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

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

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

Introduction of session

Recap:

- PMx models, including pharmacokinetics (PK), pharmacodynamics (PD), and exposure-response (E-R) models support nonclinical and clinical design, and accelerate drug discovery and development

- Nonlinear mixed-effects (NLME) PK-PD and E-R models allow utilization of rich and spares data from individuals

- Source of variability: Between subject variability (BSV) can be account by demographics (e.g. age, sex…), laboratory values (e.g. renal function, blood cell count) and disease status (e.g. mutation, stages) - covariate effects (e.g. baseline or time variant)
  - reduces unexplained variability by reducing the confounding effects of these variables and permitting meaningful evaluation of PK, efficacy and safety from sparser data sets on fewer subjects

- PK: drug concentration measured overtime in plasma, blood, urine, tissue (e.g. tumor) , fluid (e.g. CSF)
- Exposure refers to drug levels achieved in the body e.g. AUC, C_{max}, C_{min}, C_{avg}

Pharmacodynamics (PD) definition and other key concepts

- *Pharmacodynamics* can be defined as the study of the biological effects of drugs, the relationship of the effects to drug exposure and the mechanism of drug actions.

- Drugs produce a *therapeutic effect* when there is an adequate exposure at the *target site*. Despite that often the target site is distant from site of application, ***systemic exposure*** is a good substitute of exposure at active site. (e.g. key concepts when considering extrapolation)

- Drugs interact with biological structures or targets at the molecular level to induce an effect. Such targets are commonly proteins, such as *enzymes and receptors*.

- When acting on enzymes, drugs can increase or decrease activity (it, *inducer or inhibitor*).

- When acting on receptors, drugs can increase or decrease the functional response pf receptor (ie, agonist or antagonist). If they reach the maximum possible effect they are called *full agonist or antagonist*, if they do not they are *partial agonist or antagonist*.

Classification of response

Clinically is important to identify whether the response is *desired or adverse*

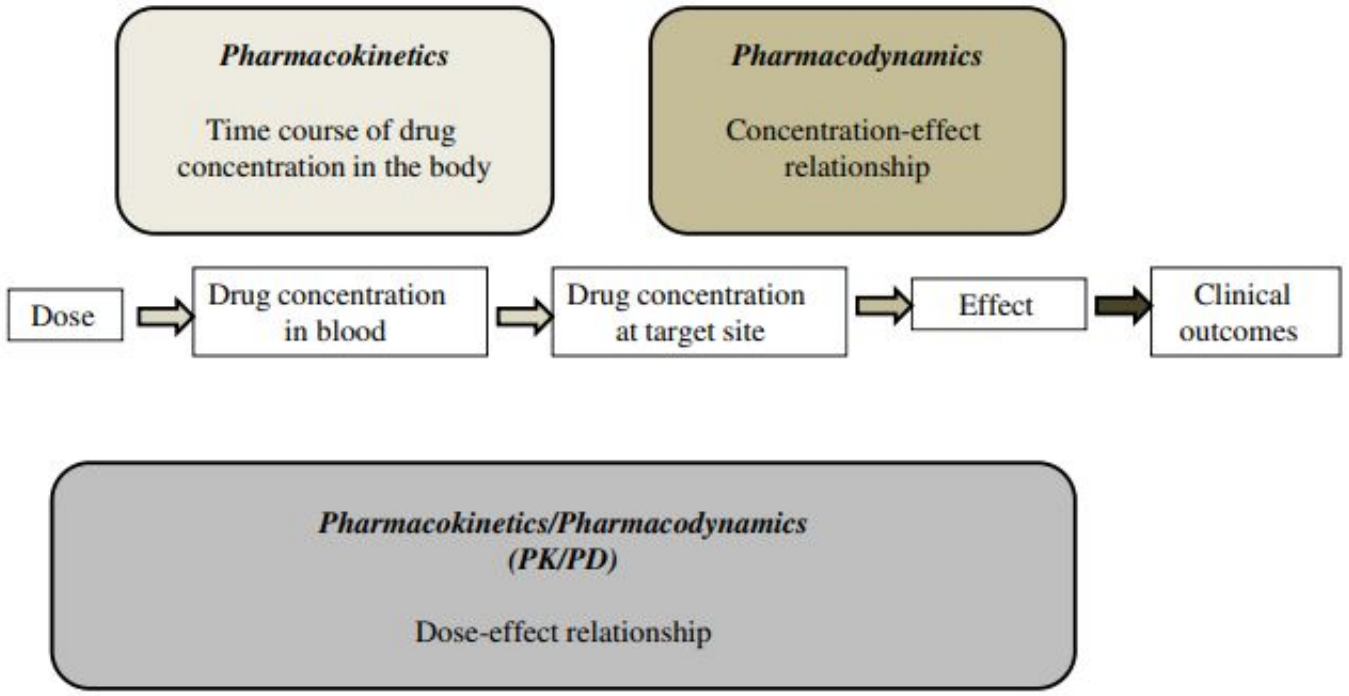
- *Desired: biological effects or efficacy*
- *Adverse: safety related, or opposite to what's desire e.g. expected to reduce temperature, but interest temperature*

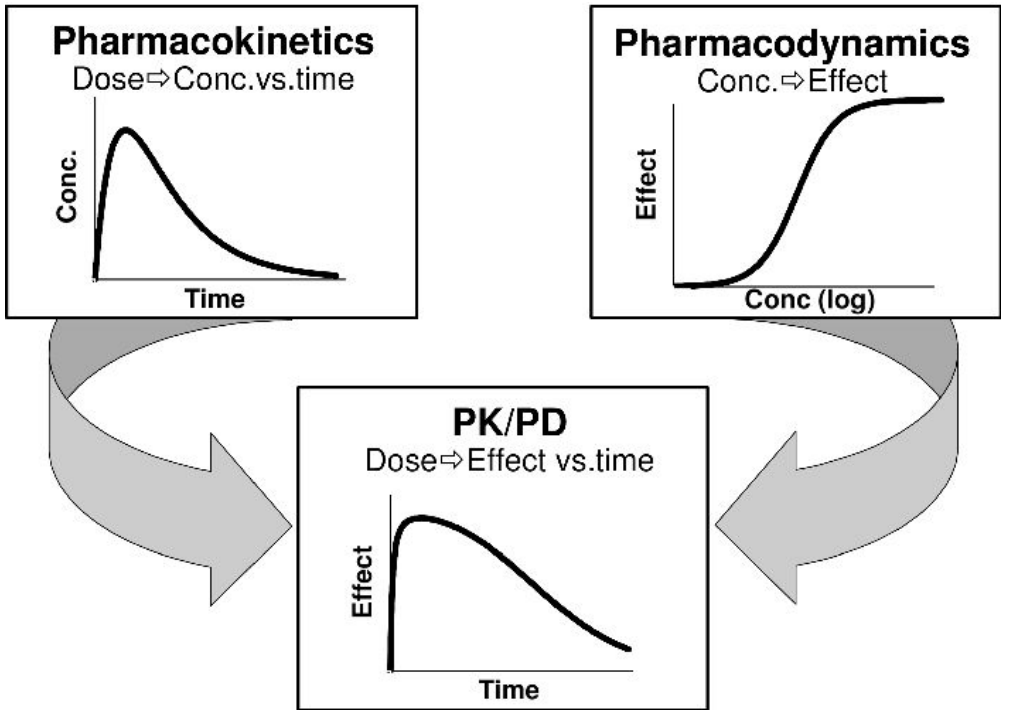
Another classification is whether the *response is a clinical response, a surrogate or a biomarker*

- Clinical responses can be divided in *subjective and objective measures*
- In case the clinical effect does not manifest for many years, a more immediate measure (*surrogate endpoint*) that causally correlates with the clinical effect is sought to guide the therapy
- A *biomarker* is any measurable effect produced by a drug. They can be related to the desired action of the drug or not (safety biomarkers)

- Finally, another classification, *Responses are graded or continuous* (e.g., blood pressure – the intensity of the response varies continuously with the drug concentration in plasma) and *quantal or dichotomus* (e.g., death).
- Analysis of these two responses requires different approaches as the first can be correlated continuously with concentration whereas the latter cannot so the overall response can be evaluated from the *cumulative frequency or likelihood* of the event with concentration.

Combining PK–PD, why?





https://www.criticalcare.theclinics.com/action/showPdf?pii=S0749-0704%2810%2900068-0

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Data: PK,PD, ER and endpoints

What's the input to PKPD or E/R modelling?

Adapted from xx's presentation **xxx**

Types of data, what can we use them for?

	Continuous	Categorical
Definition	Data obtained through measurement using a scale with infinite precision Examples: • Age • Height • Weight • Time • Dose • Plasma concentration • Exposure (C_{max}, C_{min}, AUC) • Biomarker measurements • Laboratory measurements (liver function, creatinine) • Blood cell counts • ECG (QTc, HR,BP)	Data obtained by counting or assigning to a group Examples: • Number of patients • Gender • Scores (e.g. Pain score) • Survival • CTC grades for adverse event • Incidence rate • Smoking status • Depression Scale • Presence of co-med • Fasted/fed • Clinical remission
What is require to modelling?	Data! Assumptions Mathematical equation/function	Assumptions When you model discrete data, you estimate probabilities

- Can be PK, exposure, PD and response
- For dependent variable and covariates
- On subject level data and aggregate (summary level data) → MBMA- model based meta-analysis

Oncology: what can we model as PD and efficacy?

e.g. Solid tumor such breast cancer, NSCLC, bowel cancer etc

- Biomarker → surrogate of inhibition of a pathway: blood or tissue/hair follicle e.g. pAKT
- Tumor dimension 2D or 3D (RECIST: target and non target lesion)
- Response rate: Complete response, partial response, stable disease and progressive disease:

A standard way to measure how well a cancer patient responds to treatment. It is based on whether tumors shrink, stay the same, or get bigger. To use RECIST, there must be at least one tumor that can be measured on x-rays, CT scans, or MRI scans. The types of response a patient can have are a complete response (CR), a partial response (PR), progressive disease (PD), and stable disease (SD). Also called Response Evaluation Criteria In Solid Tumors.

- Progression free survival (PFS), Overall survival (OS)

https://www.frontiersin.org/articles/10.3389/fonc.2021.800547/full

Oncology: TS and response

Both continuous and categorical

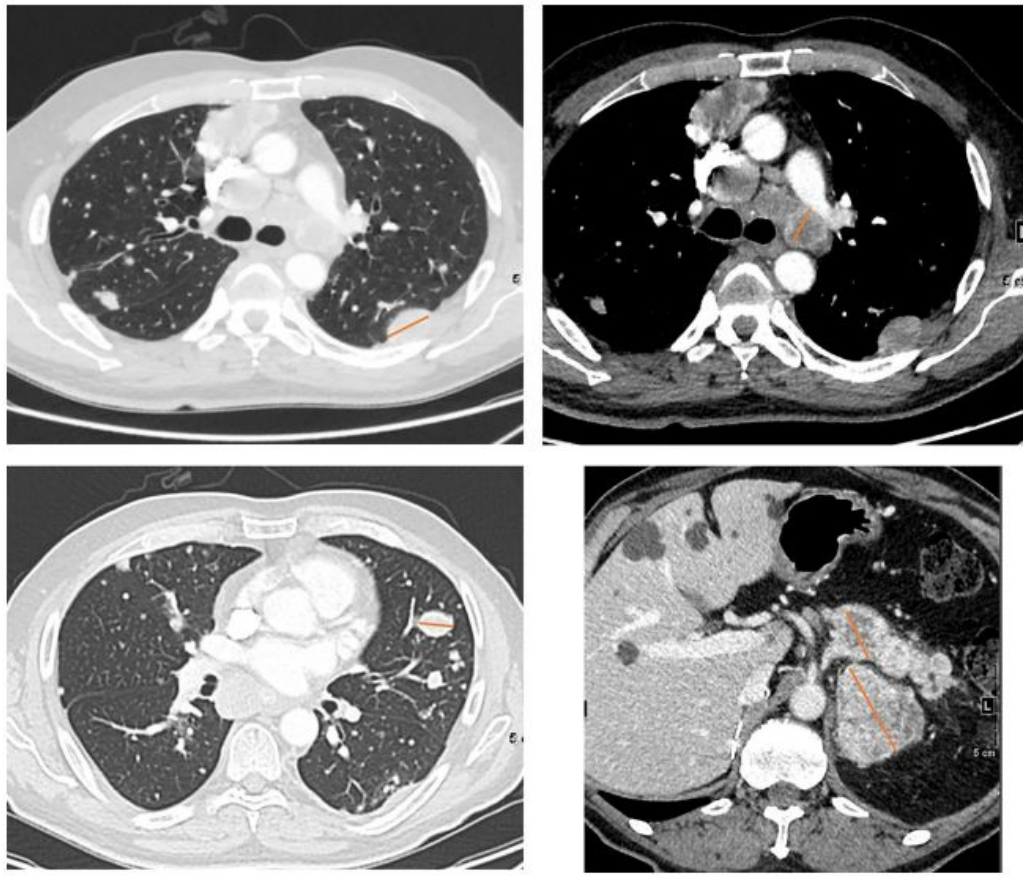

FIGURE 1 | Selecting target lesions in a 58 yo patient with metastatic renal cell carcinoma. Multiple lung, lymph node, pancreatic and adrenal metastases are present. Lymph nodes should be sampled from different locations where possible. Selection of target lesions at baseline from multiple organ sites is important for response evaluation at a patient level.

TABLE 1 | RECIST categories of response.

Overall Response	Target Lesions	Non Target Lesions	New Lesions
Definition	•Lesions with longest diameter ≥ 10 mm and limits that are sufficiently well defined for their measurement to be considered reliable •Lymph nodes: measurement of short axis, target lesion if short-axis measures ≥ 15 mm • Maximum number of selected target lesions 5/patient and 2/organ	•Lesions that are too small (< 10 mm) •Lesions for which measurement is considered unreliable as their limits are difficult to define (bone or leptomeningeal lesions, ascites, pleural or pericardial effusion, lymphangitic carcinomatosis etc.) •Measurable lesions not selected as target lesions •Lymph nodes: measurement of short axis, non-target lesion if 10 mm ≤ short-axis diameter < 15 mm •Levels of tumour markers > normal (if relevant and predefined)	
Complete response (CR)	• Disappearance of all target lesions and all nodes have short axis < 10 mm	• Disappearance of all non-target lesions and normalisation of tumour marker levels	• No
Partial response (PR)	•≥ 30% decrease in the sum of target lesions taking as reference the baseline sum	•No progression	• No
Stable disease (SD)	•Neither response nor progression	• Persistence of one or more non-target lesions and/or tumour marker levels > normal	• No
Progressive disease (PD): response is PD if at least one category of lesions meets progression criteria	•≥ 20% increase in the sum of target lesions taking as reference the smallest sum measured during follow-up (nadir) and ≥ 5 mm in absolute value	• 'Unequivocal' progression (assessed qualitatively) in lesion size (an increase in size of a single lesion is not sufficient)	• Yes [appearance of new unequivocally metastatic lesion(s)]

Oncology: PFS and OS

Tutorial 3

- Progression-free survival (PFS), the time from treatment initiation until disease progression or worsening, may be used as a direct or surrogate measure of clinical benefit for drug approvals, depending on the disease and response observed
- Overall survival (OS), the duration of patient survival from the time of treatment initiation, is a universally-accepted direct measure of clinical benefit.

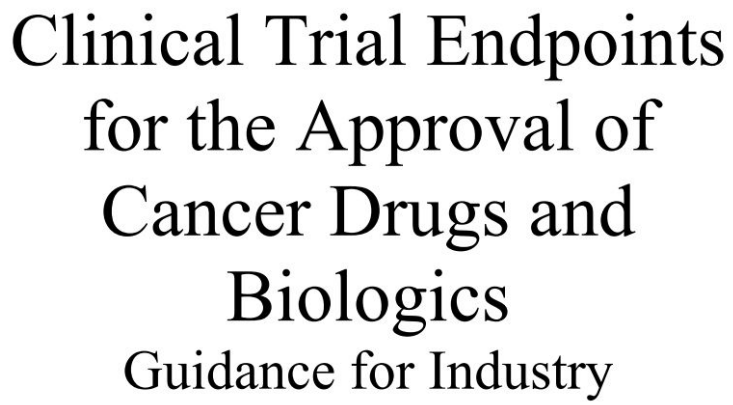

Table 1. A Comparison of Important Cancer Approval Endpoints

As noted in the table, several oncology endpoints can serve different purposes (i.e., clinical endpoint that represents clinical benefit for traditional approval, surrogate endpoint to support traditional approval, surrogate endpoint to support accelerated approval) based on the specific context of use. The determination is based on the specific diseases and is highly dependent upon factors such as effect size, effect duration, depth of response (e.g., number of CRs), available therapy, disease setting, location of disease, the clinical consequences of delaying or preventing disease progression or delaying administration of more toxic therapies, and the risk-benefit relationship. See text for details. See section V regarding recommendations for obtaining FDA feedback on endpoints and protocol design.

Endpoint	Type of Endpoint			Study Design Recommendations		
	Clinical Endpoint	Surrogate Endpoint for TA*	Surrogate Endpoint for AA**	Randomized	Single-Arm	Independent Blinded Review
Overall Survival	X			X		
Symptom Endpoints (patient-reported outcomes)	X			X		
Disease-Free Survival or Event-Free Survival	X	X	X	X		X***
Objective Response Rate	X	X	X	X	X	X
Complete Response	X	X	X	X	X	X
Progression-Free Survival or Time to Progression	X	X	X	X		X***

* TA - Traditional approval, ** AA - Accelerated approval, *** Not always recommended

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6636299/pdf/jcav10p3717.pdf

https://www.fda.gov/media/71195/download

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Oncology PD covariate?

- Demographic e.g. age
- Prior therapy
- Prior disease
- Mutation

Vaccine

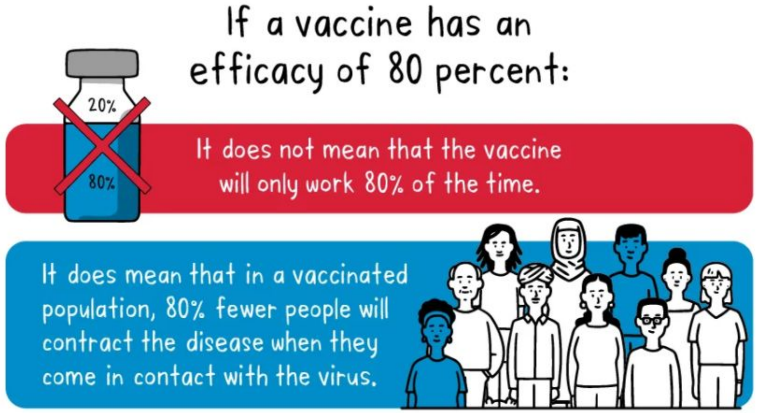
Both continuous and categorical

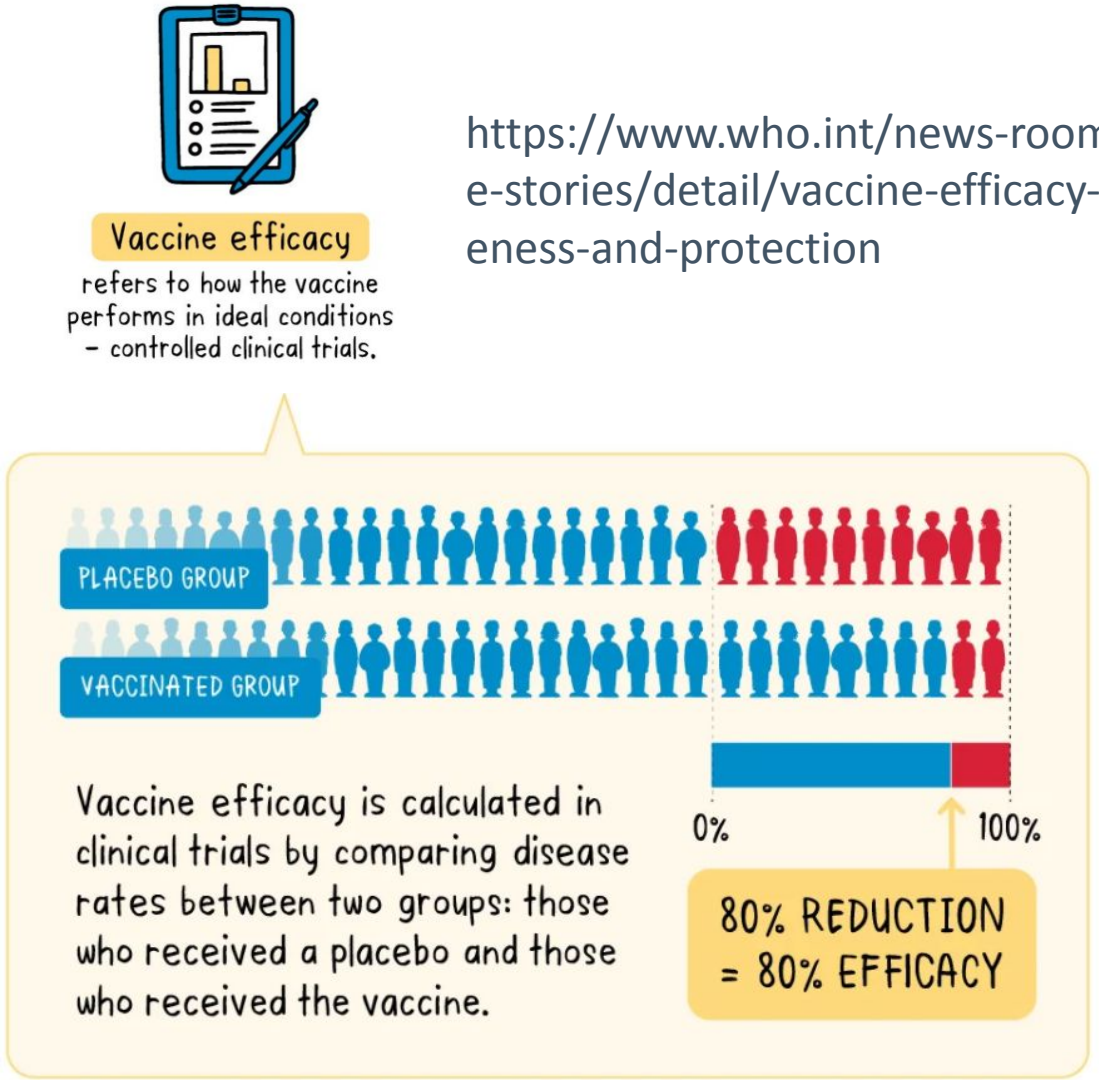
Biomarkers:

- Antibody titers or concentration
- Cytokines e.g. interferon gamma, C-reactive protein
- T-cell CD4, CD8

Efficacy:

- Hospitalization
- Incidence rate
- Case count





https://www.who.int/news-room/featu
e-stories/detail/vaccine-efficacy-effecti
eness-and-protection

Vaccine PD covariate

- Population by age: elderly, pediatric
- Prior disease
- Variant
- Dose, formulation

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

General Types

xxx

What is the goal of (dose) – PKPD and ER modeling?

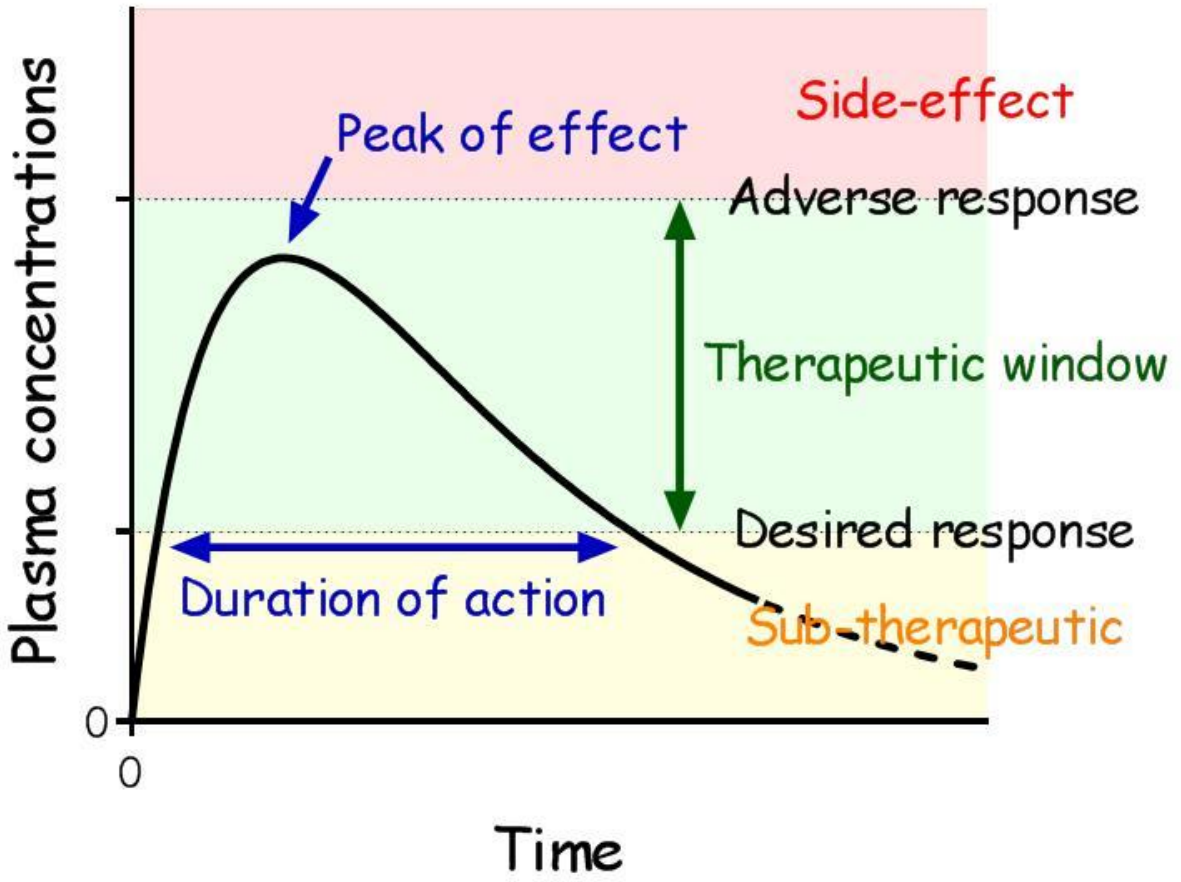
In terms of extend and duration:

1. Understanding what driving (can predict) the biological activities or efficacy?
   - PK concentration?
   - Exposure metrics parameters like C^{max}, AUC and C_{min}
   - Or PK doesn't matter as with overlapping PK across doses, so actually Dose is the drive e.g. olaparib
   - Most often nonclinical data in nonclinical species can already give some hint (if translation is good in the animal model) what might drive the biological activities or efficacy (also what concentration will need)

2. Understand what driving (can predict) safety risk/ adverse event?
   - PK concentration?
   - Exposure metrics parameters like C_{max}, AUC and C_{min}
   - Most often nonclinical data in nonclinical species can already give some hint (if translation is good in the animal model) what might drive the safety (also what concentration will need)
   - Often C_{max} drives e.g. Rash, Blood cell count drop diarrhea in oncology

- Both #1 and #2 are important to balance benefit and risk to identify dose and schedule

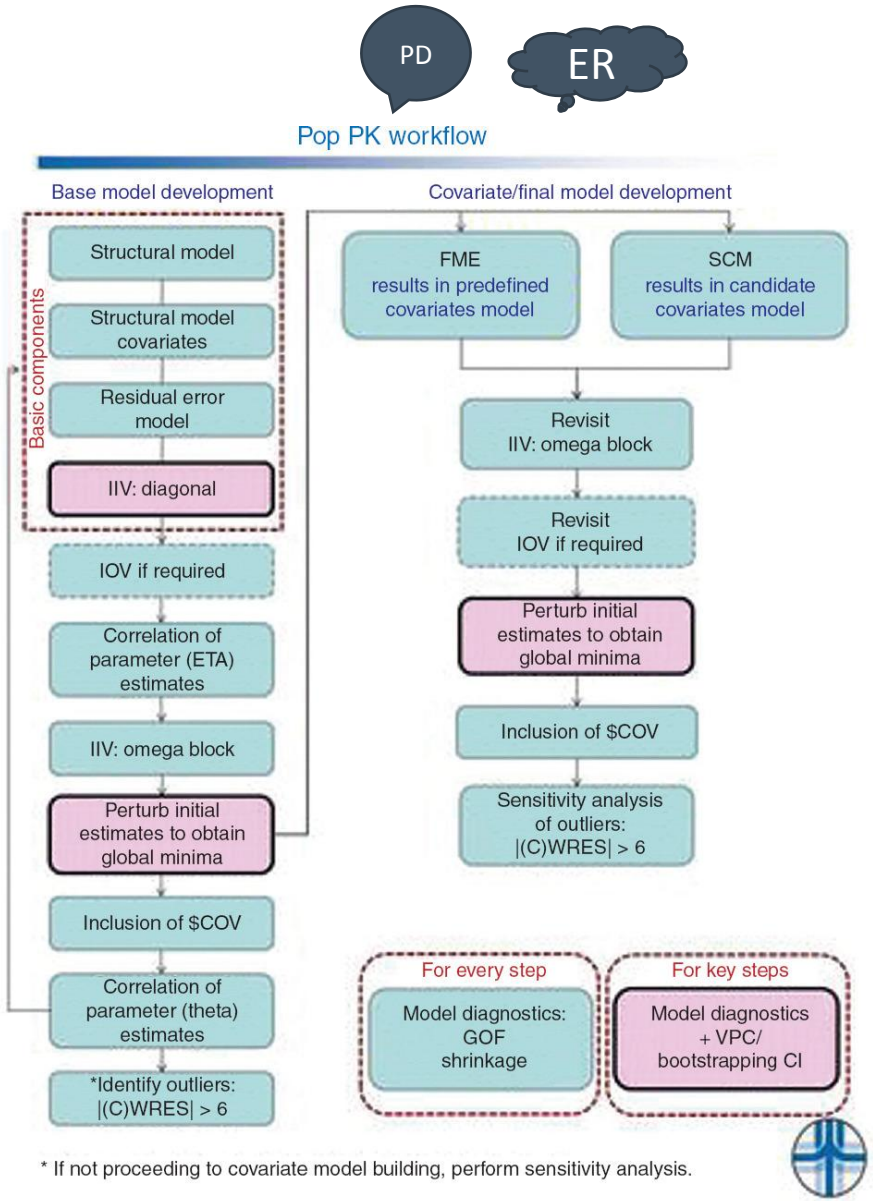
Balancing benefit and risks



PK-PD, ER and Covariates analysis, should follow the same approach as population PK (recap Module 7)

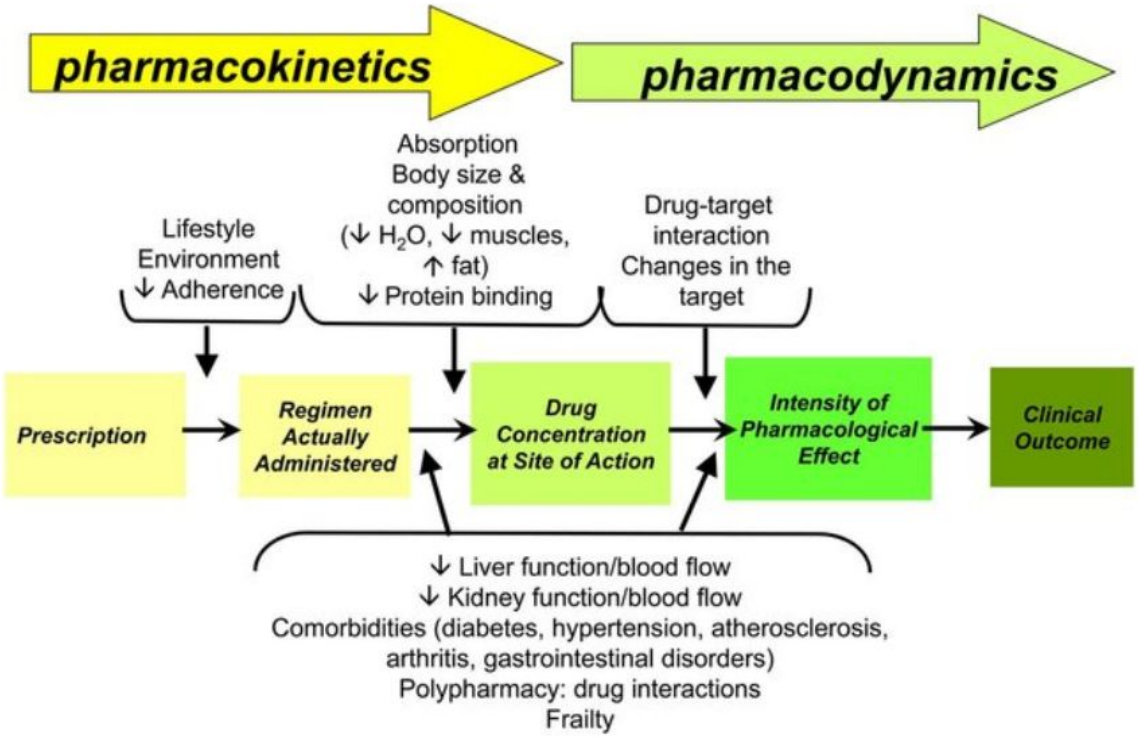
- Covariate analysis not only restricted to population PK modeling
- It should also consider for (dose) - PK-PD, PK-safety and ER analysis
- Base model and covariate model building same as popPK
- Also model evaluation and qualification should also be the same

Model evaluation	Model qualification
The use of various methods to evaluate model performance	The use of various methods to evaluate model performance **for a specific purpose**
How well does the model fit the data and satisfy the model assumptions?	Is my model suitable for the proposed application?
Performed during model building and for key models which are used for further inference	Performed for any model which will be applied (e.g. a final population PK model to be used for simulation)



Example 1: how PKPD impacted considering age

When targeting Elderly



Physiological change	Pharmacological consequence
Gastrointestinal tract	
Slight increase in gastric pH	Slightly decreased absorption (rarely clinically significant)
Delayed gastric emptying	Different bioavailability/solubility of pH-sensitive drugs
Reduced splanchnic blood flow	
Decreased absorption surface	
Decreased mobility	
Body composition and drug distribution	
Increased body fat and/or decreased lean (muscle) body mass	Increased Vd and increased half-life of lipophilic drugs
10–15% decrease in total water	Decreased Vd and increased plasma concentration of hydrophilic drugs
~10% decrease in serum albumin	Increased free fraction in plasma of highly protein-bound acidic drugs
Stable or increased α1-acid glycoprotein	Variable free fraction of basic drugs
Liver	
30–50% decrease in blood flow	First-pass metabolism less effective
20–40% decreased hepatocyte functional mass	Some phase I enzymatic families impaired
Modified architecture	Phase II enzymes usually unaffected
Kidney	
Decreased renal blood flow	Impaired elimination
Decreased glomerular filtration rate	
Changes in tissue histology	

Vd, volume of distribution.

https://pubmed.ncbi.nlm.nih.gov/26163482/

Example 2: how PKPD impacted by therapeutic areas

CNS Drug

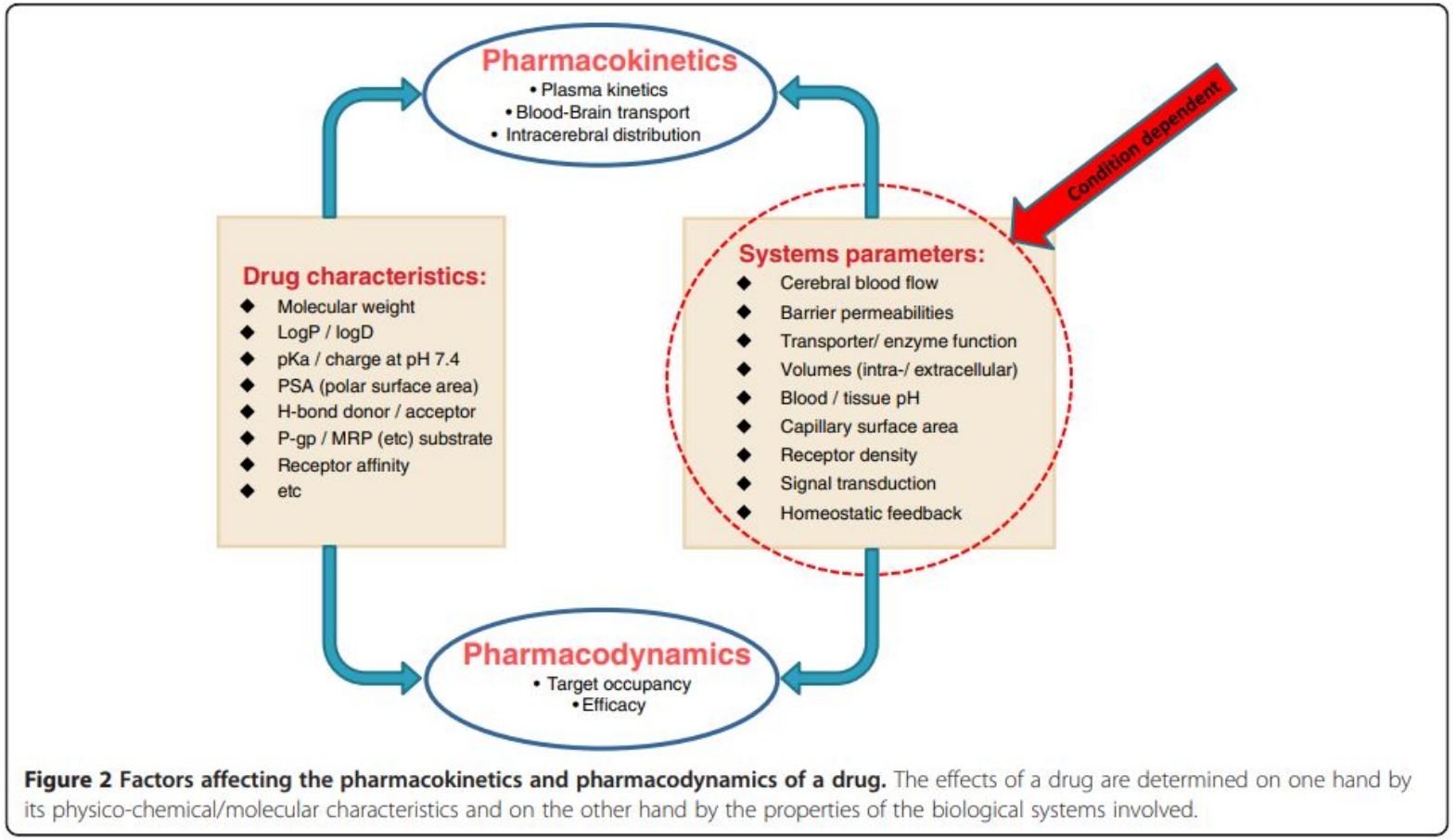


Figure 2 Factors affecting the pharmacokinetics and pharmacodynamics of a drug. The effects of a drug are determined on one hand by its physico-chemical/molecular characteristics and on the other hand by the properties of the biological systems involved.

https://fluidsbarrierscns.biomedcentral.com/articles/10.1186/2045-8118-10-12

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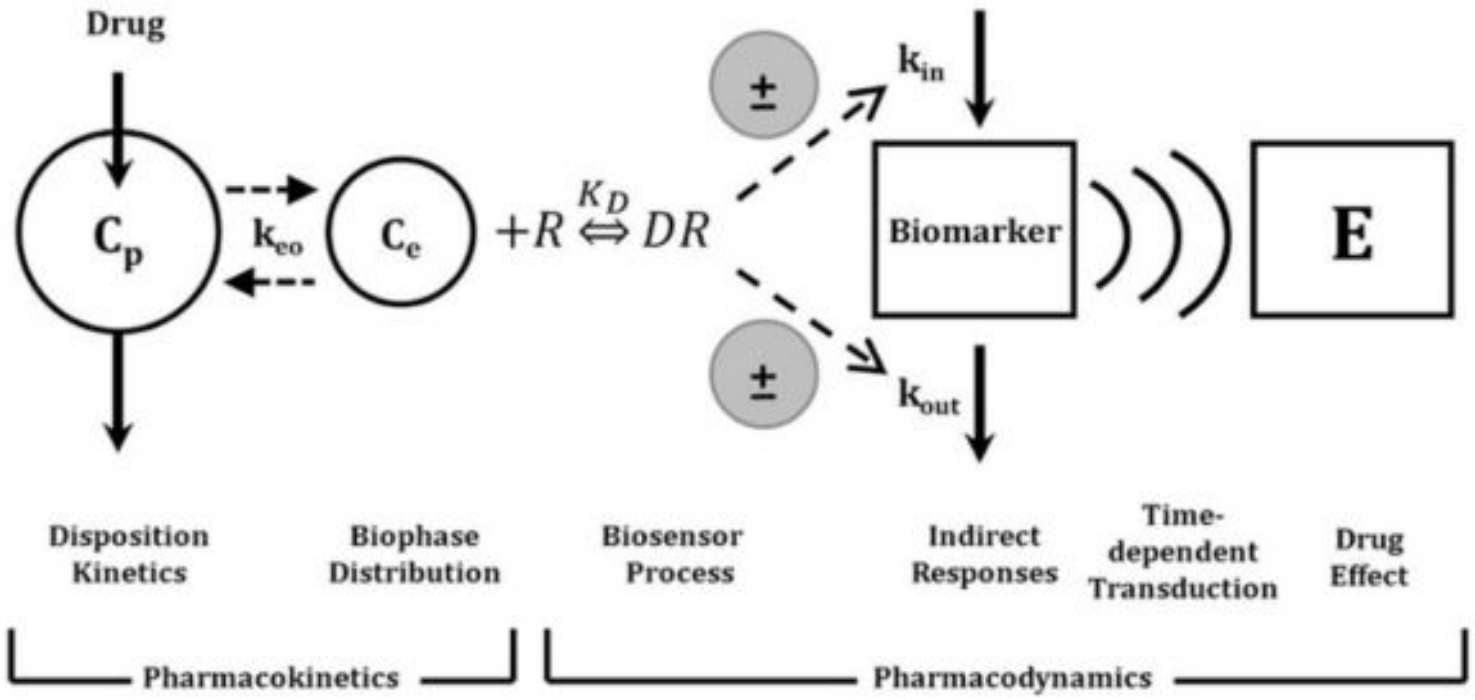
PK–PD Direct/Indirect response + Effect compartment modeling

Slide from Nathan Teuscher: ‘PKPD Modeling of Continuous Data’ – Monash-Certara Curriculum

Basic components of pharmacodynamic models



https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC3684160&blobtype=pdf

Key derived concepts

Potency is the concentration or amount needed to produce a defined effect. C_{50} is the parameter that express this value: the lower its value the greater the potency.

Specificity is greater production of desired relative to undesired effects.

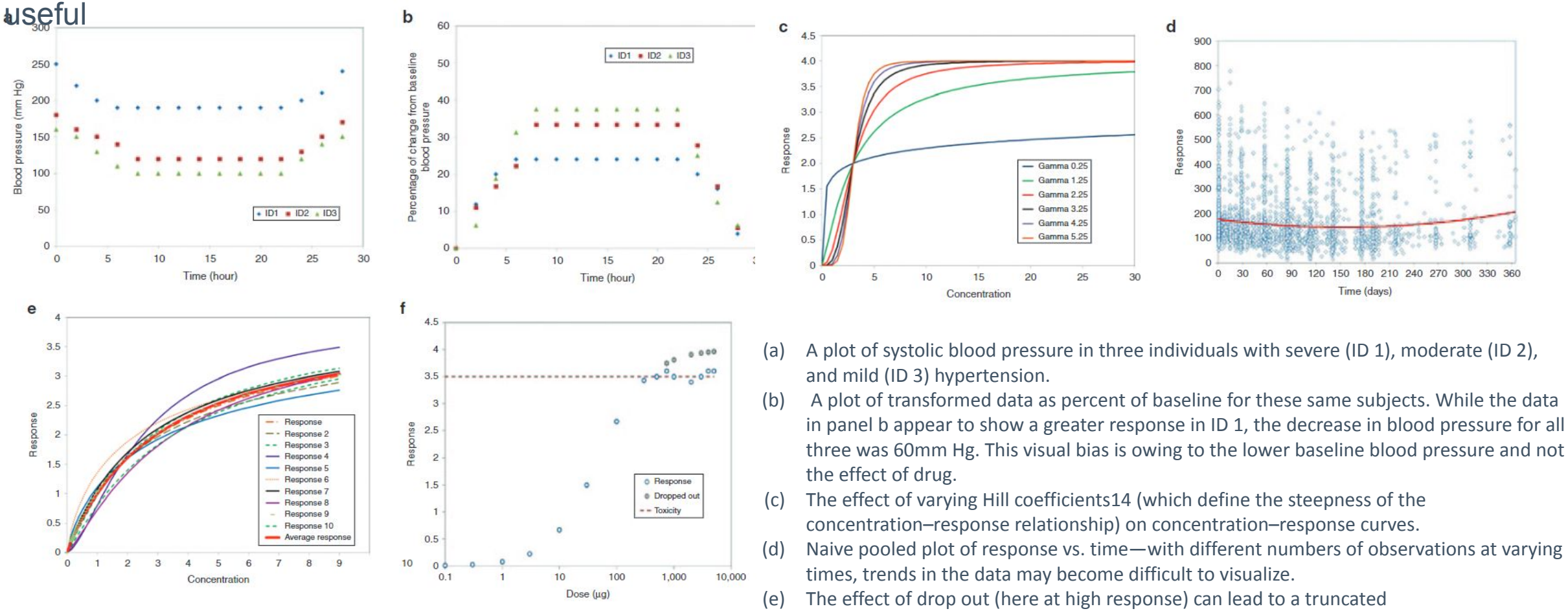
Efficacy is the degree of the effect to which different agonists produce varying responses even when occupying the same proportions of receptors.

Maximum effect is the greatest possible effect that can be achieved with the compound.

Hill coefficient is the steepness factor: the higher it is the less therapeutic value will have the compound.

Graphical exploration

Basic plots of raw vs. transformed data and potential issues with mean and pooled data. In general, it is best to work with the raw (untransformed) data but some time change from baseline (BL) or %chg from BL is useful



(a) A plot of systolic blood pressure in three individuals with severe (ID 1), moderate (ID 2), and mild (ID 3) hypertension.

(b) A plot of transformed data as percent of baseline for these same subjects. While the data in panel b appear to show a greater response in ID 1, the decrease in blood pressure for all three was 60mm Hg. This visual bias is owing to the lower baseline blood pressure and not the effect of drug.

(c) The effect of varying Hill coefficients14 (which define the steepness of the concentration–response relationship) on concentration–response curves.

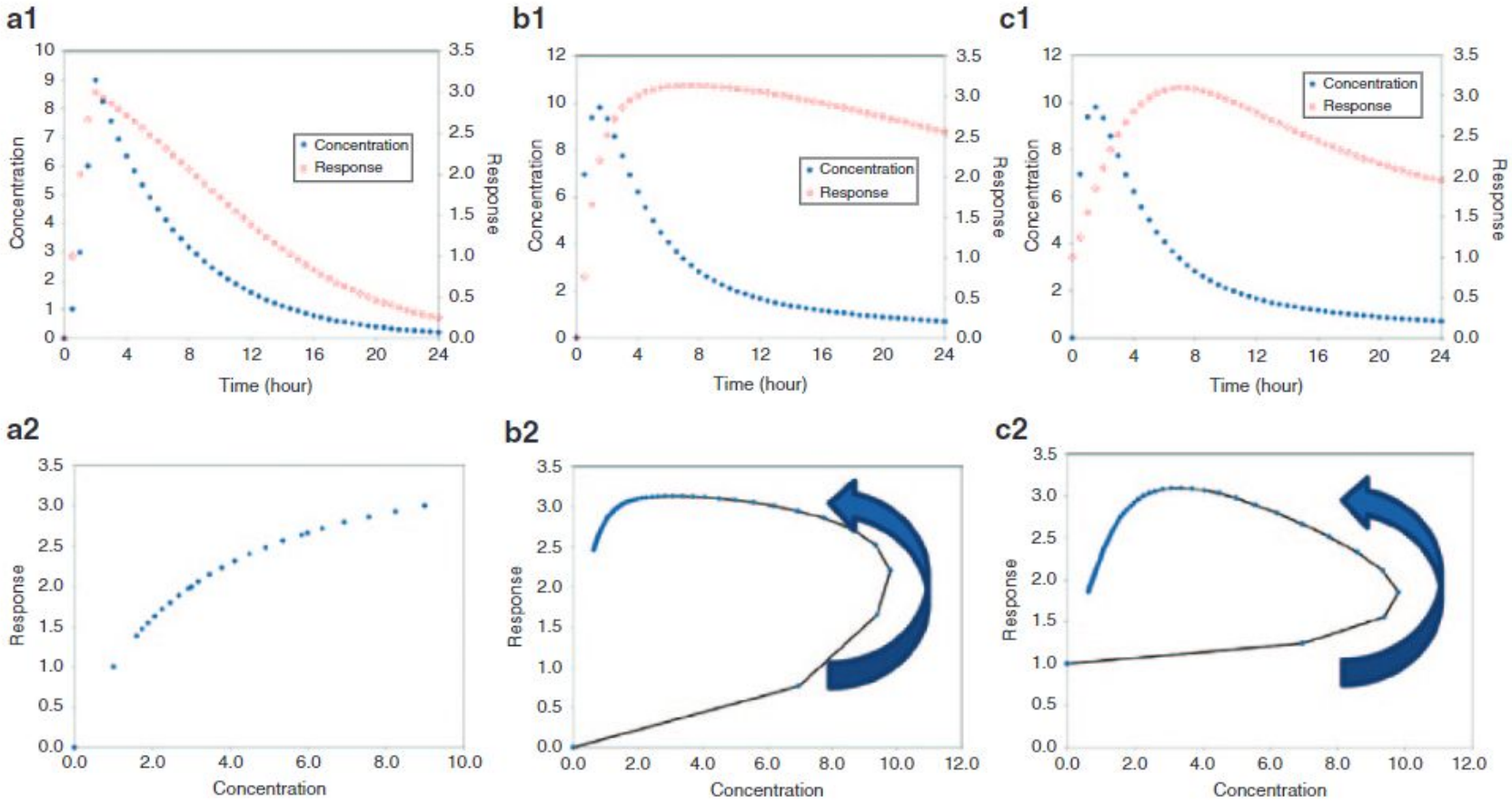
(d) Naive pooled plot of response vs. time—with different numbers of observations at varying times, trends in the data may become difficult to visualize.

(e) The effect of drop out (here at high response) can lead to a truncated concentration–response curve.

(f) Taking a mean of individual concentration response profiles can result in a shallower relationship than is evident in any individual subject.

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

Interpreting PD plots



(a1) Plot of concentration and response vs. time for a direct effect drug. Note that the peak response and peak concentration are correlated.
(a2) Shows the concentration vs. response, which shows the expected sigmoidal curve.

(b1) Shows concentration and response vs. time for a drug with a delayed onset of effect. Note that the peak concentration and peak response are shifted, reflecting a delay.
(b2) Shows the plot of concentration vs. time that results in hysteresis.

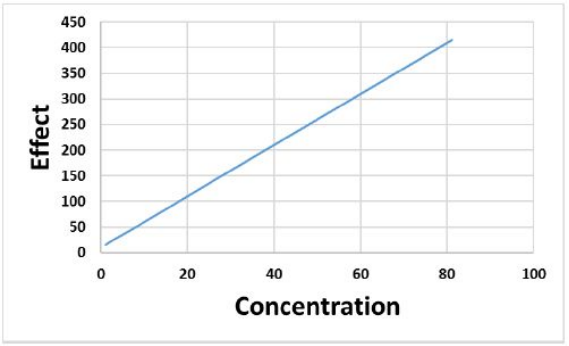
(c1,c2) Represent a longer delay between concentration and response—as the delay increases, the plot of concentration vs. response will become less and less useful

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

What type of mathematical functions are used for PD?

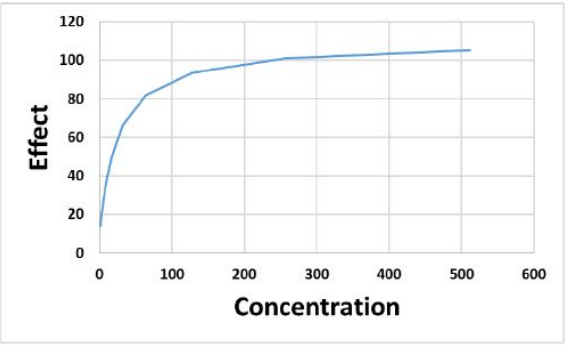
- Linear
  - E = PD response
  - E0 = Baseline PD value
  - Slope = concentration-dependent rate of change
  - Cp = plasma drug concentration

$$E = E0 + slope * Cp$$



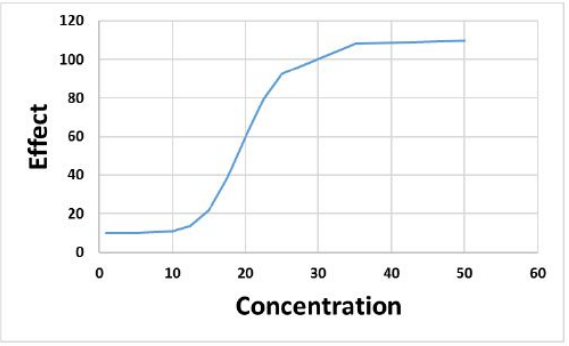
- Emax
  - Emax = maximal response
  - EC50 = drug concentration required to elicit 50% of Emax

$$E = E0 + \frac{Emax * Cp}{Cp + EC50}$$



- Sigmoid
  - gam = hill coefficient or slope factor

$$E = E0 + \frac{Emax * Cp^{gam}}{Cp^{gam} + EC50^{gam}}$$



These examples are for direct effect models.

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How to connect PK to PD with modeling

- Direct response
  - Drug concentrations measured in a biological matrix are directly correlated with a pharmacodynamic response
  - As Cp rises, PD rises
  - Uses a mathematical function like the following:
  - $PD(t)=f(Cp(t))$

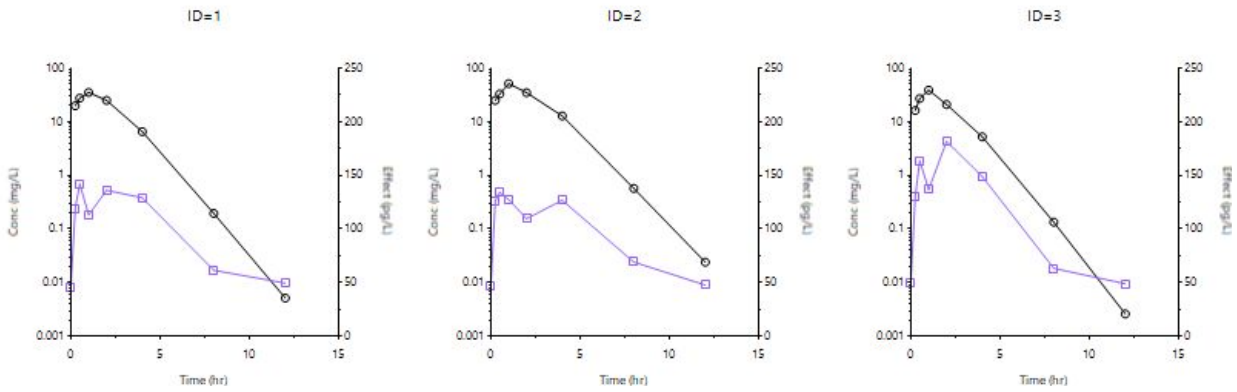
- Indirect response
  - Drug concentrations and PD responses occur on different time scales
  - Example: changes in depression occur over 2-4 weeks, but drug is administered each day and drug levels rise and fall over 1 day
  - Uses mathematical functions like the following:
  - $PD(t)=g(Ce(t))$ where $Ce(t)=h(Cp(t))$

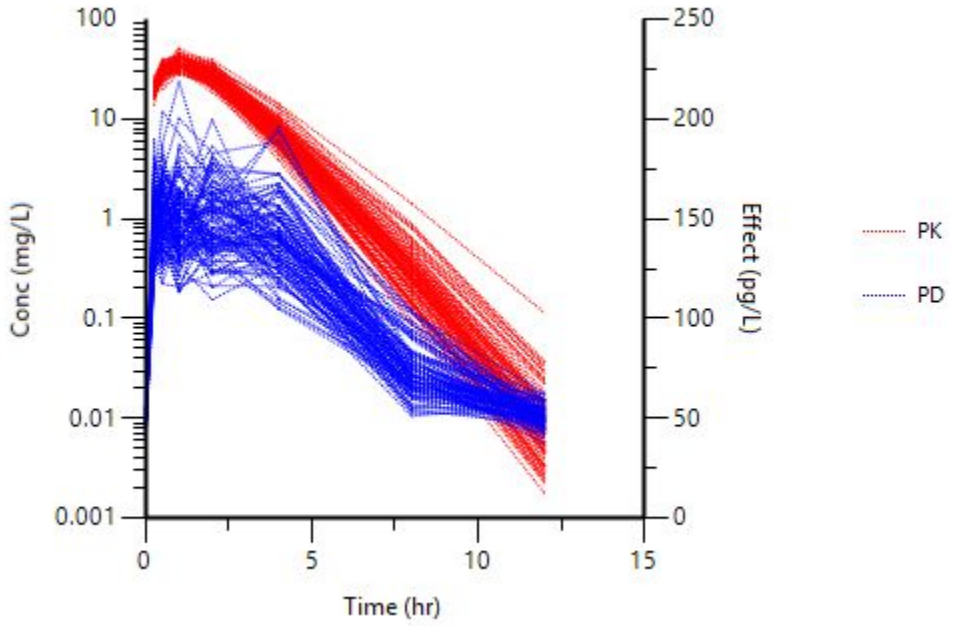
What is “Continuous” data and how do I model it?

- **Background:**
  - PK-PD study in 100 subjects
  - Time-matched PK and PD samples from pre-dose through 12 hours post-dose
  - Single oral dose of 100 mg

- **Goal:** Build a PK-PD model to describe the time course for both PK and PD
- **Steps:**
  1. Explore data
  2. Generate initial estimates
  3. Fit PK-PD model
  4. Determine best model structure

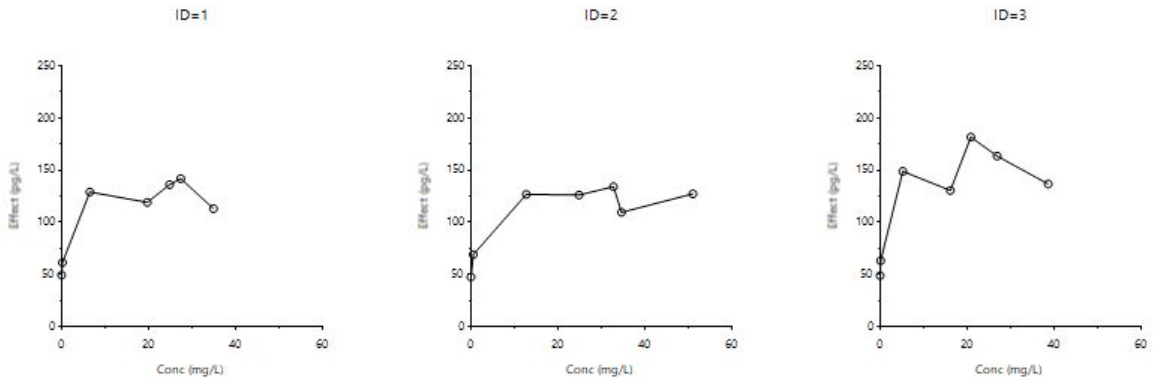
Plot Time Course of Data

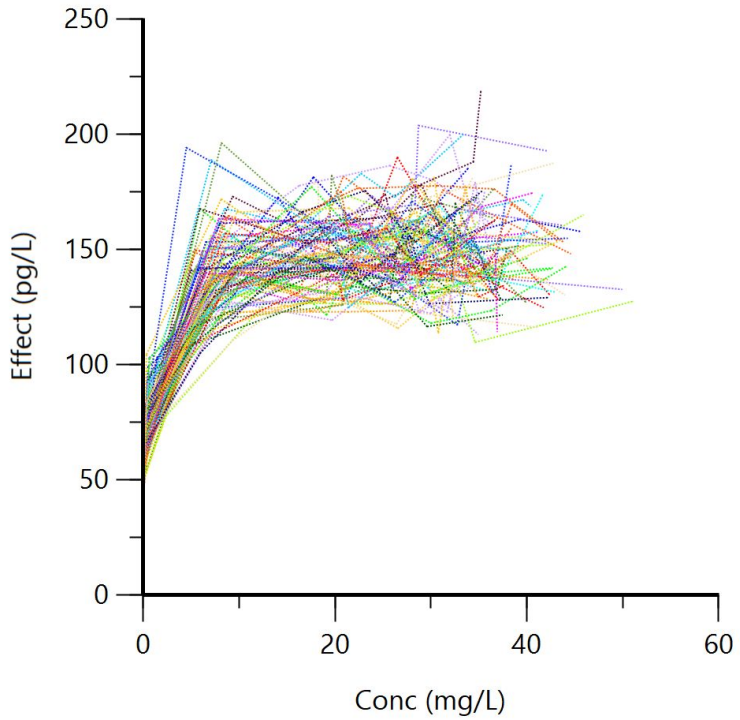




- PD and PK move in the same direction
- Small delay between PK and PD peaks
- PD is >0 at baseline
- 1-cmpt PK model
- Oral absorption

Plot Time-matched PKPD Data





- No significant hysteresis
- Rise to maximum
- Baseline > 0
- Emax model

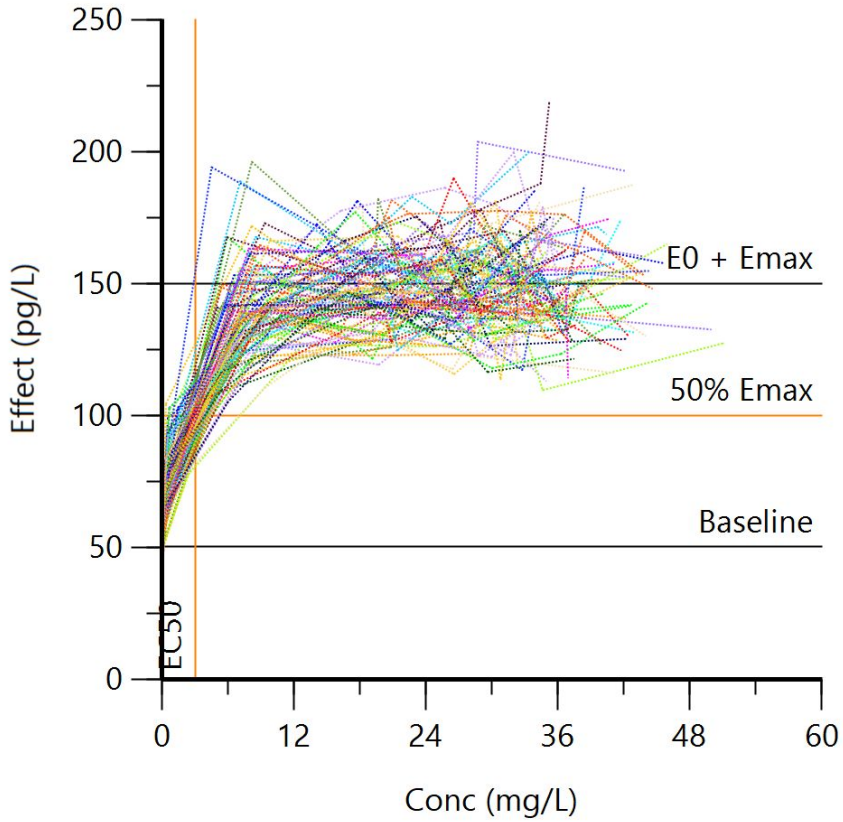
Initial Estimates for PK Model

- 1 compartment PK model with oral absorption
- Parameters needed:
  - CL/F
  - V/F
  - Ka
- Estimates from NCA
  - CL/F – use CL/F_obs
  - V/F – Use Vz/F_obs
  - Ka = 10*Kel (assumes Kel is slowest process)
- Initial estimate values
  - CL/F = 0.924 L/hr
  - V/F = 1.088 L
  - Ka = 8.49 1/hr

	Cl_F_obs (L/hr)	Vz_F_obs (L)	Lambda_z (1/hr)
N	100	100	100
Mean	0.924	1.088	0.849
Median	0.91	1.08	0.85

Initial Estimates for PD Model

- Emax model with baseline
- Parameters needed:
  - E0 (baseline)
  - Emax
  - EC50
  - Ke0 (may need it for effect compartment delay)
- Obtain estimate from graphical plots or data summaries
  - E0 – use mean at time = 0
  - Emax – use mean from plot minus E0
  - EC50 – use plot estimate
  - Ke0 – start with an estimate of 1
- Initial estimate values
  - E0 = 50.25 pg/L
  - Emax = 100 pg/L (150 – 50.25 ≈ 100)
  - EC50 = 7 mg/L
  - Ke0 = 1



Modeling using NONMEM

Build Direct Effect PKPD Model in NONMEM

	A	B	C	D	E	F	G	H
1	C	SID	TIME	DV	AMT	CMT	MDV	DVID
2	.	1	0	.	100	1	1	1
3	.	1	0	45.339	0	2	0	2
4	.	1	0.25	19.6872	0	2	0	1
5	.	1	0.25	119.159	0	2	0	2
6	.	1	0.5	27.3711	0	2	0	1
7	.	1	0.5	141.856	0	2	0	2
8	.	1	1	34.8791	0	2	0	1
9	.	1	1	113.098	0	2	0	2
10	.	1	2	24.8082	0	2	0	1
11	.	1	2	136.075	0	2	0	2
12	.	1	4	6.50201	0	2	0	1
13	.	1	4	129.031	0	2	0	2
14	.	1	8	0.194945	0	2	0	1
15	.	1	8	61.5093	0	2	0	2
16	.	1	12	0.00515	0	2	0	1
17	.	1	12	49.5248	0	2	0	2
18	.	2	0	.	100	1	1	1
19	.	2	0	46.4685	0	2	0	2
20	.	2	0.25	24.8466	0	2	0	1
21	.	2	0.25	126.112	0	2	0	2
22	.	2	0.5	32.7487	0	2	0	1
23	.	2	0.5	134.103	0	2	0	2

1. PK and PD observations should both be in the DV column of the dataset.
2. Use DVID column to distinguish between PK and PD observations.

Build Direct Effect PKPD Model in NONMEM

```
$SUBROUTINE ADVAN2 TRANS2
$PK
; Population PK parameters
 TVCL = THETA(1)
 TVV  = THETA(2)
 TVKA = THETA(3)
; Individual PK parameters
 CL = TVCL*EXP(ETA(1))
 V  = TVV*EXP(ETA(2))
 KA = TVKA*EXP(ETA(3))

; Population PD parameters
 TVE0 = THETA(4)
 TVEC50 = THETA(5)
 TVEMAX = THETA(6)
; Individual PD parameters
 E0 = TVE0*EXP(ETA(4))
 EC50 = TVEC50*EXP(ETA(5))
 EMAX = TVEMAX*EXP(ETA(6))

; Error parameters
 PKERR = THETA(7)
 PDERR = THETA(8)

 S2 = V
```

1. Use ADVAN2 for PK
2. Set “THETA” to population parameters
3. Set individual parameters by adding interindividual variability terms (“ETA”)

Build Direct Effect PKPD Model in NONMEM

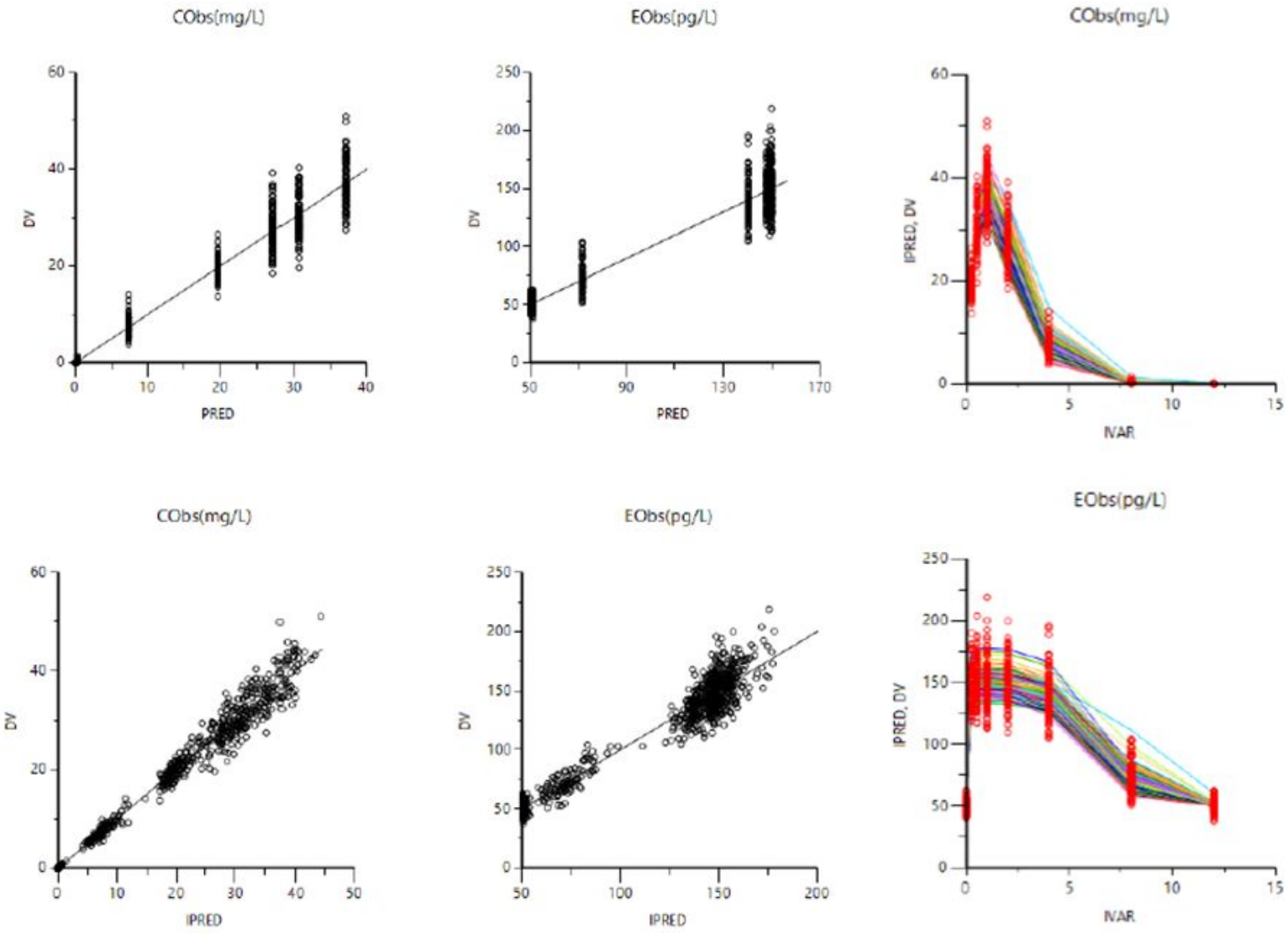
```
$ERROR
  CP = A(2)/V
  IF (DVID.EQ.1) THEN
     IPRED = CP
     Y = IPRED*(1+EPS(1)*PKERR)
     IRES = DV - IPRED
  ENDIF

  CE = CP
  EFF = E0 + EMAX*(CE/(EC50+CE))
  IF (DVID.EQ.2) THEN
    IPRED = EFF
    Y = IPRED + EPS(1)*PDERR
    IRES = DV - IPRED
  ENDIF
```

```
$ESTIMATION MAXEVAL=9999 PRINT=5 METHOD=COND INTER NOABORT
$COVRIANCE PRINT=E
```

1. Use $ERROR block to switch from PK to PD predictions
   - PK observations have DVID=1
   - PD observations have DVID=2
2. Use FOCEI estimation

Evaluate Results

Review Model Diagnostics

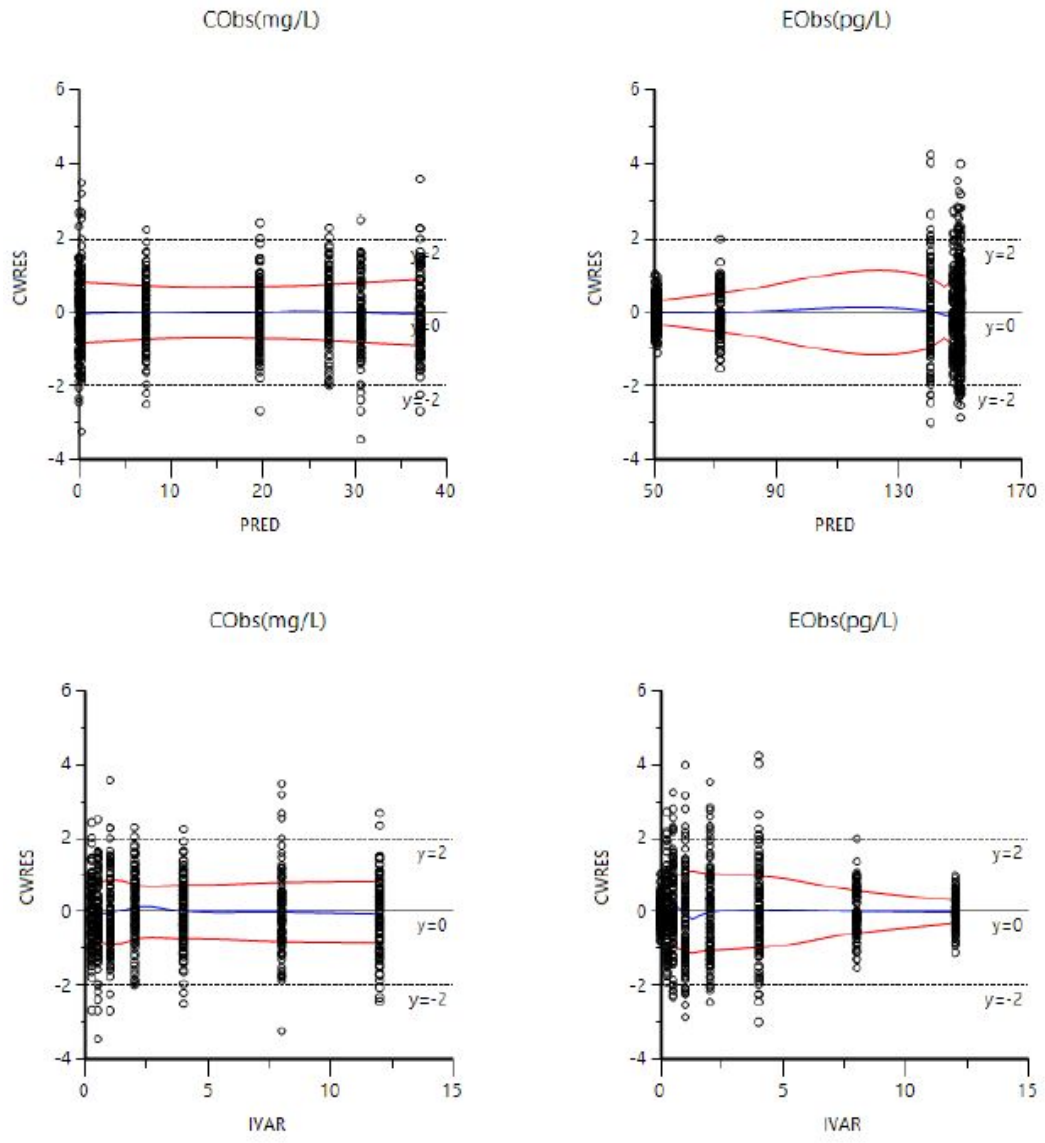


- Structural model
  - IPRED vs DV
  - PRED vs DV
  - IPRED/PRED vs TIME

- Does data lie along line of unity?
- Do model fits run through the "middle" of the observations?
- Where is there a deviation?

CERTARA

Review Model Diagnostics



- Error model
  - CWRES vs PRED
  - CWRES vs TIME
  - CWRES vs TAD

- Residual trend should be close to zero
- Are red lines (loess of absolute values) flat or sloped?
- Is there over- or under-prediction in a systematic way?

Review Model Diagnostics

RetCode	LogLik	-2LL	AIC	BIC	nParm	nObs	nSub	EpsShrinkage
1	-3804.9835	7609.9669	7637.9669	7712.352	14	1500	100	0.09383

Parameter	Estimate	Units
tvKa	0.96712488	1/hr
tvV	0.96366876	L
tvCl	0.98770339	L/hr
tvEC50	1.0299493	mg/L
tvE0	50.364744	pg/L
tvEmax	103.19186	pg/L
stdev0	0.09877233	
stdev1	12.130832	

Label	nV	nCl	nEC50	nEmax	nKa	nE0
Omega						
nV	0.0051414545					
nCl	0	0.014613928				
nEC50	0	0	0.041828219			
nEmax	0	0	0	0.0088251388		
nKa	0	0	0	0	0.00327691	
nE0	0	0	0	0	0	0.0018132379
Correlation						
nV	1					
nCl	0	1				
nEC50	0	0	1			
nEmax	0	0	0	1		
nKa	0	0	0	0	1	
nE0	0	0	0	0	0	1
Shrinkage	0.32223914	0.039894091	0.69439392	0.16325382	0.35931708	0.67791674

- Example output from Phoenix NLME is shown; however, identical outputs can be extracted from NONMEM output files.
- Parameter estimates
  - Overall table
  - Theta table
  - Omega table
- Objective function value, shrinkage, and condition number
- Parameter estimates
  - Are they reasonable?
  - Are they similar to initial estimates?
- Between subject variability
  - Are terms very small with high shrinkage?

Effect compartment model in NONMEM

Build Direct Effect PKPD Model in NONMEM

```
$DES
 GUT = A(1)
 DCP = A(2)/V
 DCE = A(3)

 RATEIN = KA*GUT
 DADT(1) = -RATEIN
 DADT(2) = RATEIN - DCP*CL
 DADT(3) = KE0*(DCP - DCE)

$ERROR
  CP = A(2)/V
  IF (DVID.EQ.1) THEN
     IPRED = CP
     Y = IPRED*(1+EPS(1)*PKERR)
     IRES = DV - IPRED
  ENDIF

  CE = A(3)
  EFF = E0 + EMAX*(CE/(EC50+CE))
  IF (DVID.EQ.2) THEN
    IPRED = EFF
    Y = IPRED + EPS(1)*PDERR
    IRES = DV - IPRED
  ENDIF
```

1. Use ADVAN6
2. Specify equations for PK and effect compartment in $DES
3. Adjust the concentration that drives the effect to the effect compartment in $ERROR

Evaluate Results

Build Direct Effect PKPD Model in NONMEM

Direct Effect

RetCode	LogLik	-2LL	AIC	BIC	nParm	nObs	nSub	EpsShrinkage
1	-3804.9835	7609.9669	7637.9669	7712.352	14	1500	100	0.09383

Effect Compartment

RetCode	LogLik	-2LL	AIC	BIC	nParm	nObs	nSub	EpsShrinkage
1	-3776.9436	7553.8872	7585.8872	7670.8987	16	1500	100	0.08534

Direct Effect

LogLik	-2LL	AIC	BIC	nParm
-3804.9835	7609.9669	7637.9669	7712.352	14

Effect Compartment

LogLik	-2LL	AIC	BIC	nParm
-3776.9436	7553.8872	7585.8872	7670.8987	16

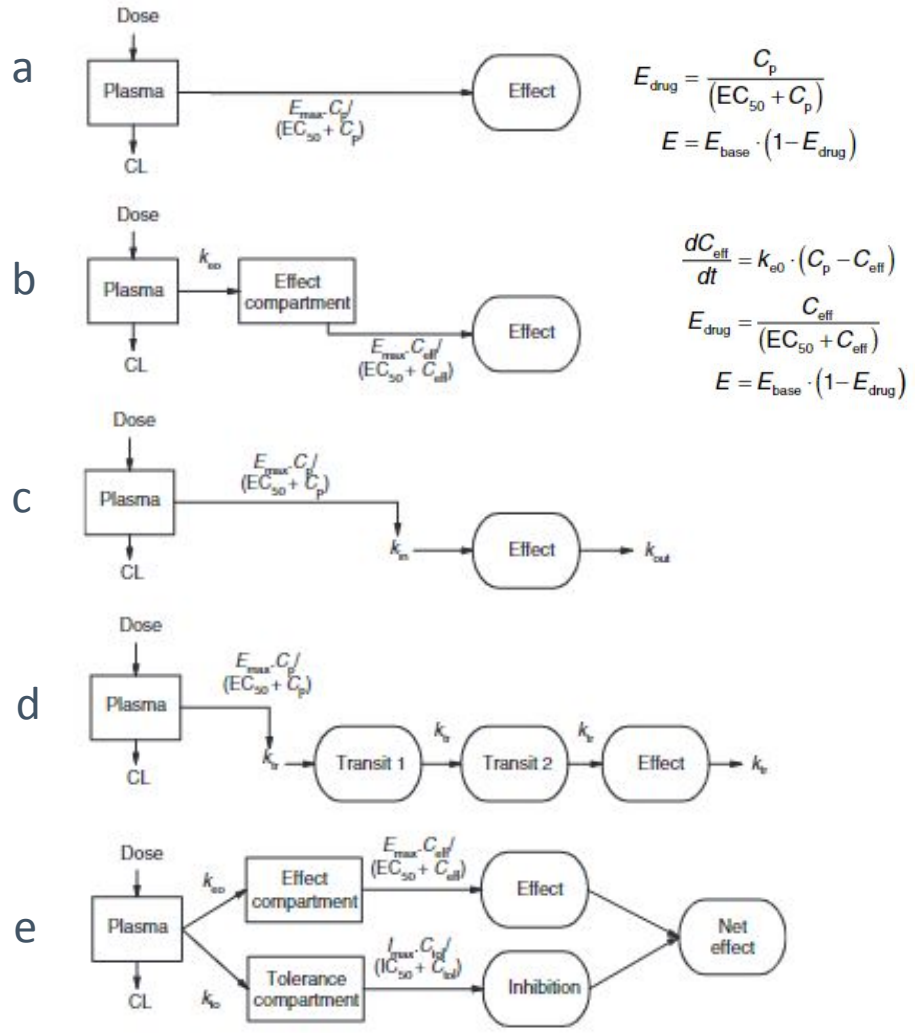
- Diagnostics are similar
- AIC is lower with effect compartment model
- Models are similar
- Is there information that would lead you to select one over the other?
  - Knowledge of pharmacology
  - Data from other studies
  - Previous analysis
- For equivalent models, choose the simpler model

Summary

- Building a continuous PK/PD model requires the following key steps:
  1. Explore data
  2. Generate initial estimates
  3. Fit PK-PD model
  4. Determine best model structure by evaluating diagnostic plots and information

- If the PD response is on the same time scale as the PK, choose a direct effect model
- If the PD response is delayed from the PK, choose an effect compartment model (or indirect response model, which is in the next part)

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).

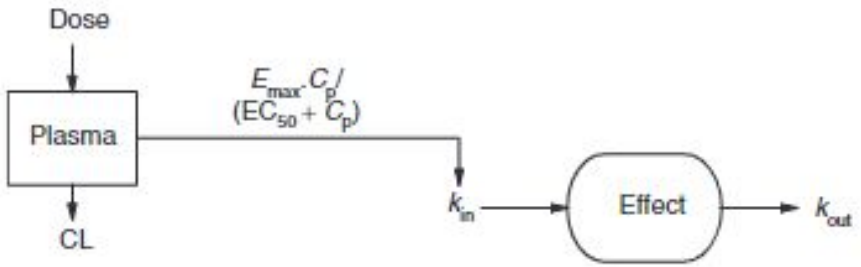
(d) A transit compartment model, where the drug effect is at the end of chain of processes and drug action is on the first process.

(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.

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

Indirect Response Model

Turnover, indirect response modle



$$E_{base} = \frac{k_{in}}{k_{out}}$$

$$\text{Turnover} = \frac{1}{k_{out}}$$

$$k_{out} = \frac{1}{\text{Turnover}}$$

$$k_{in0} = E_{base} \cdot k_{out}$$

$$E_{drug} = \frac{C}{(EC_{50} + C)}$$

$$k_{in} = k_{in0} \cdot (1 - E_{drug})$$

$$\frac{dE}{dt} = k_{in} - k_{out} \cdot E$$

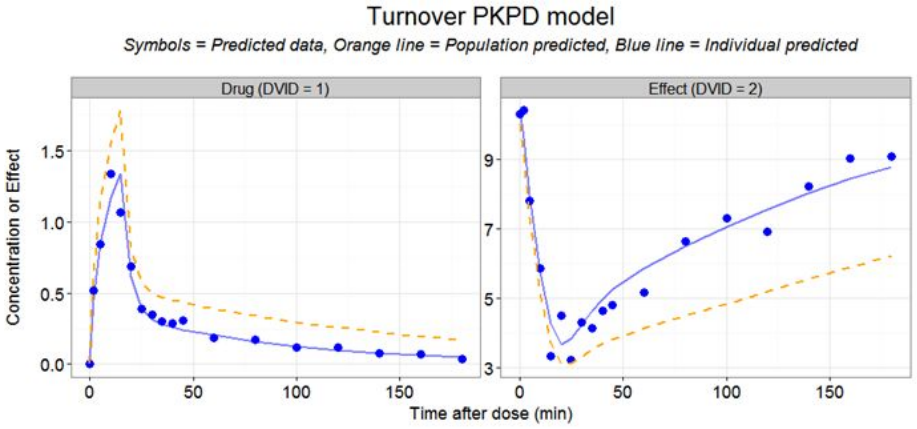
A turnover/indirect response model where drug effect is a balance between an apparent production rate (kin) and an apparent removal rate (kout). Drug affects the net effect by altering kin or (kout)

Effect compartment model and turnover model may fit a given data set equally well, and the choice between the two may need to be made on mechanistic grounds.
Effect compartment models are perhaps better suited to relatively short delays;
Turnover models may favor longer delays. Indeed, both an effect compartment process (biophase equilibration)

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

Example of NM code of indirect response model

- This model is a two compartment pharmacokinetic model with zero order infusion. Drug effect is via E_{max} relationship acting on K... of a turnover/indirect response compartment.



NONMEM control stream 3_turnover.ctl

```
$PROBLEM AN EXAMPLE TURNOVER MODEL AS DIFFERENTIAL EQUATIONS
;Two compartment pharmacokinetic model with zero order infusion
;Emax model acting on KIN
;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=(TURNOVER)
```

```
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 E to zero
  EC50  = THETA(5)
  EBASE = THETA(6)*EXP(ETA(3))   ;Baseline
  TURN =  THETA(7)   ;Turnover - cannot be zero!

  ;Calculate turnover compartment rate constants
  KOUT = 1/TURN
  KIN0 = EBASE*KOUT   ;Baseline KIN
  A_0(3)= EBASE       ;Set turnover compartment 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
 KIN     = KIN0*(1-EDRUG)
 DADT(3) = KIN - KOUT*A(3)      ;Differential equation for turnover compartment
```

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

 0.3    ;POPEC50
 10    ;POPEBASE
 10  ;POPTURN


$OMEGA ;investigate omega blocks structures when fitting data
 0.05   ;BSVCL
 0.05   ;BSVV1
 0.05   ;BSVEBASE

$SIGMA
 0.02  ;RUVPROPCP
 0.2   ;RUVADDE


$ERROR
 CP=A(1)/V1   ;Plasma concentration needs to be calculated again outside of $DES
 E=A(3)       ;Turnover compartment amount reflect 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 EMAX EBASE EC50 TURN CP E DVID MDV SIM IPRED NOPRINT ONE-
HEADER FILE=*.fit
```

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

Friberg model and application

A Special Type of PK/PD Model

Application of myelossupression model

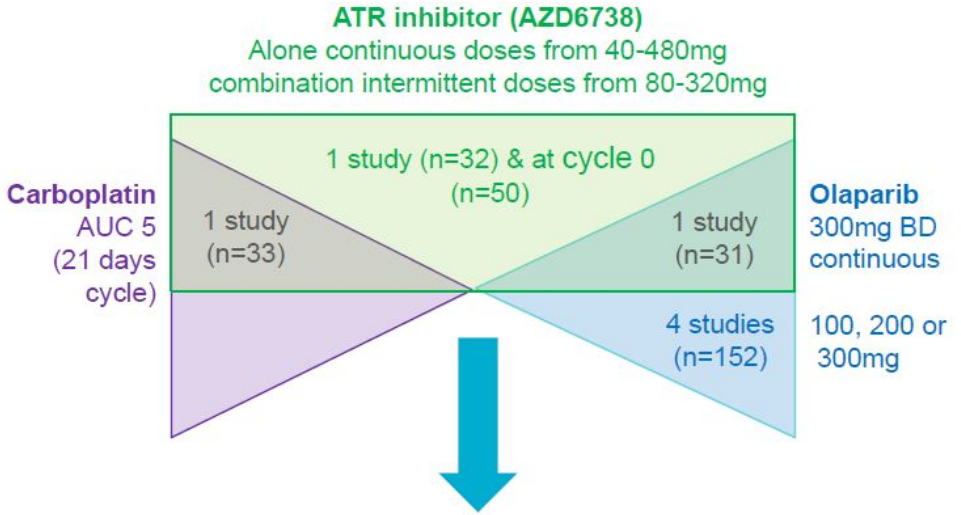
Optimising Phase 1 oncology dosing schedule of an ATR inhibitor in real time using a model informed approach to predict myelosuppression

S. Y. Amy Cheung[1], Alienor Berges[1], James W. T. Yates[1], Nuria Buil Bruna[1], Graham Ross[1], Simon Smith[1], Brunella Felicetti[1], Musaddiq Khan[1], Christine Stephens[1], Jean-Charles Soria[2], Kevin Harrington[3], Magnus Dillon[3] and Simon J Hollingsworth[1]

Innovative Medicines and Early Development, AstraZeneca UK[1], Institut Gustave Roussy, Paris, France[2], The Institute of Cancer Research/The Royal Marsden Hospital, London[3]

- AZD6738 is a potent, highly specific ATR kinase inhibitor being tested in phase 1 clinical trials in patients with solid malignancies as monotherapy and in combination:
  - An AZ sponsored phase 1 study with a modular protocol:
    - Module 1, combining AZD6738 with chemotherapy, carboplatin
    - Module 2, combining with a PARP-1 inhibitor olaparib.
  - An externally sponsored research (ESR) phase 1 study (PATRIOT) to access AZD6738 as a single agent and in combination with palliative radiation therapy.
- Thrombocytopenia and neutropenia are known adverse events with carboplatin monotherapy, hence the understanding of the relationship between AZD6738, carboplatin dose and exposure to platelet or neutrophil nadir is essential for selection of tolerated dose and schedule in combination.
- As part of a model informed drug development [2], a PK-safety modelling approach was applied by integrating data across phase 1 studies to support dose-regimen selection.

Emerging plasma concentration (PK), absolute platelet count (APC) and absolute neutrophil count (ANC) data from 2 phase 1 studies of AZD6738 dosed alone or in combination intermittent doses with carboplatin and olaparib were used.

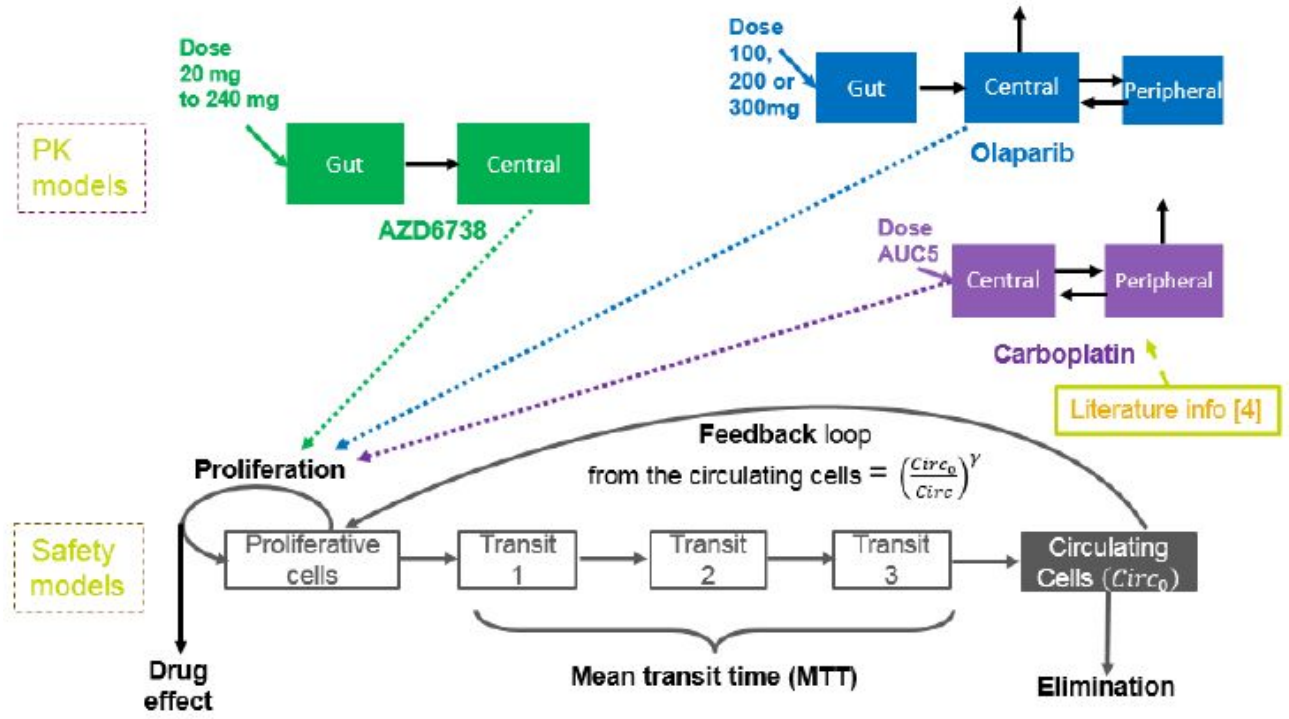


Modelling PK-PD (safety)

https://pubmed.ncbi.nlm.nih.gov/12488418/
https://www.page-meeting.org/pdf_assets/3911-AmyCheung_AZD6738_PAGEposter2017_v5.pdf

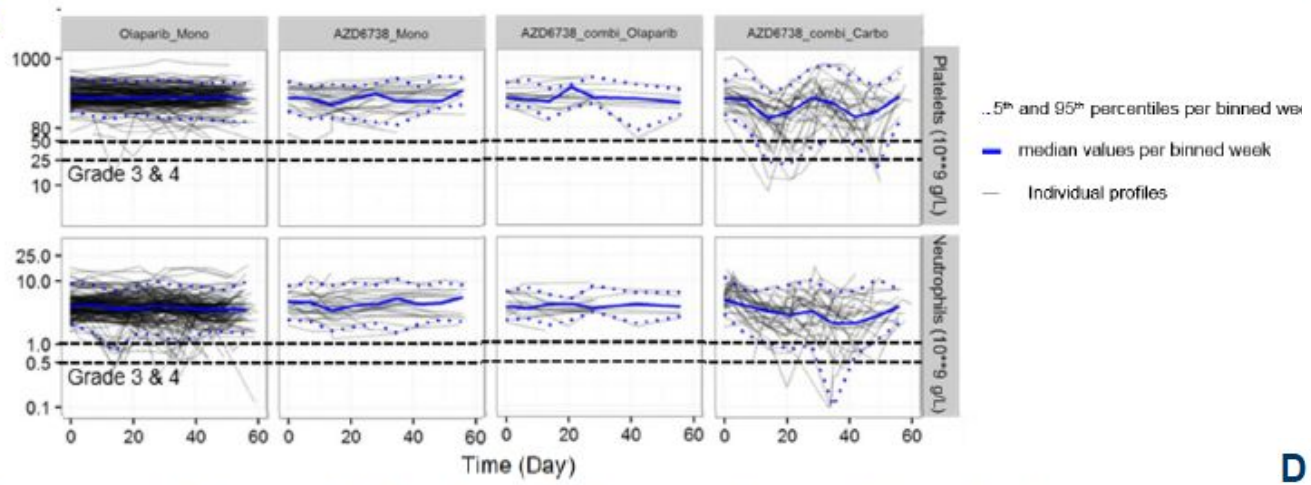
PK–safety modeling

The PK-safety modelling [3] was performed sequentially using FOCEI in NONMEM 7.3 and PSN. The myelosuppression model [3] describes the baseline circulating count, a linear relationship between drug concentration and reduced proliferation in the bone marrow precursor cell population, a mean transit time (MTT) for the delay before reduction is seen in circulating cell counts and homeostasis increasing precursor proliferation to return cell counts to baseline combination effect was tested by an additional effect when both drugs were present. Simulations of the model in the software R were used to explore dose and schedule options.



Results

A



Summary of observed blood count changes observed in patients.

B

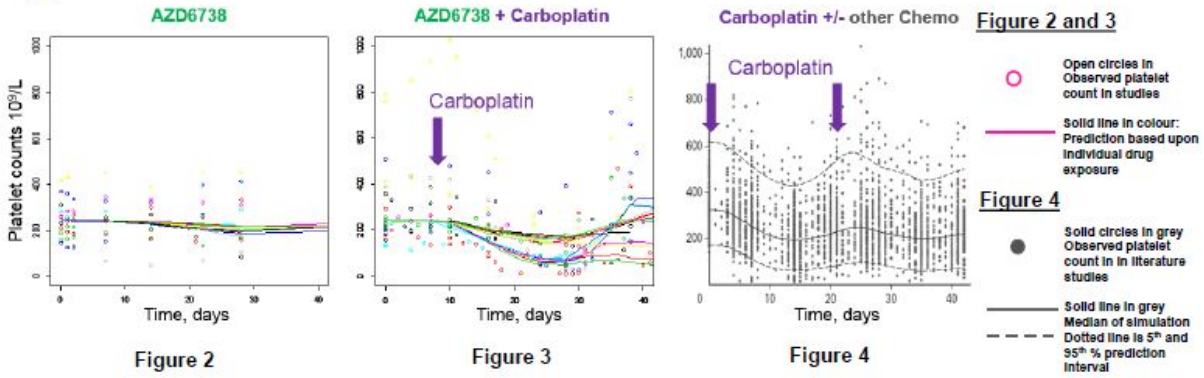


Figure 2 Figure 3 Figure 4

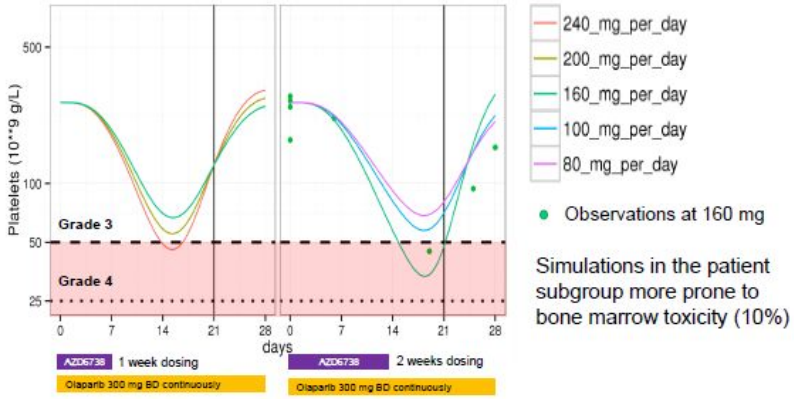
Predictions, platelet model & carboplatin combination example.
Good data description by the model, following AZD6738 alone and in combination with carboplatin AUC5 every 3 weeks and olaparib 300mg twice daily continuous dosing. A comparison with the literature is shown [4].

C

PD variable	Mean values	Historical data [4]
Baseline level (10^9/L, $Cric_0$)	235.6	332 to 358
Mean transit time (h, MTT)	208.5	203 to 245
Feedback (γ)	0.259	0.5 to 0.6
$slope_{Carboplatin}$ (mL/ng)	6.61×10^{-4}	5×10^{-4} to 6.58×10^{-4}
$slope_{AZD6738}$ (mL/ng)	4.35×10^{-6}	NA

Parameter estimation, platelet model & carboplatin combination example: AZD6738 alone showed a minimal impact on blood cell count (platelet) compared to carboplatin. No synergy with carboplatin or olaparib could be estimated.

D



Simulations in the patient subgroup more prone to bone marrow toxicity (10%)

Simulations, platelet model and olaparib combination example:

- Simulations for olaparib combination indicates total platelet counts recover to 90% baseline 21 days after AZD6738 first dose.
- Continued reductions in cell counts are not predicted by the model whereas some patients with grade 2 reductions on cycle 1 experienced grade 4 on repeated cycles: Evaluation of alternative mathematical myelosuppression models [5] to describe potential cumulative toxicity resulted from targeted treatment is ongoing.

Further Read: Other considerations on the Friberg model

Clinical Pharmacology & Therapeutics

Review

Understanding Hematological Toxicities Using Mathematical Modeling

Chiara Fornari, Lenka Oplustil O'Connor, James W.T. Yates, S.Y. Amy Cheung, Duncan I. Jodrell, Jerome T. Mettetal, Teresa A. Collins

First published: 31 March 2018 | https://doi.org/10.1002/cpt.1080 | Citations: 8

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Abstract

Balancing antitumor efficacy with toxicity is a significant challenge, and drug-induced myelosuppression is a common dose-limiting toxicity of cancer treatments. Mathematical modeling has proven to be a powerful ally in this field, scaling results from animal models to humans, and designing optimized treatment regimens. Here we outline existing mathematical approaches for studying bone marrow toxicity, identify gaps in current understanding, and make future recommendations to advance this vital field of safety research further.

https://ascpt.onlinelibrary.wiley.com/doi/abs/10.1002/cpt.1080

Meta-Analysis › J Pharmacokinet Pharmacodyn. 2018 Feb;45(1):79-90.

doi: 10.1007/s10928-018-9569-x. Epub 2018 Feb 2.

Structural identifiability for mathematical pharmacology: models of myelosuppression

Neil D Evans [1], S Y Amy Cheung [2], James W T Yates [3]

Affiliations + expand

PMID: 29396780 DOI: 10.1007/s10928-018-9569-x

Abstract

Structural identifiability is an often overlooked, but essential, prerequisite to the experiment design stage. The application of structural identifiability analysis to models of myelosuppression is used to demonstrate the importance of its considerations. It is shown that, under certain assumptions, these models are structurally identifiable and so drug and system specific parameters can truly be separated. Further it is shown via a meta-analysis of the literature that because of this the reported system parameter estimates for the "Friberg" or "Uppsala" model are consistent in the literature.

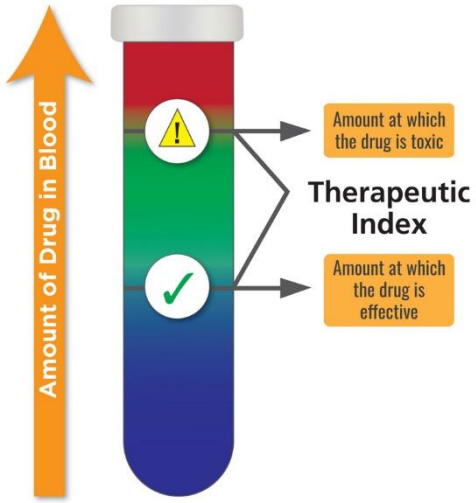
Keywords: Mathematical pharmacology; Myelosuppression; Structural identifiability; System

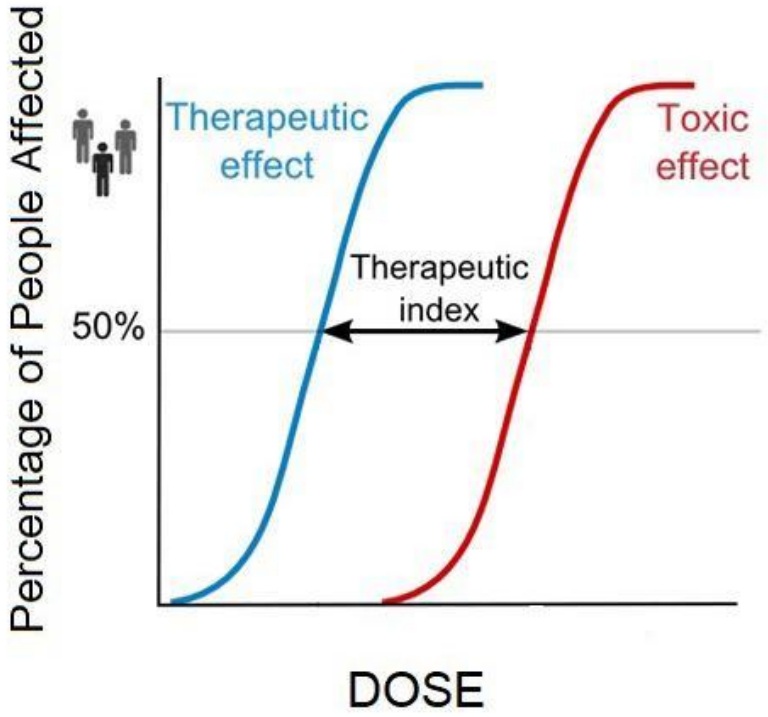
https://pubmed.ncbi.nlm.nih.gov/29396780/#:~:text=The%20application%20of%20structural%20identifiability,parameters%20can%20truly%20be%20separated.

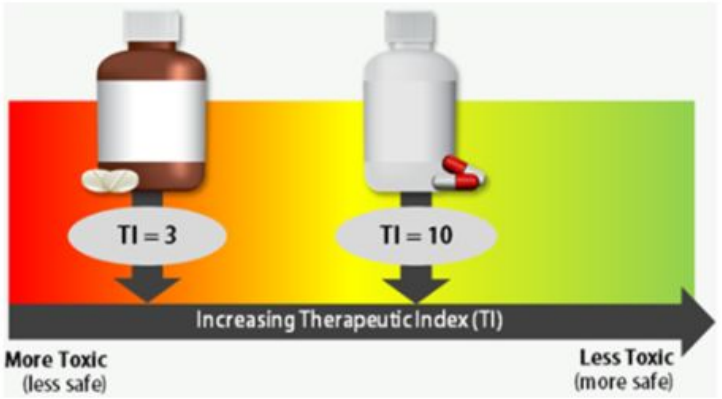
CERTARA

Therapeutic Index and impact to labeling

Therapeutic Index and how to make a decision balancing safety and efficacy?







Here are some example of low TI drugs:
- Warfarin (blood thinner)
- Digoxin (various heart conditions)

And some examples of high TI drugs:
- Benadryl (diphenhydramine, antihistamine, sleep aid)
- Valium (sedative, hypnotic)

$$TI = \frac{\text{Toxic Dose}}{\text{Effective Dose}} = \frac{TD50}{ED50}$$

https://toxedfoundation.org/how-safe-is-this-drug/

Narrow Therapeutic Index Drugs?

- How safe and effective is the drug?
- What is the disease being treated?
- What is the duration of treatment?
- What is the degree or severity of adverse events?
- What is the duration of adverse events?

JPP Journal of Pharmacy and Pharmacology

Journal of Pharmacy and Pharmacology, 2021, Vol 73, 1285–1291
https://doi.org/10.1093/jpp/rgab102
Review
Advance Access publication 4 August 2021

OXFORD

Review

Narrow Therapeutic Index drugs: clinical pharmacology perspective

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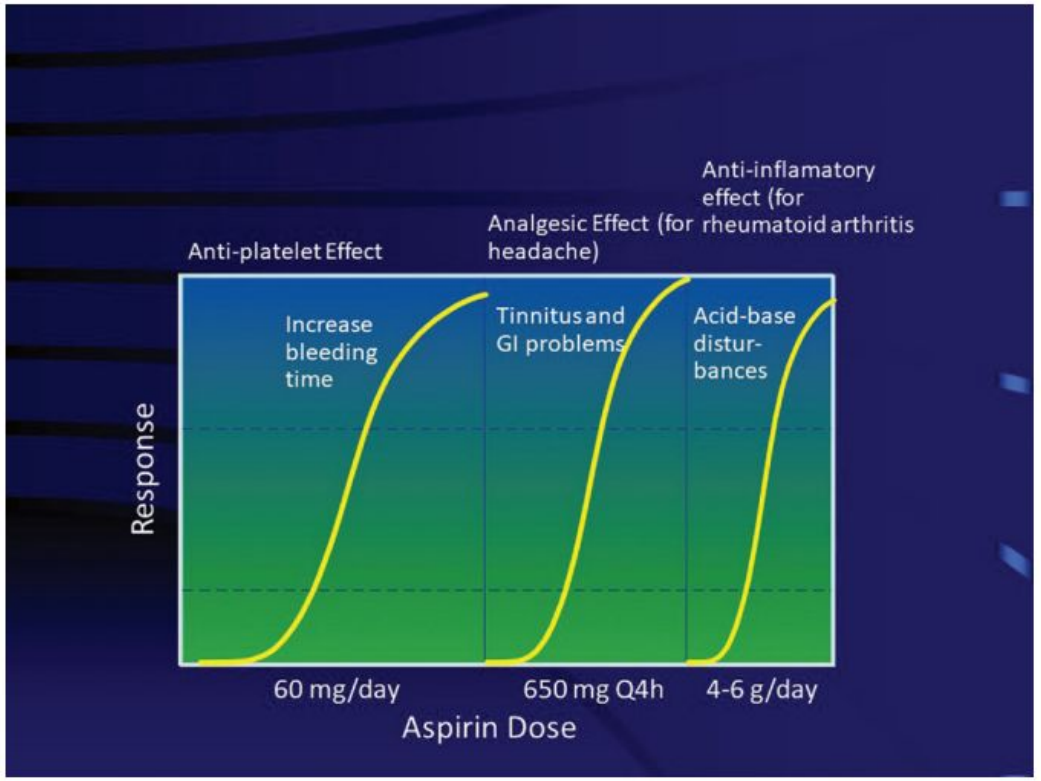

Figure 3 Dose–response relationship for aspirin as example of atypical drug with multiple indications and multiple dose–response profiles (response depends on individual patient sensitivity to aspirin).

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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/)

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