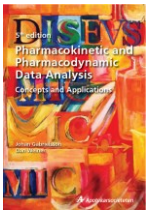
CERTARA

PML School: PK32 Turnover III – Nonlinear Disposition



Note: The exercise is based on exercise PK32 in the text: Gabrielsson, J. & Weiner, D.L. (5th ed., 2016). *Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications.* Swedish Pharmaceutical Press, Stockholm.

PK32: Objective

- Characterize turnover of an endogenous compound
- Analyse multiple intravenous infusion data with nonlinear disposition
- Find estimates for
  - V_{max} – Maximum metabolic capacity
  - K_m – Michaelis-Menten constant
  - V – Volume of distribution
  - k_{in} – Rate of synthesis, turnover rate
  - Cl – Plasma clearance

PK32: Problem specification

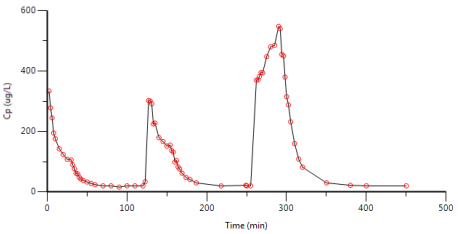
- A volunteer was given multiple intravenous bolus doses and infusions:

	Rapid IV 1	Infusion 1	Rapid IV 2	Infusion 2	Rapid IV 3	Infusion 3
Dose (µg)	1669	1131.8	1701	1884.4	1733	6300
Interval (start time to stop time, min)	Bolus at t=0	0-30.1	125-126	125.2-154.3	260-261	260.1-290.1

- Plasma concentrations were sampled over 450 minutes.

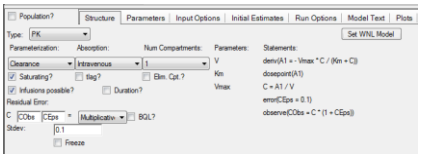
PK32: Exploratory Data Analysis

- Linear plot of concentration versus time

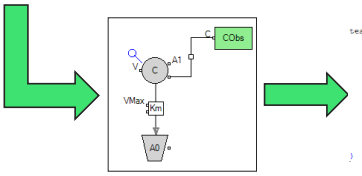


PK32: One-compartment turnover model

PK32: From Built-In to Graphical to Textual Model



Need to add synthesis of endogenous compound




```
test(){
    deriv(A1 = -Vmax * C / (Km + C))
    dosepoint(A1)
    C = A1 / V
    error(CEps = 0.1)
    observe(CObs = C * (1 + CEps))
    stparm(V = tvV)
    stparm(Km = tvKm)
    stparm(Vmax = tvVmax)
    fixef(tvV = c(, 1, ))
    fixef(tvKm = c(, 1, ))
    fixef(tvVmax = c(, 1, ))
}
```

PK32: Model Equations + Textual Model

$$V \cdot \frac{dC}{dt} = In + K_{in} - Cl \cdot C$$ Linear model

$$Cl = \frac{V_{max}}{K_m + C}$$ Saturated Clearance

$$V \cdot \frac{dC}{dt} = In + K_{in} - \frac{V_{max} \cdot C}{K_m + C}$$ Turnover Model

```
test(){
    deriv(A1 = [redacted] - Vmax * C / (Km + C))   # amount in central compartment
    dosepoint(A1)                                  # dosepoint specifies drug amount for IV input
    C = A1 / V                                     # convert amounts to concentrations
    # residual error model
    error(CEps = 0.1)                              # residual error initially set to 10 %CV
    observe(CObs = C * (1 + CEps))                 # multiplicative residual error
    # structural parameters
    stparm(V = tvV)
    stparm(Km = tvKm)
    stparm(Vmax = tvVmax)
    [redacted]
    # fixed effects - the actual parameters to be
    # estimated (lower bound, initial estimate, upper bound)
    fixef(tvV = c(, 1, ))
    fixef(tvKm = c(, 1, ))
    fixef(tvVmax = c(, 1, ))
    [redacted]
}
```


PK32: Initial Estimates

$$Cl = \frac{Dose}{AUC} = \frac{8{,}000}{26{,}000} \sim 0.35$$

$$V = \frac{Dose}{C_0} = \frac{1{,}669}{334} \sim 5$$

$$K_{in} = C_{baseline} \cdot C \sim 20 \cdot 0.35 = 7$$

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

PK32: Secondary Parameters

$$Cl_0 = \frac{V_{max}}{K_m}$$

$$t_{1/2} = \frac{\ln(2) * V * K_m}{V_{max}}$$

$$K_{out} = \frac{V_{max} \cdot V}{K_m}$$

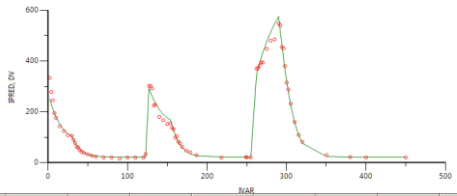
$$MRT = \frac{1}{K_{out}}$$

```
test(){
    deriv(A1 = Kin - Vmax * C / (Km + C))   # amount in central compartment
    dosepoint(A1)                           # dosepoint specifies drug amount for IV input
    C = A1 / V                              # convert amounts to concentrations
    # residual error model
    error(CEps = 0.1)                       # residual error initially set to 10 %CV
    observe(CObs = C * (1 + CEps))          # multiplicative residual error
    # structural parameters
    stparm(V = tvV)
    stparm(Km = tvKm)
    stparm(Vmax = tvVmax)
    stparm(Kin = tvKin)
    # fixed effects - the actual parameters to be
    # estimated (lower bound, initial estimate, upper bound)
    fixef(tvV = c(, 5, ))
    fixef(tvKm = c(, 450, ))
    fixef(tvVmax = c(, 800, ))
    fixef(tvKin = c(, 15, ))
    #secondary parameter
    [redacted]
}
```

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

Demo

PK32: Results



	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Var. Inf. factor
1	tvV	6.02256		0.17358859	2.8823058	5.6760753	6.3690447	2.4649
2	tvKm	503.695	ug/L	55.43194	11.005061	393.05226	614.33774	235410
3	tvVmax	362		23.83296	6.5836907	314.42916	409.57084	43796
4	tvKin	15.0915		0.92621272	6.1373138	13.24277	16.94023	63.048
5	stdev0	0.116413		0.0098317343	8.4455639	0.096788755	0.13603725	

PK32: Summary

- Developed Turnover Model
  - Setup of multiple intravenous infusions
  - Obtained initial estimates for Michaelis-Menten equation
  - Derived secondary parameters
  - Fitted the model and examined results
- Compared with simple linear model

Questions?

Coming up…

MAR 16

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

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