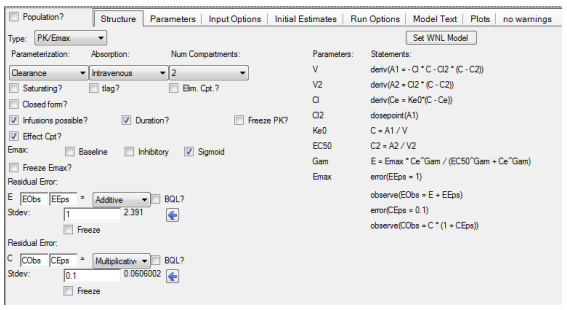


PD22: Exploratory Data Analysis II

- Hysteresis Plot



PD22: Built-in PKPD model



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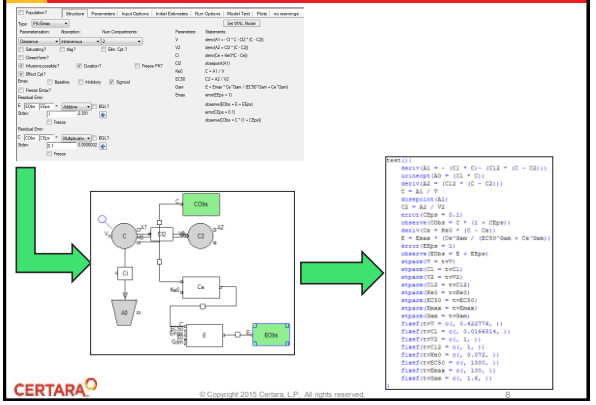
PD22: Graphical and Textual PKPD Model



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PD22: Model Equations + Textual Model

$$V \cdot \frac{dC}{dt} = In - Cl \cdot C - Cl_2 \cdot (C - C_2)$$

2-compartment model with IV input

$$\frac{dC_e}{dt} = K_{e0} \cdot (C - C_e)$$

Effect Compartment

$$E = \frac{E_{max} \cdot C_e^{\gamma}}{EC_{50}^{\gamma} + C_e^{\gamma}}$$

Emax Model

```
test(){
    ## PK Model ##
    deriv(A1 = -Cl * C - Cl2 * (C - C2))      # Amount in central compartment
    deriv(A2 = Cl2 * (C - C2))                # Amount in peripheral compartment
    dosepoint(A1)                             # Concentration in effect compartment
    C = A1 / V                                # dosepoint specifies drug amount for IV input
    C2 = A2 / V2                              # conversion of amounts into concentrations

    ## PD Model ##
    error(EEps = 1)                           # Hill equation with slope factor gamma
    observe(EObs = E + EEps)                  # residual error for effect set to 1
    error(CEps = 0.1)                         # additive residual error model on effect
    observe(CObs = C * (1 + CEps))            # residual error set to 10%??
                                              # multiplicative residual error model for concentration

    ## Fixed Effects ##
    fixef(V = c(, 0.422776, ))
    fixef(V2 = c(, 1.8252, ))
    fixef(Cl = c(, 0.0166514, ))
    fixef(Cl2 = c(, 0.035661, ))
    fixef(Ke0 = c(, 0.072, ))
    fixef(EC50 = c(, 1000, ))
    fixef(Gam = c(, 1.6, ))
    fixef(Emax = c(, 100, ))
}
```

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PD22: Textual PKPD Model with Delay Statement

New feature in Phoenix 7.0

- Delay differential equations included within PML using a single command

```
test(){
    ## PK Model ##
    deriv(A1 = - Cl * C - Cl2 * (C - C2))
    deriv(A2 = Cl2 * (C - C2))
    dosepoint(A1)
    C = A1 / V
    C2 = A2 / V2

    ## New Delay Statement ##

    ## PD Model ##
    E = Emax * Ce^Gam / (EC50^Gam + Ce^Gam)
    error(EEps = 1)
    observe(EObs = E + EEps)
    error(CEps = 0.1)
    observe(CObs = C * (1 + CEps))

    ## Fixed Effects ##
    fixef(V = c(, 0.422776, ))
    fixef(V2 = c(, 1.8252, ))
    fixef(Cl = c(, 0.0166514, ))
    fixef(Cl2 = c(, 0.035661, ))
    fixef(Tlag = c(, 1, ))
    fixef(EC50 = c(, 1000, ))
    fixef(Gam = c(, 1.6, ))
    fixef(Emax = c(, 100, ))
}
```

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PD22: Textual PD Model with explicit concentrations

- When fitting classical PKPD models, the assumption is that the PD data does not impact the fit of the PK model (no PD parameters are shared with the PK models). Thus the PK model only serves as a smoothing function to get PK data at the same times as the PD data
- In such situations we can often use the observed Cp data rather that modeling Cp, even if there are temporal effects (like hysteresis).

```
test(){
    covariate(Cp)
    deriv(Ce = Ke0 * (Cp - Ce))
    E = Emax * (Ce^Gam / (EC50^Gam + Ce^Gam))
    error(EEps = 1)
    observe(EObs = E + EEps)
    fixef(Ke0 = c(, 1, ))
    fixef(EC50 = c(, 1000, ))
    fixef(Emax = c(, 100, ))
    fixef(Gam = c(,2, ))
}
```

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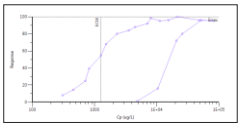
PD22: Initial Estimates

- PK:
  - V – from NCA (Dose/C0)
  - V_2 – from NCA (Vss – V1)
  - Cl – from NCA (CL_obs
  - Cl_2 – set equal to CL
- PD:
  - E_{max} – from plot
  - EC_{50} – from plot (downswing arm)
  - gamma – initially set to 2
  - k_{e0} – initially set to 1



Gabrielsson & Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 5th Edition, Swedish Pharmacology Press (2015)

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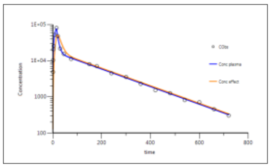
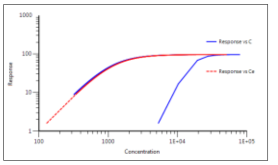
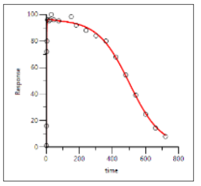
Demo

PD22: Results







	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Var. Inf. factor
1	tvV	0.42254		0.012912784	3.055991	0.39623757	0.44884243	0.044381
2	tvV2	1.82249		0.053004717	2.908368	1.7145231	1.9304569	8.75836
3	tvCl	0.0166392		0.00026408332	1.5871155	0.016101281	0.017177119	1.8933E-05
4	tvCl2	0.0357833		0.0021069172	5.8879901	0.031491659	0.040074941	0.0012349
5	tvKe0	0.0991182	1/min	0.0065315389	6.5896464	0.085813918	0.11242248	0.011538
6	tvEC50	1150.49		39.347173	3.420036	1070.3426	1230.6374	420160
7	tvGam	1.86647		0.08646213	4.6323879	1.6903528	2.0425872	1.9123
8	tvEmax	96.2747		0.92603996	0.9618726	94.388422	98.160978	224.23
9	stdev0	2.391		0.3691883	15.440749	1.6389896	3.1430104	
10	stdev1	0.0606002		0.0093914323	15.497362	0.041470518	0.079729882	

PD22: Summary

- Build Effect Compartment Model
  - Introduced delay differential equations
  - Turned PKPD model into PD model
  - Fitted the model and examined results
- Setup and run a Simulation
  - Setup of multiple intravenous infusions
    - Using ADDL function

Questions?

Coming up…

Modeling PK/PD Systems with Distributed Delays
Speaker(s): Wojciech Krzyzanski
Date: May 16, 2017
Time: 11 am EST
Duration: 1 hour

Turnover Model 1: IV Bolus Dosing
Model Warfarin-PCA interaction
June 8, 2017 | 10am EST
Presenter: Chris Mehl