



PKPD Models

ACCP Pre-Meeting Workshop

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Direct and Effect-Compartment Models

Joga Gobburu PhD
Pharmacometrics, FDA

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Topics

- Objectives of Modeling
- Direct Effect Models
- Effect Compartment Models
- Examples – Subsequent session

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Modeling Goals - Yates

- Conceptualize the system
- Codify current facts
- Test competing hypotheses
- Identify controlling factors
- Estimate inaccessible system variables
- Predict system response under new conditions

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Definitions

- Exposure
 - **Measure of drug amount at a particular site**
e.g.: Plasma, CSF concentrations
- Response
 - **Biological measure**
e.g.: Blood glucose, BP
- Effect
 - **Change in biological measure from reference**
e.g.: change in BP from baseline

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Definitions

- Phrases – “PKPD, Exposure-response, concentration-effect” are used interchangeably
- **Misconception** – PD refers to effects on biomarker versus response refers to surrogates or clinical outcomes
- PD could be a biomarker, surrogate or clinical outcome (e.g.: death).

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Types of Responses

- **Continuous**
 - e.g.: Blood glucose, BP
- **Non-continuous (Discrete)**
 - **Categorical**
 - Binary – Had nausea or not?
 - Ordinal – Was the nausea mild or severe?
 - **Events**
 - Counts – How many seizures in 28 days?
 - Survival type – Time to dialysis or death?

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Types of Responses

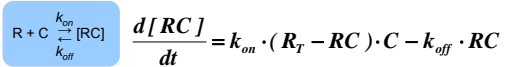
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Occupational Receptor Theory



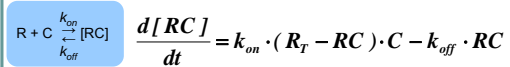
R_T = Maximum Receptor Density
 RC = Receptor-Drug Complex
 C = Drug Concentration
 k_{on} = RC Association Rate Constant (second-order)
 k_{off} = RC Dissociation Rate Constant (first-order)

Ariens EJ. Affinity and intrinsic activity in the theory of competitive inhibition. Arch. Int. Pharmacodyn. 99: 32-49 (1954)

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Occupational Receptor Theory



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Variants of Emax model

$$R(t) = R(0) + E$$

Additive effects model
Drug effects are independent of the baseline response

$$E = \frac{E_{max} \cdot Cp}{EC_{50} + Cp}$$

$$R(t) = R(0) \cdot (1 + E)$$

Proportional effects model
Drug effects are dependent on the baseline response

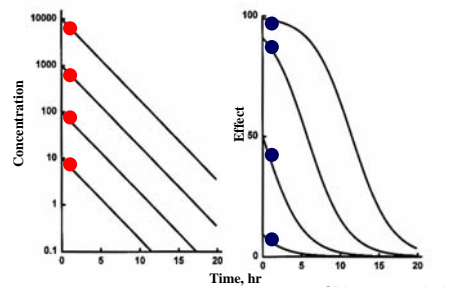
$$E = \frac{S_{max} \cdot Cp}{SC_{50} + Cp} \quad E = -\frac{I_{max} \cdot Cp}{IC_{50} + Cp}$$

$R(0)$ = Response at baseline
 $R(t)$ = Response at time 't'
 S_{max} = Maximal stimulation
 I_{max} = Maximal inhibition
 IC_{50} = Cp required for $I_{max}/2$
 SC_{50} = Cp required for $S_{max}/2$

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Steady-State PD

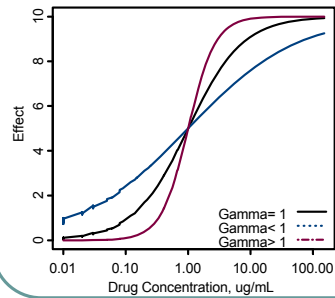


Slide courtesy: Jusko

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Steady-State PD (● versus ●)



Gamma determines the steepness of the concentration-effect relationship

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Hill Coefficient: Implications

- Useful to determine dose titration, to effect or exposure, strategies
- Useful to appreciate the influence of non-compliance
 - High coefficients: Pronounced influence of non-compliance
 - Low coefficients: More 'pardoning' to non-compliance

Levy G. What are narrow therapeutic index drugs? *Clin Pharmacol Ther.* 1998 May;63(5):501-5.

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Non Steady-State PD

- Development of sophisticated tools allowed estimation of the time-course of effect
 - Better computers
 - Nonlinear regression algorithms
 - Novel models to "link" exposure-response

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Non-SS versus SS Models

Feature	Non Steady-State PD	Steady-State PD
Time course description	Yes	No
Dose selection	Yes	Yes
Regimen selection	Yes	No

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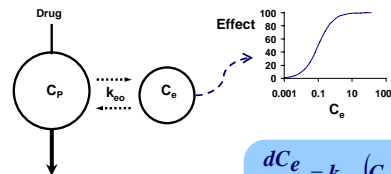
Lewis Sheiner



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Effect Compartment Model



C_p = Plasma drug concentration
 k_{eo} = equilibration rate constant

$$\frac{dC_e}{dt} = k_{eo}(C_p - C_e)$$

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

Segre, *J Pharmacol* (1968)
 Sheiner et. al., *CPT* (1979)

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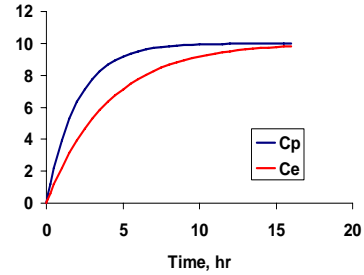
Effect Compartment Model

- Delay reflects time needed to reach another PK compartment
 - Also referred to as 'distributional' delay
- Similar to a linear PK model, T_{max} in effect compartment is dose-independent.

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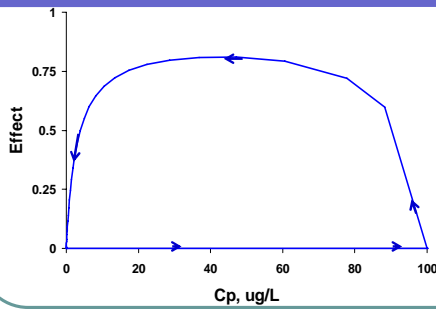
Concentration-Effect Profiles



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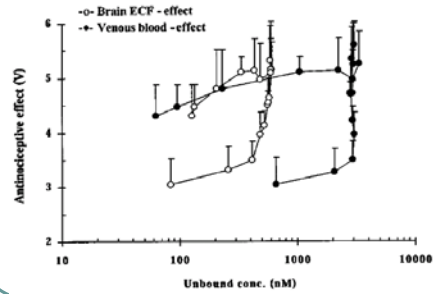
Hysteresis (anti-clockwise)



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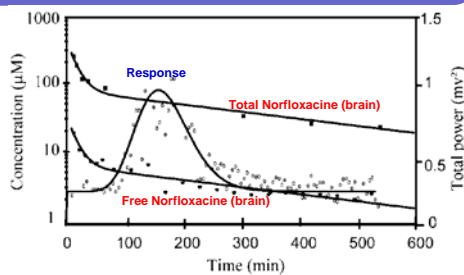
Hysteresis: Morphine analog for nociceptive pain relief



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Norfloxacin PKPD



Chenel M et al. Br J Pharmacol. 2004 May;142(2):323-30.

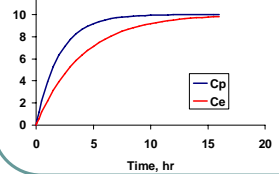
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Simplified Effect Compartment Model

- Frequently only steady-state sparse PK data are available from trials

$$C_{e,ss} = C_{p,ss} \cdot (1 - e^{-k_{e0}t})$$



Holford NH, Peace KE. Proc Natl Acad Sci U.S.A. 1992 Dec 1;89(23):11471-5.

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Interpretation of Ke0

Table 2. Full data set parameter estimates

Parameter class	Parameter	Estimate	SE	Population CV, %	SE CV
Disease	ξ_1 units	28.7	0.44	37.7	7.8
	α units/year	6.17	1.27	208	141
Pharmacodynamic	β_1 units/80	-2.99	0.67	126	74
	β_2 units	-1.42	0.20	128	
	Delay* days/80	177.6	41.7		
Pharmacokinetic	$t_{1/2,plasma}$ days	20.9	6.0		
	$t_{1/2,eff}$ days	61.0	28.6		
	$t_{1/2,met}$ days	1.58	0.56		
Scale	$t_{1/2,met}$ day	13.5	3.4		
	PKA	1.08	0.03		
	FF _{pl}	1.76	0.25		
	FF _{met,pl}	2.78	1.09		
Error	SD ADASC	3.14	0.08		

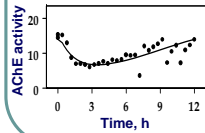
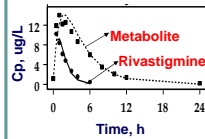
A PK delay of 21 and 61 days. What does that really reflect?

Holford NH, Peace KE. *Proc Natl Acad Sci U S A*. 1992 Dec 1;89(23):11471-5.

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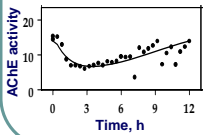
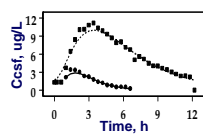
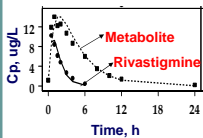
How to Model AChE Activity?



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How to Model AChE Activity?



AChE activity is determined by an ex-vivo assay, in this case using Ccsf.

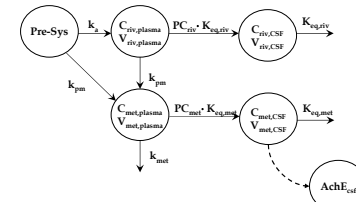
Enzyme activity is a direct effect

Gobburu JV et al. *J Clin Pharmacol*. 2001 Oct;41(10):1082-90.

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Ccsf Modeled Using Modified Effect Compartment Approach



$$\frac{d(C_{riv,CSF})}{dt} = k_{eq,riv} \cdot (PC_{riv} \cdot C_{riv,plasma} - C_{riv,CSF})$$

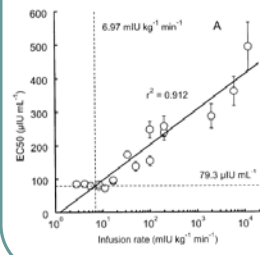
Partition Coefficient

Gobburu JV et al. *J Clin Pharmacol*. 2001 Oct;41(10):1082-90.

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Insulin PD using link model



Authors employed a effect compartment model to describe the delay between insulin and glucose effects.

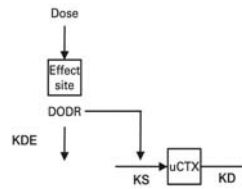
Selection of the appropriate "link" model is not a statistical issue – it should be driven by mechanism

Miyazaki M et al. *J Pharm Pharmacol*. 2001 Sep;53(9):1235-46.

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KPD Model: Does not Use PK



where:
Dose = ibandronate dose
DODR = dose-driving rate
KDE = equilibration rate constant
uCTX = urinary CTX
KS = uCTX formation rate
KD = uCTX degradation rate

Do not ignore PK if available and use caution to extrapolate using KPD model

Pillai G et al. *Br J Clin Pharmacol*. 2004 Dec;58(6):618-31.

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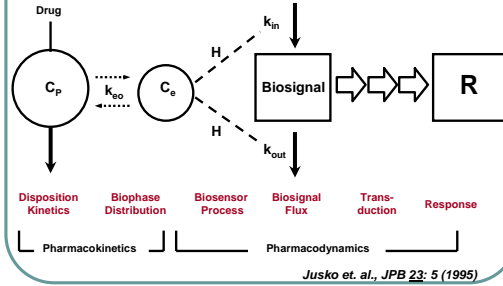
Topics

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Conceptual Framework: PKPD Model



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References

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- Jusko WJ, Ko HC. Physiologic indirect response models characterize diverse types of pharmacodynamic effects. *Clin Pharmacol Ther.* 1994 Oct;56(4):406-19.
- Jusko WJ, Ko HC, Edling WF. Convergence of direct and indirect pharmacodynamic response models. *J Pharmacokinet Biopharm.* 1995 Feb;23(1):5-8; discussion 9-10.
- Sharma A, Jusko WJ. Characterization of four basic models of indirect pharmacodynamic responses. *J Pharmacokinet Biopharm.* 1996 Dec;24(6):611-35.
- Gobburu JV, Jusko WJ. Role of dosage regimen in controlling indirect pharmacodynamic responses. *Adv Drug Deliv Rev.* 2001 Mar 1;46(1-3):45-57.

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