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Overview of PK-PD/E-R (safety + efficacy) – part 2

Module 11: Building on PopPK – Exposure response and PK-PD

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Learning Objectives

Recognise the range of exposure response models for safety and efficacy
Analyse exposure-response data using direct, indirect and delayed response models
Defend the choice of models subject to the type of data and the research question

Lecture outline

Other Types of Exposure-Response Models

- Understand how to:
  - Recap key concepts from Tutorial 1
  - What is indirect response, tolerance + rebound, receptor binding, signal transduction/transit model

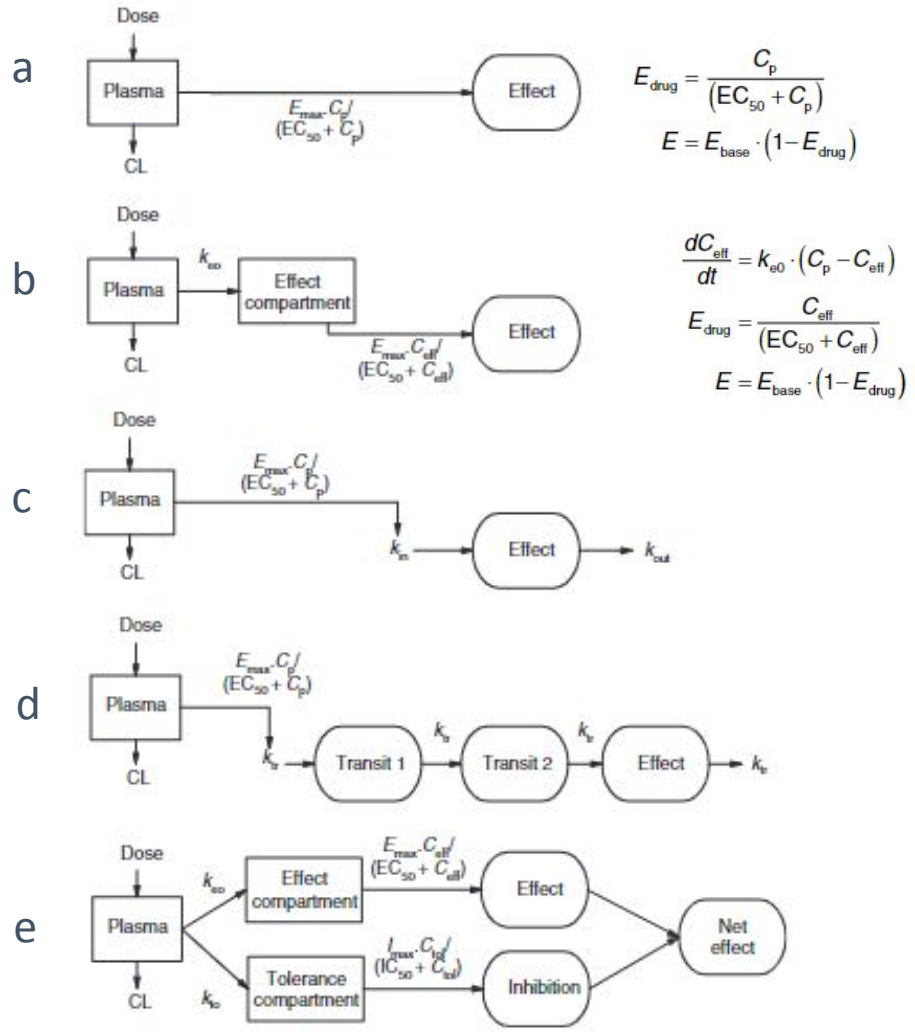
Recap key concepts from Tutorial 1

Lecture outline

Overview of PK-PD/E-R (safety + efficacy) - part 1

- Understand:
  - What are the data types used in PK-PD, E-R (safety and efficacy) modeling?
  - What's the difference between PK-PD and E-R analysis?
  - Which type of PD models are available
  - Focus on PK-PD
    - Direct/ Indirect response modeling
    - Effect compartment modeling
  - Application of PK-PD modelling with Friberg myelosuppression model and structural identifiability
  - What's is therapeutic Index and its impact to labeling

Continuous PD models



(a) A direct response model where effect is driven by the plasma drug concentration.

(b) An effect compartment model where effect is driven by the effect compartment drug concentration, which is delayed relative to the plasma concentration by a first-order rate constant ke0.

(c) A turnover model where drug effect is a balance between an apparent production rate (kin) and an apparent removal rate (kout). Drug affects the net effect by altering kin or (kout).

(d) A transit compartment model, where the drug effect is at the end of chain of processes and drug action is on the first process.

(e) A tolerance compartment model, where the drug effect is described by an effect compartment and the development of tolerance is described by a slower inhibitory compartment that reduces the net drug effect with time.

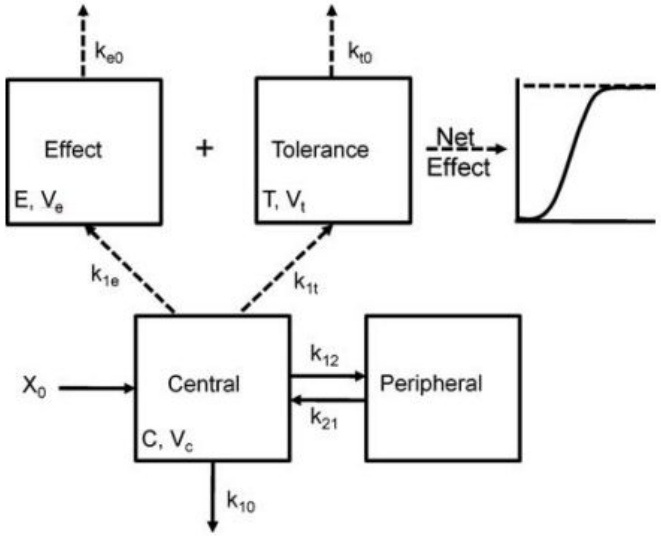
Tolerance + Rebound Model

Tolerance/ rebound model

- Used to describe biological system with homeostatic control, and when perturbed by drug, they tend to return to baseline state (set point)

- An example is the development of tolerance to opioids on the right

- Tolerance models can also be derived from turnover models, where tolerance acts by altering kin or kout or via depletion of a precursor pool when additional compartments are added to turnover models



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Review Article

Themed Issue: Therapeutic Tolerance: Pharmacokinetic-Pharmacodynamic Mechanisms
Guest Editors: Kathleen M. K. Boje and Gary M. Pollack

Opioid Tolerance Development: A Pharmacokinetic/Pharmacodynamic Perspective

Emily O. Dumas[1,2] and Gary M. Pollack[1]

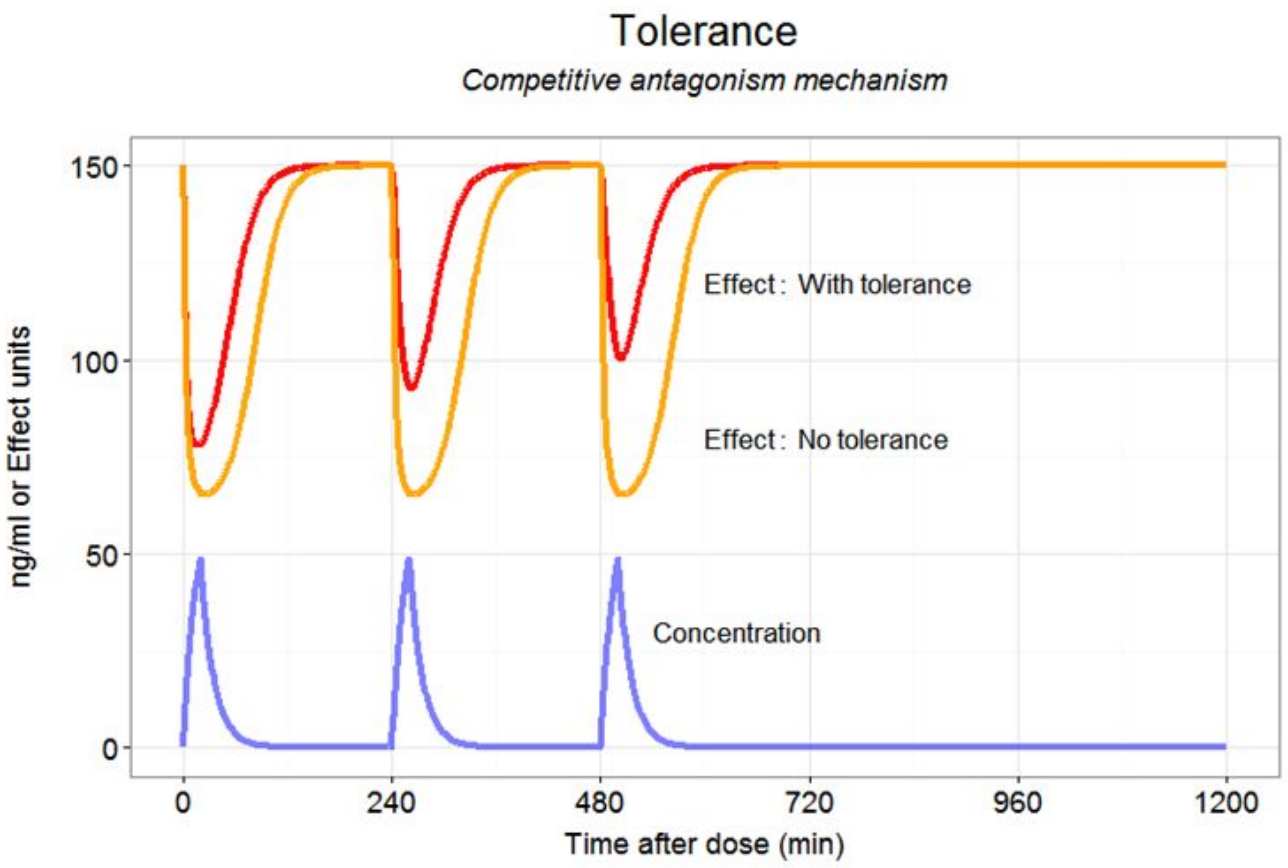
Received 19 February, 2008; accepted 14 July, 2008; published online 7 November 2008

Abstract. The opioids are commonly used to treat acute and severe pain. Long-term opioid administration eventually reaches a dose ceiling that is attributable to the rapid onset of analgesic tolerance coupled with the slow development of tolerance to the untoward side effects of respiratory depression, nausea and decreased gastrointestinal motility. The need for effective-long term analgesia remains. In order to develop new therapeutics and novel strategies for use of current analgesics, the processes that mediate tolerance must be understood. This review highlights potential pharmacokinetic (changes in metabolite production, metabolizing enzyme expression, and transporter function) and pharmacodynamic (receptor type, location and functionality; alterations in signaling pathways and cross-tolerance) aspects of opioid tolerance development, and presents several pharmacodynamic modeling strategies that have been used to characterize time-dependent attenuation of opioid analgesia.

KEY WORDS: opioid; pharmacodynamics; pharmacokinetics; tolerance.

- Scheme depicting the PK-PD model of tolerance following multiple morphine i.v. bolus doses.
- The time course of morphine concentrations following multiple i.v. bolus doses was described by a two-compartment model with a central volume of distribution Vc, distribution between the central and peripheral compartment according to the rate constants k12 and k21, and elimination from the central compartment by the first-order rate constant k10.
- The time course of antinociception was described using an approach derived by Porchet et al. where the first-order rate constants of effect onset, k1e and k1t, link the central compartment to the effect (E) and tolerance (T) compartments of volumes Ve and Vt and, effect offset is governed by the first-order rate constants ke0 and kt0 [Adapted from Ouellet and Pollack]

Detecting PD tolerance in observed data

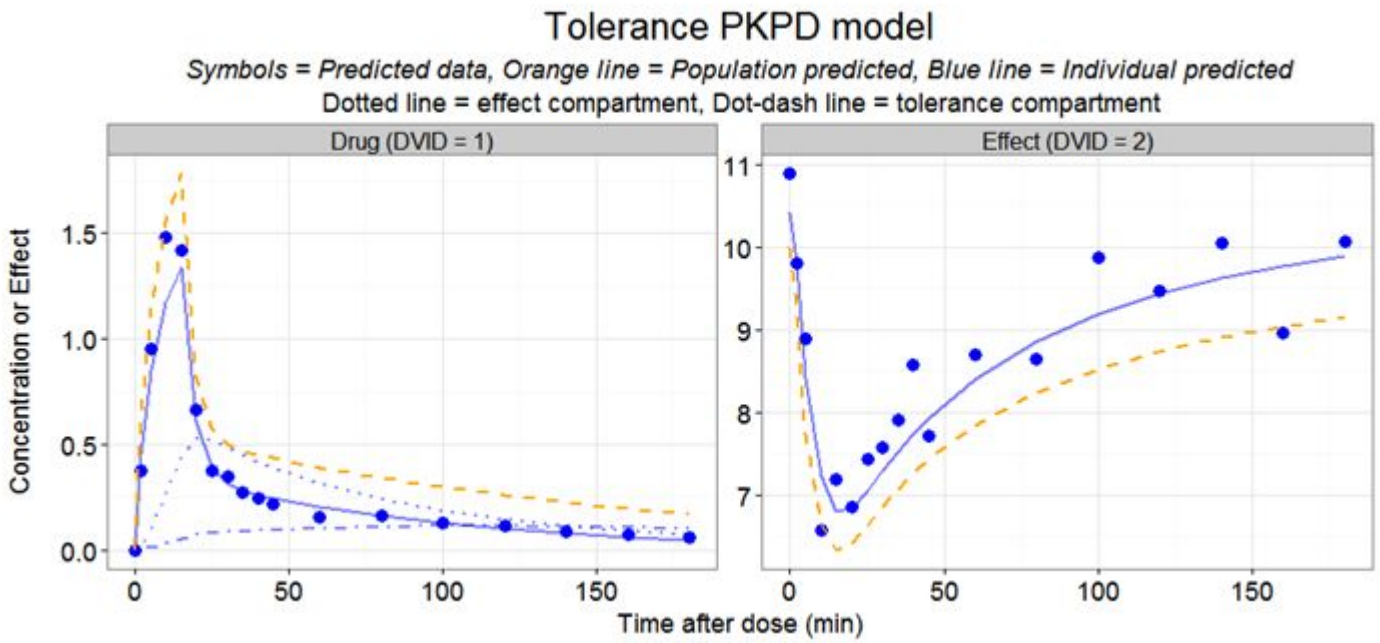


https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1038/psp.2013.71

- Simulation where a hypothetical drug is infused for 20 minutes on three occasions 4 hours apart.
- The resultant plasma concentrations (Cp) are shown in blue. The drug effect has a baseline of 150 units, and the time-course of effect is shown for a PD system with (red) and without (orange) a tolerance mechanism.
- The drug effect was described by an effect compartment (giving effect compartment concentrations, Ceff) and Emax model that decreased effect from baseline (ke0= 0.1, Emax = 90, EC50= 50).
- For the tolerance model, a tolerance compartment (giving tolerance compartment concentrations, Ctol) was used to generate a slower evolving (kt0= 0.001, Imax = 50 , IC50= 5) inhibitory effect that countered the drug effect by a competitive antagonism mechanism, as describe by:
- Effect = Base - (Emax*Ceff)/Ceff + (EC50/IC50)*Ctol + EC50)

Tolerance PKPD model

- 2-compartment PK model with zero order infusion.
- Drug effect is via an effect compartment via an Emax model with proportional decrease from baseline.
- A tolerance compartment with an inhibitory Imax relationship provides the net drug effect via competitive antagonism.



https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1038/psp.2013.71

Example control stream for a tolerance model (1)

NONMEM control stream 5_tolerance.ctl

```
$PROBLEM AN EXAMPLE TOLERANCE MODEL AS DIFFERENTIAL EQUATIONS
;Two compartment pharmacokinetic model with zero order infusion
;Effect compartment with an Emax model with decrease from baseline; Proportional relationship to
baseline
;Tolerance compartment with an inhibitory Imax model and net drug effect via competitive antago-
nism
;units are ug, L and min.  concentration is ug/L = ng/ml
;DVID = 0 for dose, 1 for PK, 2 for PD

$INPUT ID TIME AMT RATE DV DVID MDV

$DATA testdata1.csv IGNORE=C

$SUBROUTINES  ADVAN13 TOL=9

$MODEL
  COMP=(CENTRAL)
  COMP=(PERIPH)
  COMP=(EFFECT)
  COMP=(TOL)

$PK
  ;PK parameters
   CL = THETA(1)*EXP(ETA(1))
   V1 = THETA(2)*EXP(ETA(2))
   Q =  THETA(3)
   V2 = THETA(4)

 ;PD parameters
   EBASE = THETA(5)*EXP(ETA(3))

   KE0   = THETA(6)
   EMAX  = THETA(7)
   EC50  = THETA(8)*EXP(ETA(4))

   KT0   = THETA(9)
   IMX   = THETA(10)  ;Don't use IMAX as a variable - a known bug
   IC50  = THETA(11)
```

```
$DES
  C1      =  A(1)/V1  ;Turn amounts into concentrations
  C2      =  A(2)/V2
  C3      =  A(3)
  C4      =  A(4)

  DADT(1) =  -Q*C1 +Q*C2 -CL*C1  ;Differential equation for central PK compartment
  DADT(2) =   Q*C1 -Q*C2         ;Differential equation for peripheral PK compartment
  DADT(3) =   KE0*(C1 - C3)      ;Differential equation for effect compartment
  DADT(4) =   KT0*(C1 - C4)      ;Differential equation for tolerance compartment


$THETA
 1.5   ; POPCL

 25    ; POPV1
 5     ; POPQ
 150   ; POPV2

 10     ;POPEBASE

 0.04   ;POPKE0
 10     ;POPEMAX
 0.3    ;POPEC50

 0.004  ;POPKT0
 5      ;POPIMX
 0.03    ;POPIC50
```

https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1038/psp.2013.71

Example control stream for a tolerance model (2)

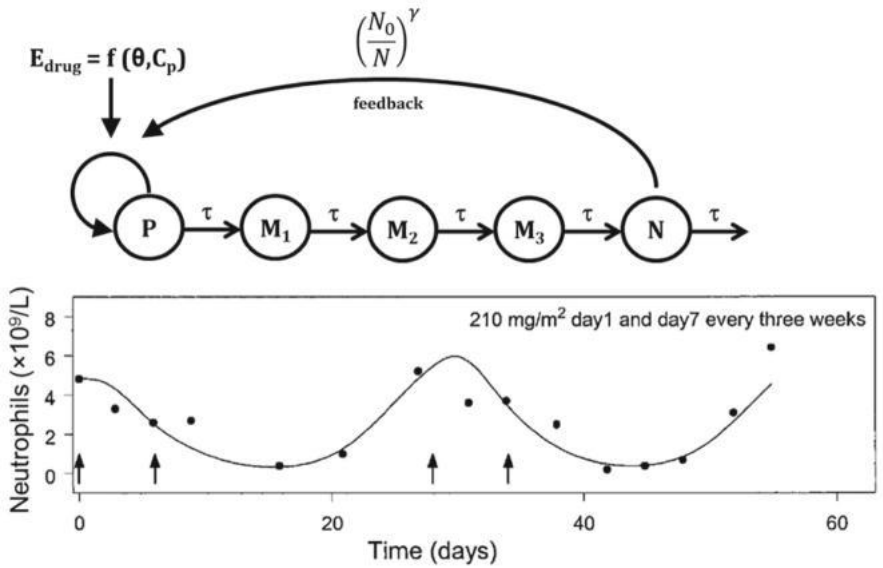
```
$ERROR
 CP=A(1)/V1   ;Plasma concentration needs to be calculated again outside of $DES
 CEFF=A(3)      ;Apparent Effect compartment concentration needs to be calculated again outside
of $DES
 CTOL=A(4)      ;Apparent Tolerance compartment concentration needs to be calculated again out-
side of $DES
 E = EBASE-(EMAX*CEFF)/(CEFF+EC50/IC50*CTOL+EC50) ;Drug effect via competitive antagonism

 IF (DVID.LE.1) THEN
    IPRED = CP
    Y = IPRED*(1+ERR(1))  ;Proportional residual error for drug concentration
 ENDIF

 IF (DVID.EQ.2) THEN
    IPRED = E
    Y = IPRED+ERR(2)      ;Additive residual error for effect
 ENDIF


 SIM = IREP   ;Simulation counter


$SIM (123) ONLYSIM NSUB=1

$TABLE ID TIME AMT CL V1 Q V2 EBASE  KE0 EMAX EC50 KT0 IMX IC50 CP CEFF CTOL E DVID MDV SIM
IPRED NOPRINT ONEHEADER FILE=*.fit
```

https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1038/psp.2013.71

Signal Transduction/Transit Model

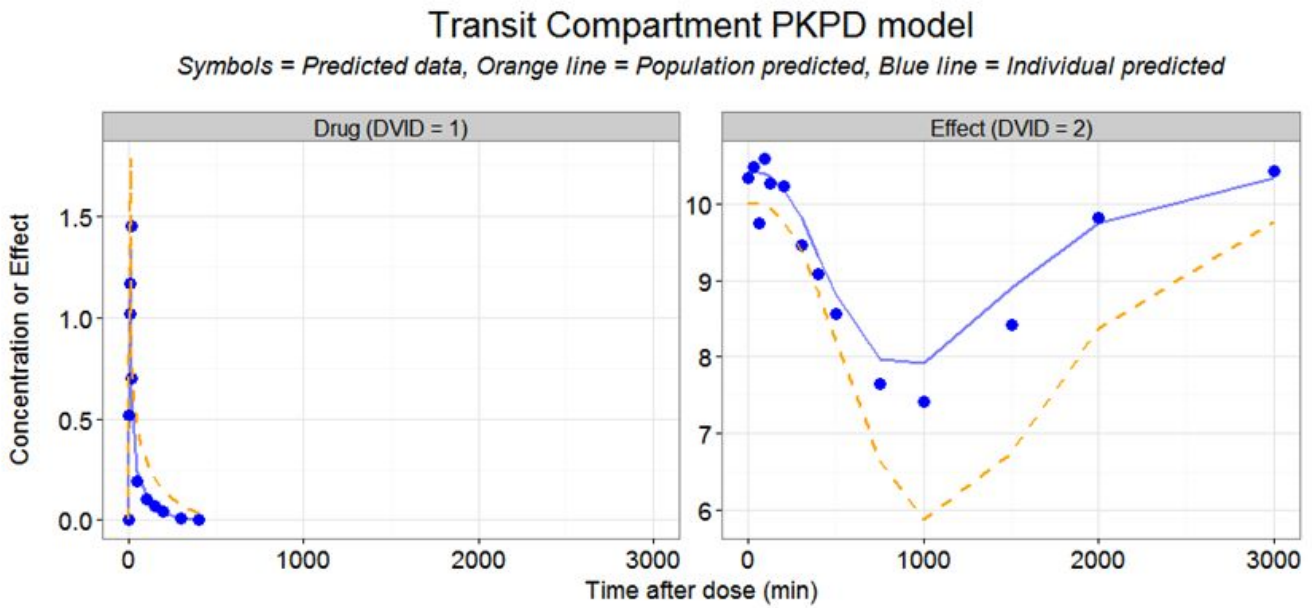
Transit model

- An example is the Friberg model (Module 11, Tutorial 1)
- Neutrophils are formed from progenitor myeloblasts in the bone marrow which undergo maturation through at least five distinct cell populations before becoming neutrophils.
- Antineoplastics affect myelo-blast formation, lowering neutrophil counts only when the decreased production rate has propagated down the matu-ration pathway—often 5–7 days after antineoplastic administration.
- Each distinct cell population can be represented as transit compartment linked in series.
- While it may be feasible to define the kin and kout rate constants for each transit compartment, in practice, only one step is rate limiting, which is represented as a transit compartment rate constant (ktr), which is the same for each compartment
- The greater the number of transit compartments and the slower ktr, the greater the delay between drug administration and first observable effect and the time of the peak drug effect. Transit compartment models are most easily represented as differential equations.



Transit model

- This model is a two compartment pharmacokinetic model with zero order infusion. Drug effect is via E_{max} relationship acting on K_{TR} for the first transit compartment of a three transit compartment model. Drug effect is represented by the third transit compartment.



https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1038/psp.2013.71

Example control stream for a transit model

NONMEM control stream 4_transit.ctl

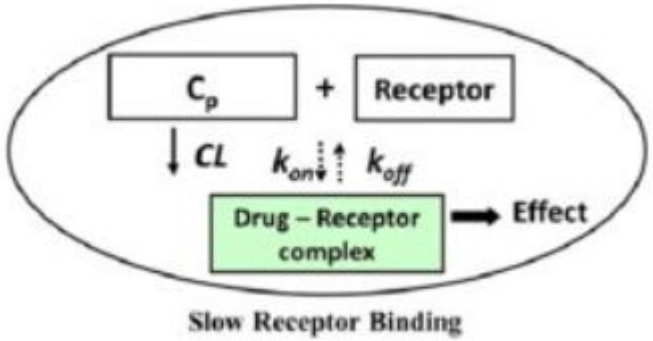
```
$PROBLEM AN EXAMPLE TRANSIT COMPARTMENT PD MODEL AS DIFFERENTIAL EQUATIONS
;Two compartment pharmacokinetic model with zero order infusion
;Emax model acting on KTR
;units are ug, L and min.  concentration is ug/L = ng/ml
;DVID = 0 for dose, 1 for PK, 2 for PD

$INPUT ID TIME AMT RATE DV DVID MDV

$DATA testdata2.csv IGNORE=C

$SUBROUTINES  ADVAN13 TOL=9

$MODEL
  COMP=(CENTRAL)
  COMP=(PERIPH)
  COMP=(TRANSIT1)
  COMP=(TRANSIT2)
  COMP=(TRANSIT3)

$PK
 ;PK parameters
  CL = THETA(1)*EXP(ETA(1))
  V1 = THETA(2)*EXP(ETA(2))
  Q =  THETA(3)
  V2 = THETA(4)

;PD parameters
  EMAX  = 1    ;Emax set to 1 so that maximal drug effect reduces KTR to zero
  EC50  = THETA(5)
  EBASE = THETA(6)*EXP(ETA(3))    ;Baseline
  MTT =  THETA(7)    ;Transit compartment rate constant

  ;Calculate turnover compartment rate constants
  KTR = 3/MTT          ;Baseline KTR
  A_0(3)= 1            ;Set transit compartment1 initial value
  A_0(4)= 1            ;Set transit compartment2 initial value
  A_0(5)= 1            ;Set transit compartment3 initial value

$DES
  C1      =  A(1)/V1  ;Turn amount into concentrations - plasma concentration
  C2      =  A(2)/V2  ;Turn amount into concentrations - peripheral compartment concentration

  DADT(1) =  -Q*C1 +Q*C2 -CL*C1  ;Differential equation for central PK compartment
  DADT(2) =   Q*C1 -Q*C2         ;Differential equation for peripheral PK compartment

  EDRUG   = EMAX*C1/(EC50+C1)                ;Plasma concentration modifies first transit com-
partment rate constant
  ;Baseline value of transit compartments is 1 - used to scale Ebase
  DADT(3) = KTR*(1-EDRUG) - KTR*A(3)         ;Differential equation for transit compartment1
  DADT(4) = KTR*A(3) - KTR*A(4)              ;Differential equation for transit compartment2
  DADT(5) = KTR*A(4) - KTR*A(5)              ;Differential equation for transit compartment3

$THETA
 1.5   ; POPCL
 25    ; POPV1
 5     ; POPQ
 150   ; POPV2

 0.01    ;POPEC50
 10     ;POPEBASE
 1000    ;POPMTT

$ERROR
 CP=A(1)/V1          ;Plasma concentration needs to be calculated again outside of $DES
 E=A(5)*EBASE        ;Last transit compartment amount reflects drug effect

 IF (DVID.LE.1) THEN
    IPRED = CP
    Y = IPRED*(1+ERR(1))  ;Proportional residual error for drug concentration
 ENDIF

 IF (DVID.EQ.2) THEN
    IPRED = E
    Y = IPRED+ERR(2)  ;Additive residual error for effect
 ENDIF

 SIM = IREP   ;Simulation counter


$SIM (123) ONLYSIM NSUB=1

$TABLE ID TIME AMT CL V1 Q V2 EDRUG KTR EMAX EBASE EC50 CP E DVID MDV SIM IPRED NOPRINT ONE-
HEADER FILE=*.fit
```

https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1038/psp.2013.71

Receptor Binding Model

Receptor Binding Model

- Receptors: a ligand binds and alters the biochemical activity (note that a ligand may do this by inhibiting the effects of endogenous substances from stimulating the receptor)
- Any macromolecular tissue site where a drug may bind can be considered a binding site and if this site has some functional activity then it is a receptor
- Drug response is a result of chemical interactions between a drug and a binding site
- The drug concentration at the site of the receptor determines the intensity of a drug's effect

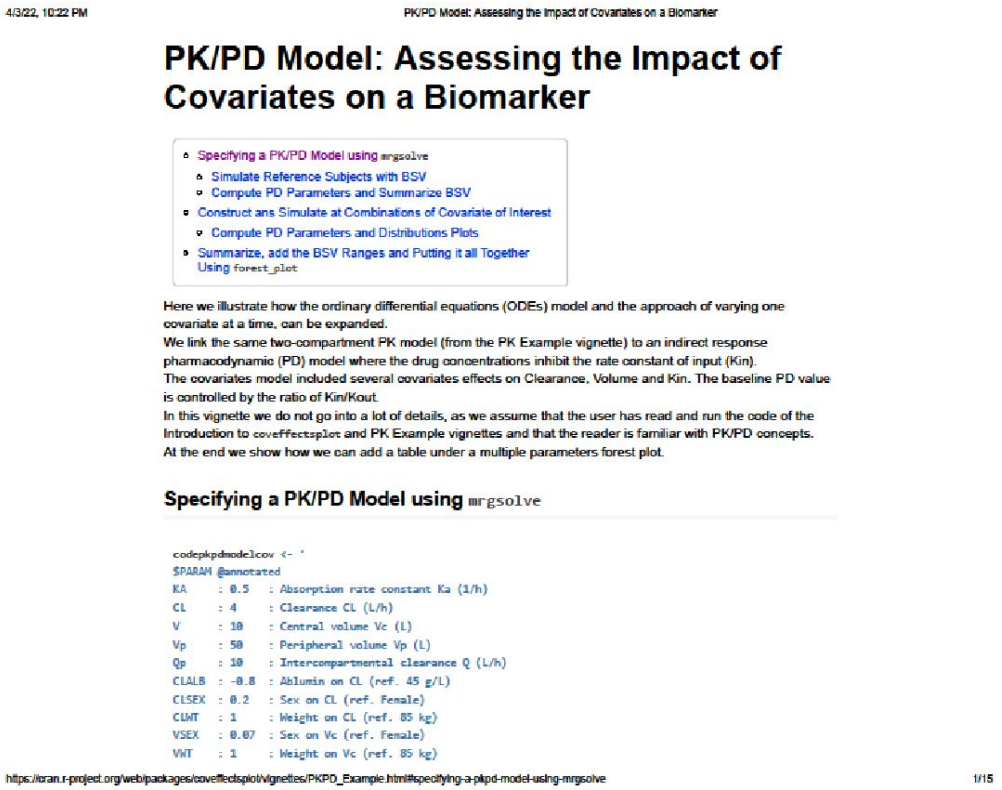


Slow Receptor Binding

https://pharmrev.aspetjournals.org/content/72/2/414.long

PK/PD Model: Assessing the Impact of Covariates on a Biomarker

https://cran.r-project.org/web/packages/coveffectsplot/vignettes/PKPD_Example.html#specifying-a-pkpd-model-using-mrgsolve



4/3/22, 10:22 PM PK/PD Model: Assessing the Impact of Covariates on a Biomarker

PK/PD Model: Assessing the Impact of Covariates on a Biomarker

- Specifying a PK/PD Model using `mrgsolve`
  - Simulate Reference Subjects with BSV
  - Compute PD Parameters and Summarize BSV
- Construct ans Simulate at Combinations of Covariate of Interest
  - Compute PD Parameters and Distributions Plots
- Summarize, add the BSV Ranges and Putting it all Together Using `forest_plot`

Here we illustrate how the ordinary differential equations (ODEs) model and the approach of varying one covariate at a time, can be expanded.
We link the same two-compartment PK model (from the PK Example vignette) to an indirect response pharmacodynamic (PD) model where the drug concentrations inhibit the rate constant of input (Kin).
The covariates model included several covariates effects on Clearance, Volume and Kin. The baseline PD value is controlled by the ratio of Kin/Kout.
In this vignette we do not go into a lot of details, as we assume that the user has read and run the code of the Introduction to `coveffectsplot` and PK Example vignettes and that the reader is familiar with PK/PD concepts.
At the end we show how we can add a table under a multiple parameters forest plot.

Specifying a PK/PD Model using `mrgsolve`

```
codepkpdmodelcov <- '
$PARAM @annotated
KA    : 0.5   : Absorption rate constant Ka (1/h)
CL    : 4     : Clearance CL (L/h)
V     : 10    : Central volume Vc (L)
Vp    : 50    : Peripheral volume Vp (L)
Q     : 10    : Intercompartmental clearance Q (L/h)
CLALB : -0.8  : Ablumin on CL (ref. 45 g/L)
CLSEX : 0.2   : Sex on CL (ref. Female)
CLWT  : 1     : Weight on CL (ref. 85 kg)
VSEX  : 0.07  : Sex on Vc (ref. Female)
VWT   : 1     : Weight on Vc (ref. 85 kg)
```

https://cran.r-project.org/web/packages/coveffectsplot/vignettes/PKPD_Example.html#specifying-a-pkpd-model-using-mrgsolve 1/15

Double click to open

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Questions?

Additional resources – Textbooks

- Introduction to pharmacokinetics and pharmacodynamics, Tozer and Rowland
- Pharmacokinetic and Pharmacodynamics data analysis, Gabrielson and Weiner

Additional Resources – Journal Articles

- Derendorf H, Meibohm B. Modeling of pharmacokinetic/pharmacodynamic (PK/PD) relationships: concepts and perspectives. Pharm Res. 1999;16(2):176-185. doi:10.1023/a:1011907920641
- Sharma A, Ebling WF, Jusko WJ. Precursor-dependent indirect pharmacodynamic response model for tolerance and rebound phenomena. J Pharm Sci. 1998;87(12):1577-1584. doi:10.1021/js980171q
- Gabrielsson J, Hjorth S. Pattern Recognition in Pharmacodynamic Data Analysis. AAPS J. 2016;18(1):64-91. doi:10.1208/s12248-015-9842-5
- Mould, D., Walz, A.-C., Lave, T., Gibbs, J. and Frame, B. (2015), Developing Exposure/Response Models for Anticancer Drug Treatment: Special Considerations. CPT Pharmacometrics Syst. Pharmacol., 4: 12-27. https://doi.org/10.1002/psp4.16

Additional resources – links

- FDA Guidance. Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications (May 2003). https://www.fda.gov/media/71277/download
- MI210: Essentials of Population PK-PD Modeling and Simulation (https://www.metrumrg.com/course/mi210-essentials-population-pk-pd-modeling-simulation/)
- MI212: Advanced Topics in Population PK-PD Modeling & Simulation (https://www.metrumrg.com/course/mi212-advanced-topics-population-pk-pd-modeling-simulation/)
- https://www.page-meeting.org/pdf_assets/2573-time-to-event-tutorial.pdf

Finally…

- If you have any question, please contact Kemi and Amy ☺️ (Anna is away…)
- Thanks to Rik, Colin, Rita, Anna
- Thanks to Nathan for his slides

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