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The utility of Pharmacokinetics/Pharmacodynamics modeling & simulation in clinical research

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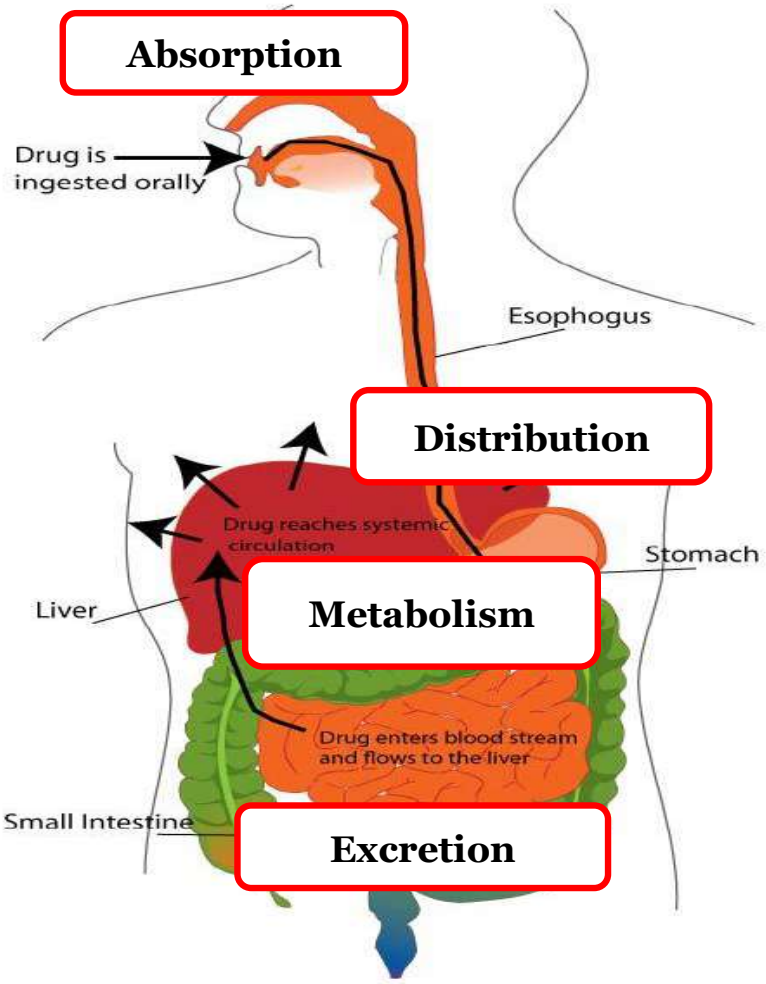
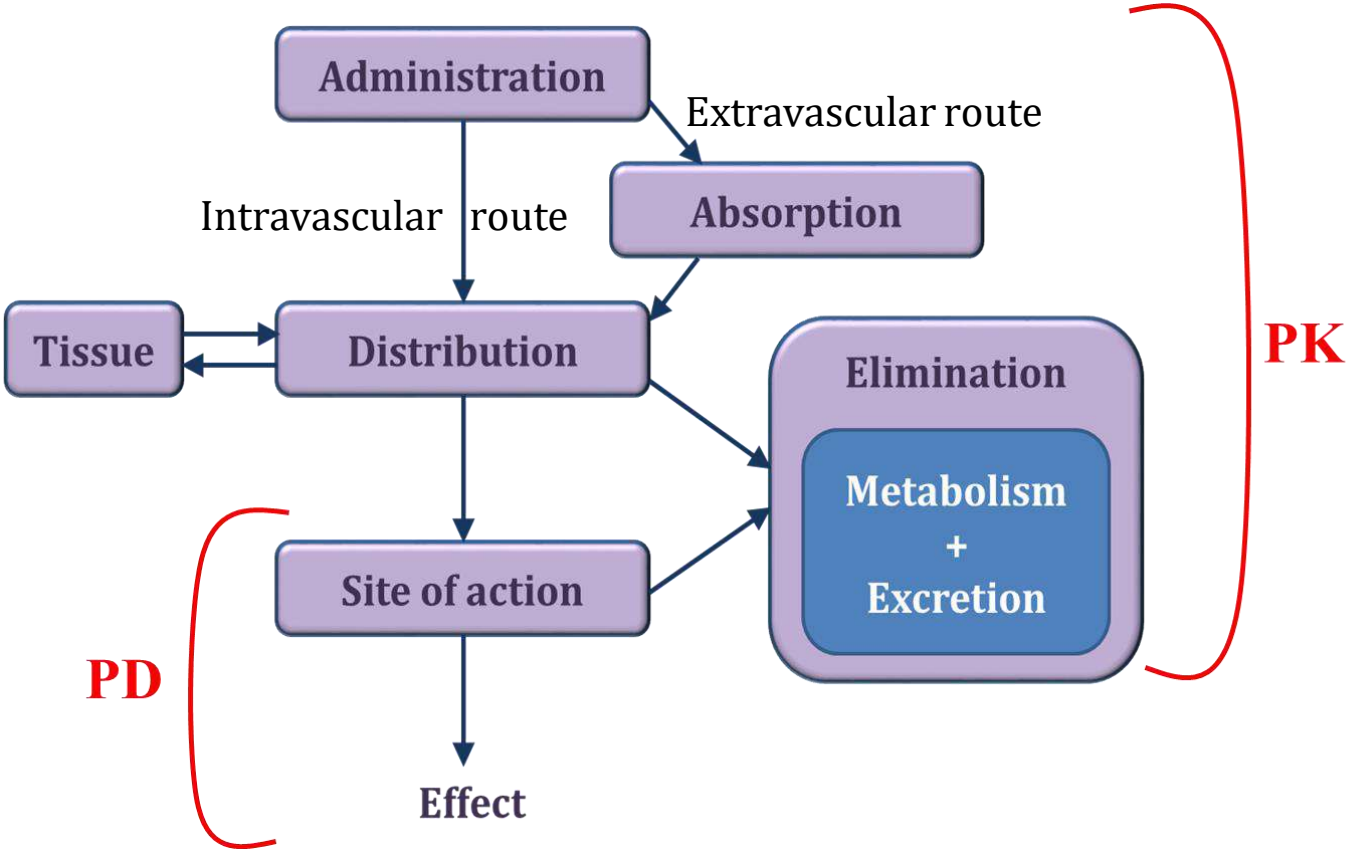
Pharmacokinetics (PK) & Pharmacodynamics (PD)

- What is PK ?
  - What the body does to the drug
  - 투여된 용량에서의 시간에 따른 약물 농도 경과를 해석

- What is PD ?
  - What the drug does to the body
  - 혈장이나 작용부위의 약물 농도와 약물의 효과와의 관계
  - 시간에 따른 약물의 효과 (치료효과, 부작용 등)



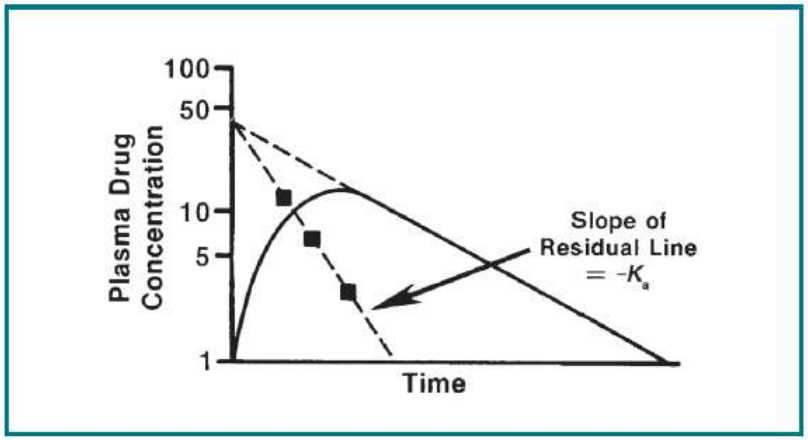
Pharmacokinetics (PK) & Pharmacodynamics (PD)



- Absorption
  - Bioavailability (F)
    - 전신 순환에 도달하는 투여약물의 분획
    - Amount of drug reaching systemic circulation/ total amount of drug

$$F = \frac{\mathrm{AUC_{Extravascular}}/\mathrm{Dose_{Extravascular}}}{\mathrm{AUC_{IV}}/\mathrm{Dose_{IV}}} \times 100 \qquad relative\ bioavailability = \frac{[AUC]_A * dose_B}{[AUC]_B * dose_A}$$

  - Absorption rate (K_a, 1/hr)
    - 약물이 전신순환에 도달하는 속도
    - How to interpret the results?
      - 2.3 (hr^{-1})



Pharmacokinetics (PK) & Pharmacodynamics (PD)

- Distribution
  - Volume of distribution (V_d, L, L/kg) : 체액과 조직으로의 약물 분포 범위를 나타내는 지표

$$V_d = V_p + V_T\left(\frac{f_u}{f_{uT}}\right)$$

$$V_d = CL \times \frac{t_{1/2}}{0.693}$$

$$V_C = \frac{Dose}{C_{initial}}$$

  - Protein binding: 혈장 단백에 결합하는 약물의 분획

Pharmacokinetics (PK) & Pharmacodynamics (PD)

- Metabolism
  - 약물이 생체 내에서 생화학적 반응 후, 보다 비 활성적인 형태로 변화하는 현상
  - Liver
    - Primary outcome of drug metabolism
    - Usually convert pro-drugs (inactive) to an active state

Pharmacokinetics (PK) & Pharmacodynamics (PD)

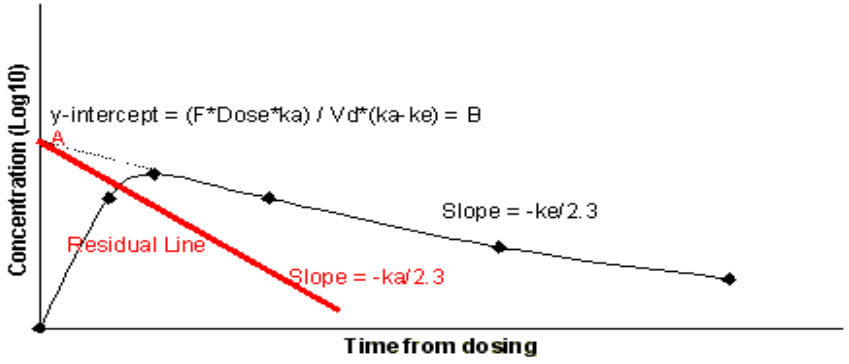
- Elimination
  - Clearance (CL, L/hr): 일정 시간 당 약물이 제거되는 부피
  - Elimination rate constant (K_{el}, 1/hr): 약물이 시간 당 체내에서 제거되는 속도
  - Elimination half-life ($t_{1/2}$, hr): 체내에서 약물 양이 절반으로 줄어드는데 걸리는 시간

$$CL_{\text{total body}} = CL_{\text{liver}} + CL_{\text{renal}} + CL_{\text{other}}$$

$$CL = V_d \times k \qquad CL = \frac{\text{Dose}}{\text{AUC}}$$

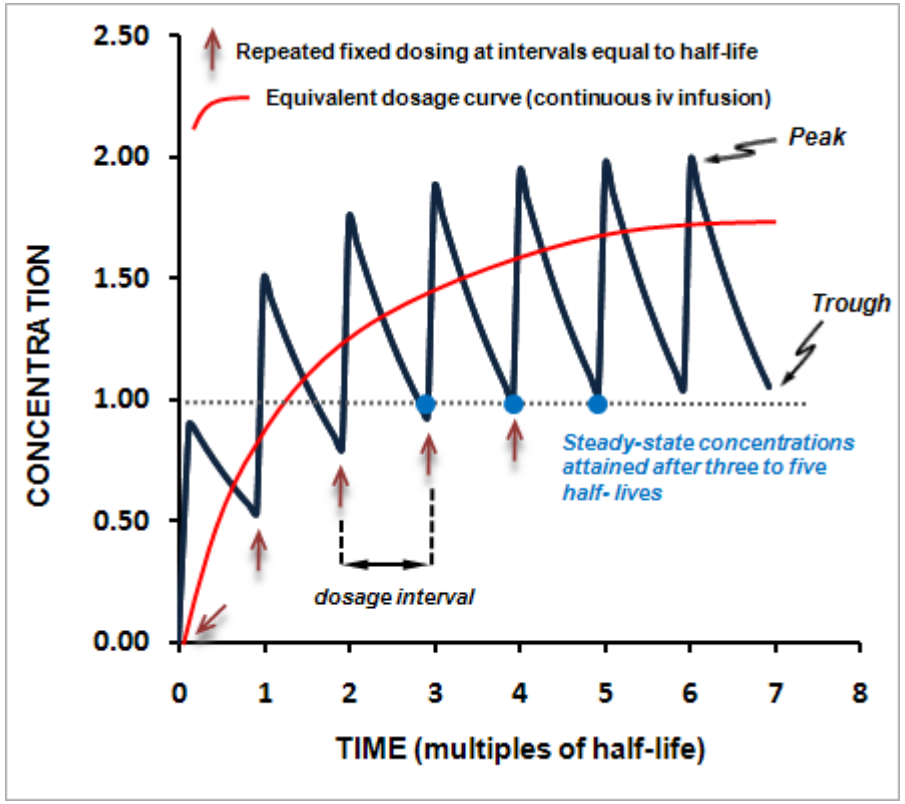
$$k = \frac{0.693}{t_{1/2}}$$

$$t_{1/2} = \frac{V_d \times 0.693}{CL}$$



Pharmacokinetics (PK) & Pharmacodynamics (PD)

- Steady state (SS)
  - 투여 간격 동안 흡수된 약물의 양과 제거된 약물의 양이 같은 시점 (Rate in = Rate out)
  - 4-5 half-lives to reach steady state
  - Important when interpreting drug concentrations in TDM or assessing clinical response

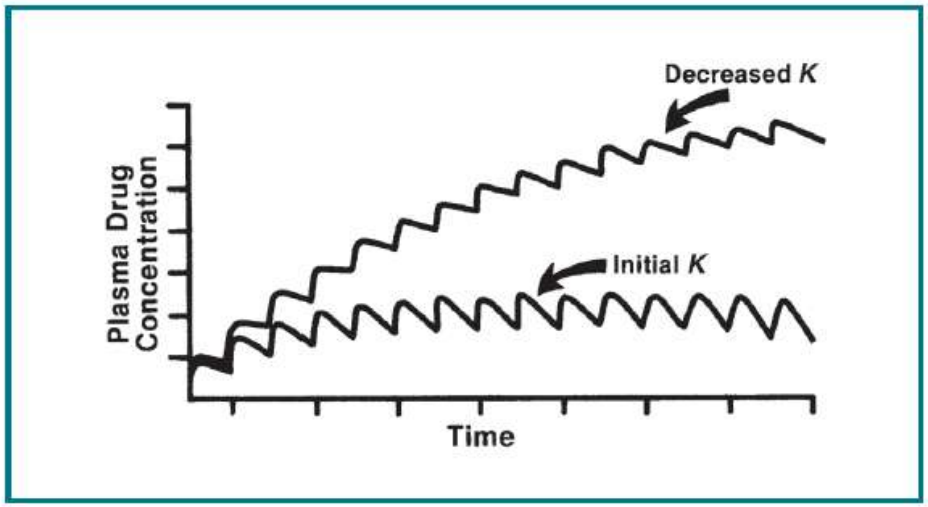


$$C_{\max n} = C_{\max 1}\frac{(1-e^{-nK\tau})}{(1-e^{-K\tau})}$$

$$C_{\min n} = C_{\max 1}\frac{(1-e^{-nK\tau})}{(1-e^{-K\tau})}\cdot e^{-K\tau}$$

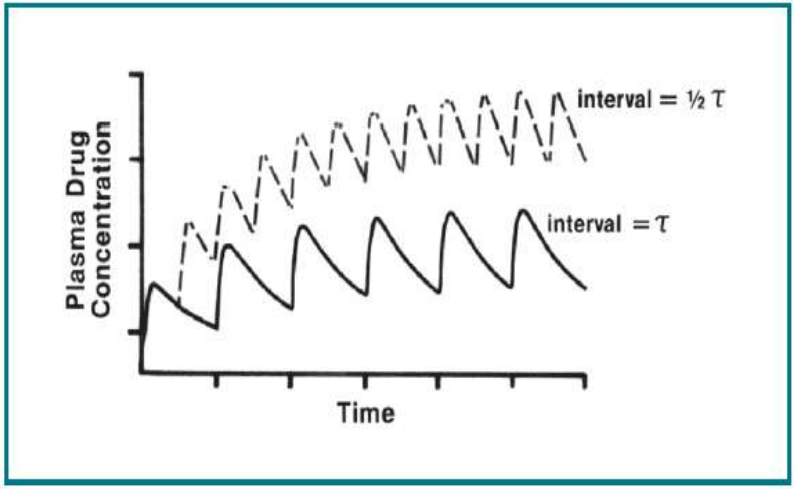
Pharmacokinetics (PK) & Pharmacodynamics (PD)

- 소실속도상수의 변화 (K_{el})
  - 투여량, 분포용적, 투여간격은 일정
  - 소실속도상수 (Kel) 감소 (∵ 신장이나 간의 기능 감소)
    - Peak, trough 농도 차이 감소
    - Peak, trough 농도는 각각 증가
    - Kel 감소로 인해, 반감기 증가 & SS에 도달하는 시간 증가



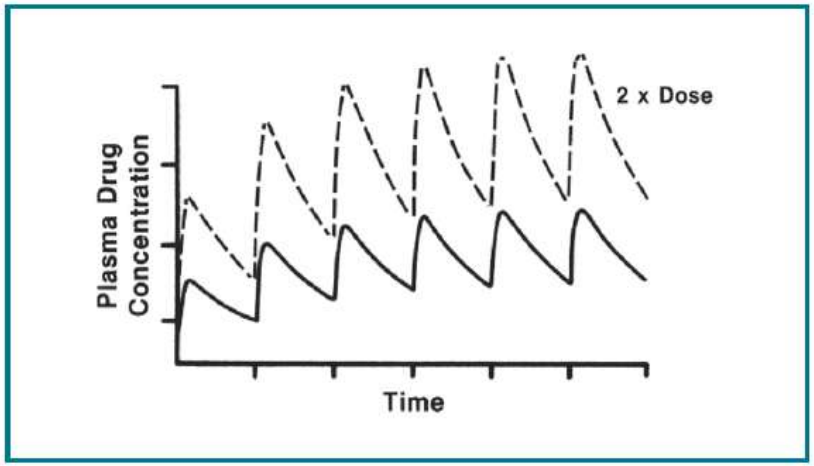
Pharmacokinetics (PK) & Pharmacodynamics (PD)

- 투여 간격의 변화
  - 투여량, 분포용적, 소실속도는 일정
  - 투여 간격 (τ) 감소
    - Peak, trough 농도 사이의 차이 감소
    - Peak, trough 농도, 각각 전보다 증가
    - Kel 변화가 없으므로, 반감기 & SS에 도달하는 시간 변화 없음



Pharmacokinetics (PK) & Pharmacodynamics (PD)

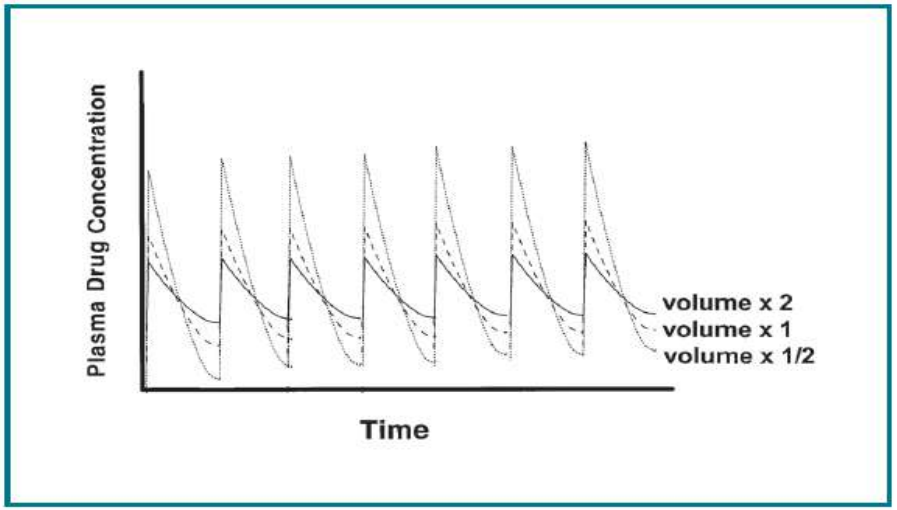
- 투여량의 변화
  - 투여간격, 분포용적, 소실속도는 일정
  - 투여량 증가
    - Peak, trough 농도 차이 증가
    - Peak, trough 농도, 각각 이전보다 증가
    - Kel 변화가 없으므로, 반감기 & SS에 도달하는 시간 변화 없음



- 분포 용적의 변화
  - 분포 용적의 증가
    - 신장, 심장 질환, 패혈증과 같은 감염성 질환 환자
    - 저알부민혈증 (hypoalbuminemia)이나 단백결합이 displacer에 의해 감소한 경우 (ex. Phenytoin ↔ valproate)

$$V_d = V_p + V_T\left(\frac{f_u}{f_{uT}}\right)$$

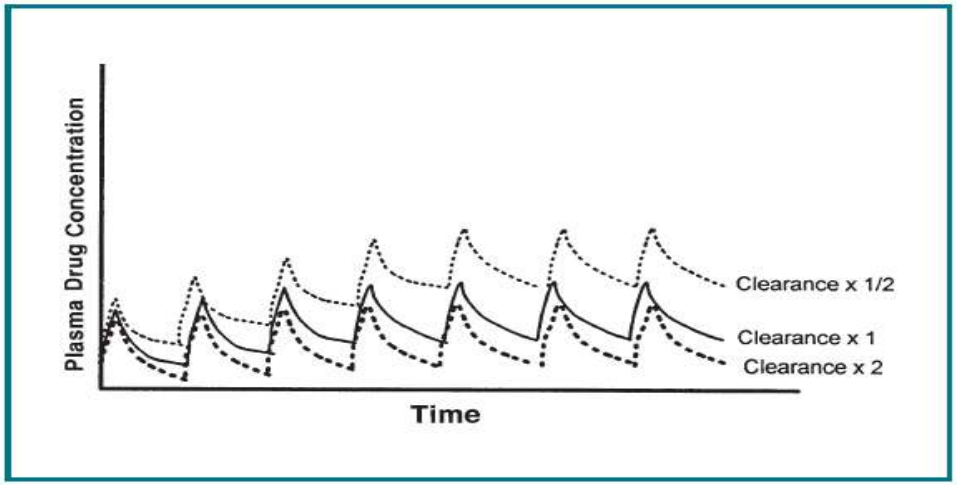
    - 심각한 외상이나 화상에 의한 전신 감염증 (systemic inflammation response syndrome)



- 청소율의 변화
  - 청소율 감소
    - Probenecid 와 penicillin 동시 투여
    - 간의 혈류를 저하시키는 약물 (ex, propranolol, indomethacin) 또는 간경변 등으로 인한 간 효소 대사능 저하

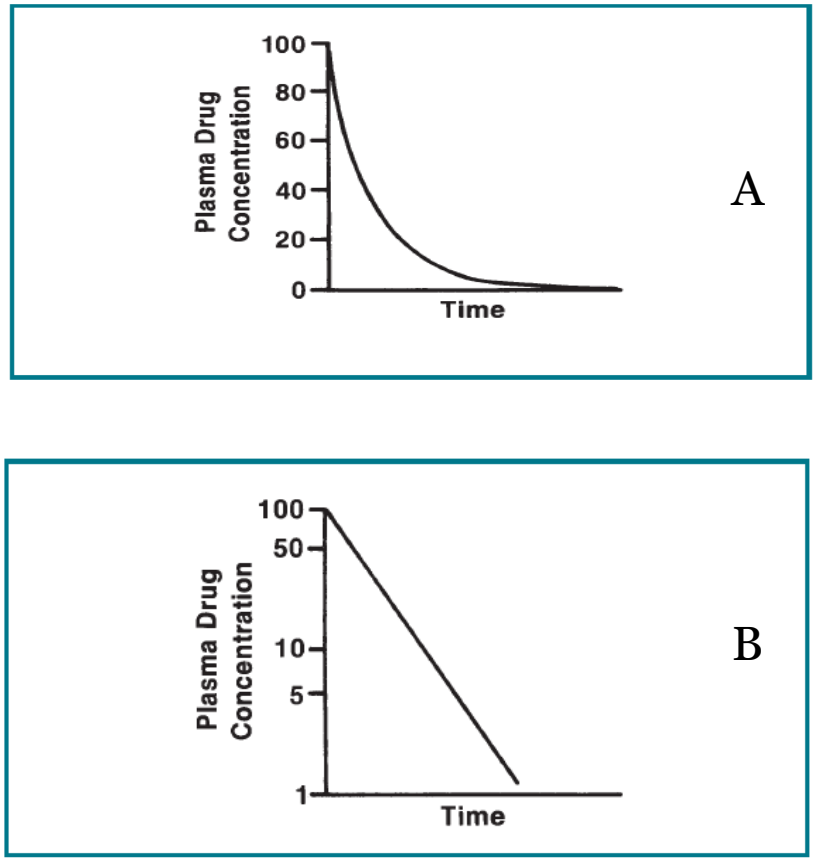
장기의 Clearance $= Q \times E$

$$Cl_{organ} = Q \times \frac{C_{in} - C_{out}}{C_{in}} \text{ or } Cl_{organ} = QE$$

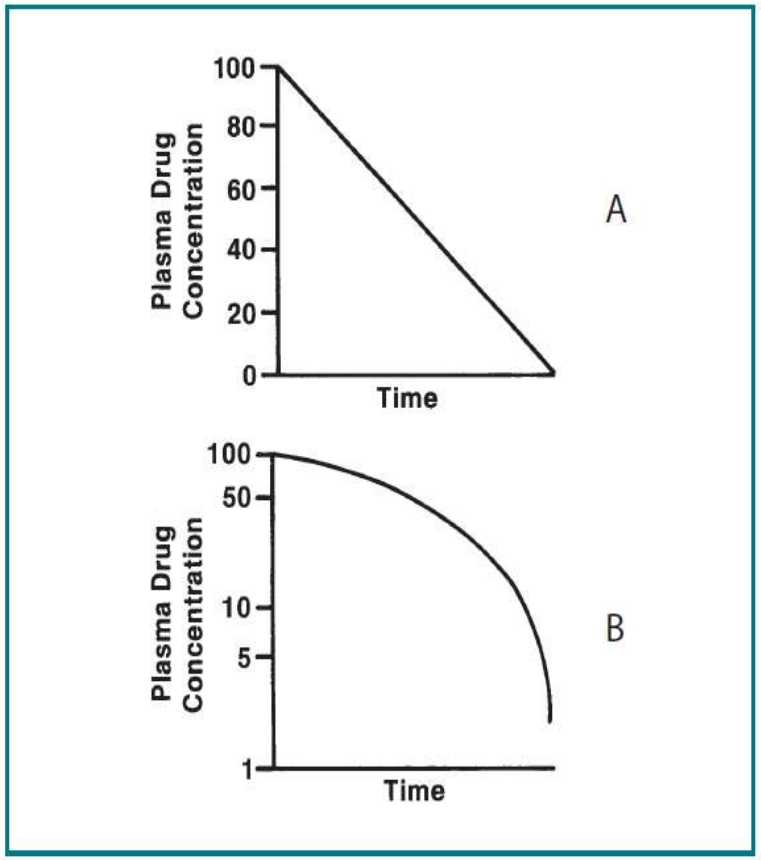


Pharmacokinetics (PK) & Pharmacodynamics (PD)

• 1차 속도



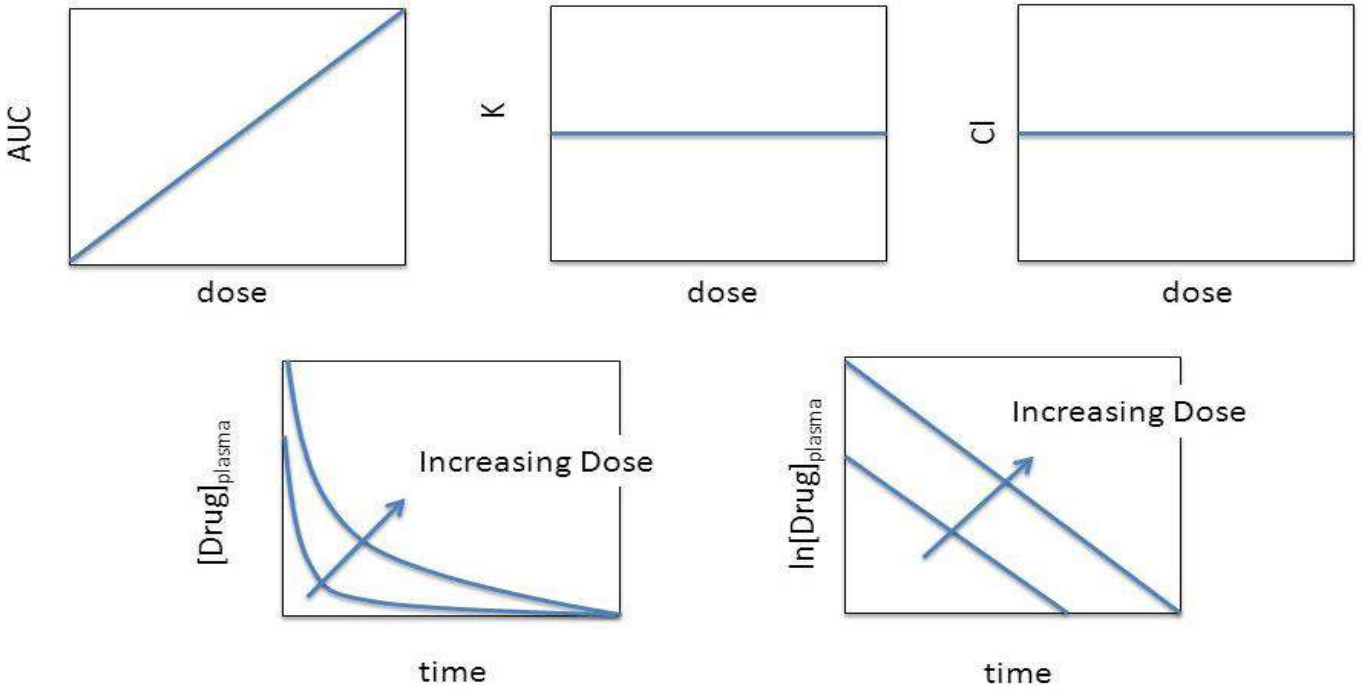
• 0차 속도



A: Y axis is normal scale, B: Y axis is log scale

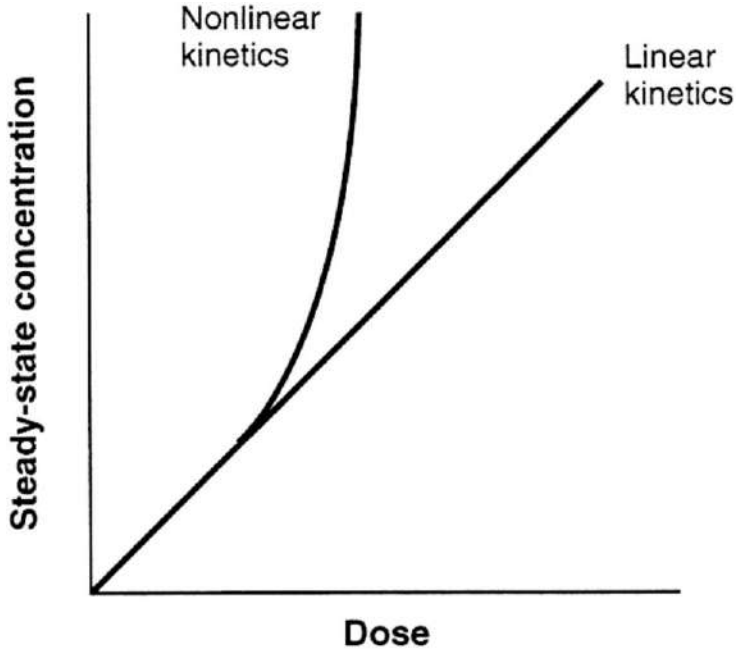
Pharmacokinetics (PK) & Pharmacodynamics (PD)

- Linear pharmacokinetics
  - All elimination and absorption kinetics are 1st order
  - most drugs follow linear pharmacokinetics
  - Concentration that results from the dose is proportional to that dose
  - the rate of elimination of the drug is proportional to the concentration



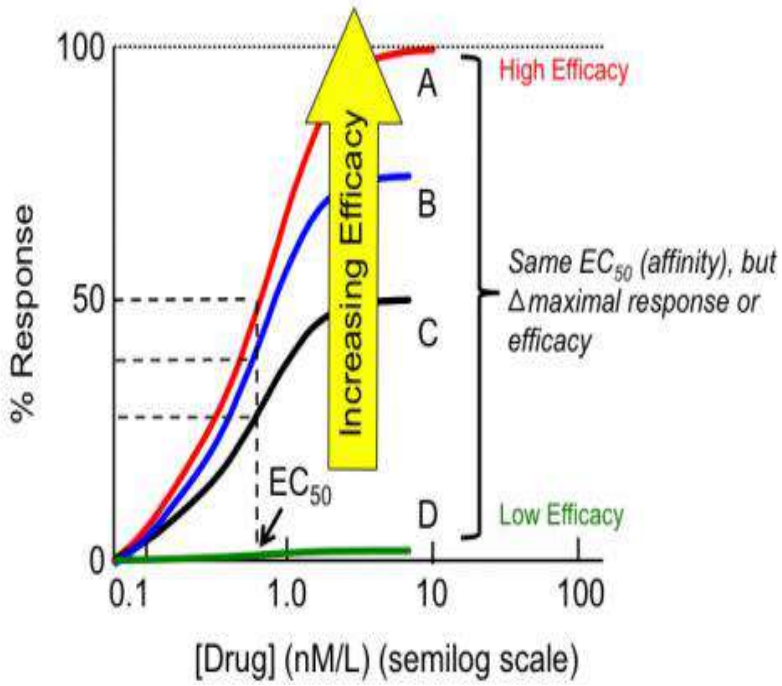
Pharmacokinetics (PK) & Pharmacodynamics (PD)

- Non-linear pharmacokinetics
  - Capacity-limited, dose or concentration-dependent, saturable pharmacokinetics
  - Occurs usually due to capacity-limited metabolism (e.g., phenytoin)
  - CL is not constant, it decreases with the increase of drug concentration.
  - SS concentration increases progressively with the rate of dosing and is poorly predictable !!



Pharmacokinetics (PK) & Pharmacodynamics (PD)

- Pharmacodynamics
  - Assumption: 대부분 수용체의 약물 농도가 약효를 결정함!
  - E_{max}
    - The maximum effect of drug
    - Associated with drug 'efficacy'
  - EC_{50}
    - Drug concentration at half efficacy of Emax
    - Associated with drug 'potency'



Pharmacokinetics (PK) & Pharmacodynamics (PD)

- Q) If patients or healthy volunteers have same PK parameters or PD parameters….Does the TDM or f/u or population approach is needed?

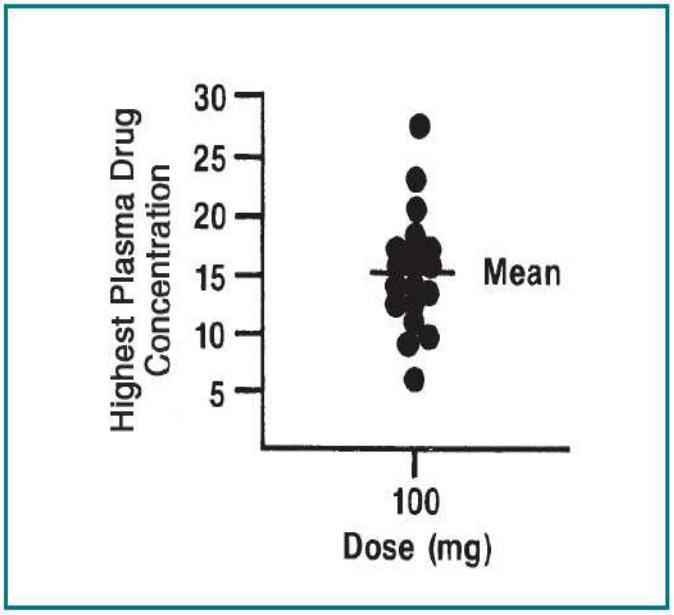


그림 1-8

같은 용량의 약물을 투여받은 환자 사이에 혈장 약물 농도가 다양하게 나타나는 예.

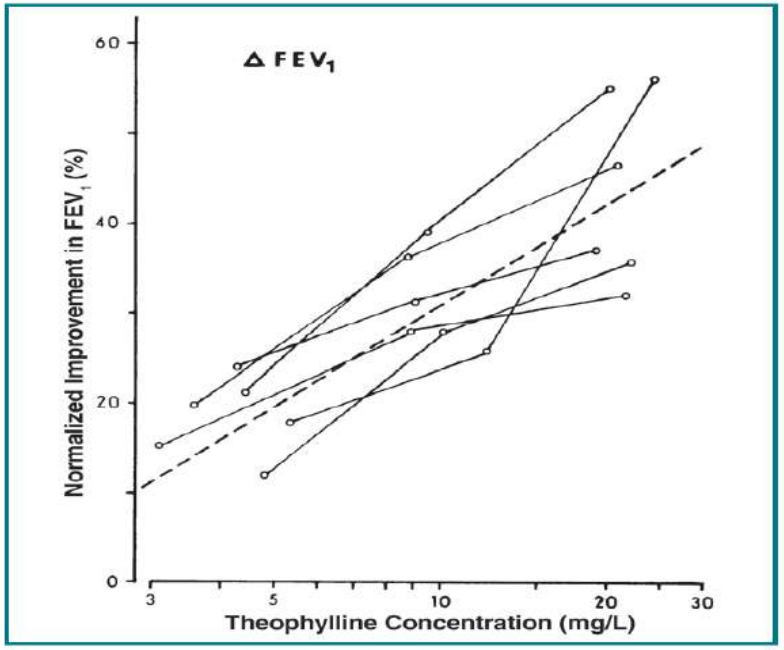


그림 1-10

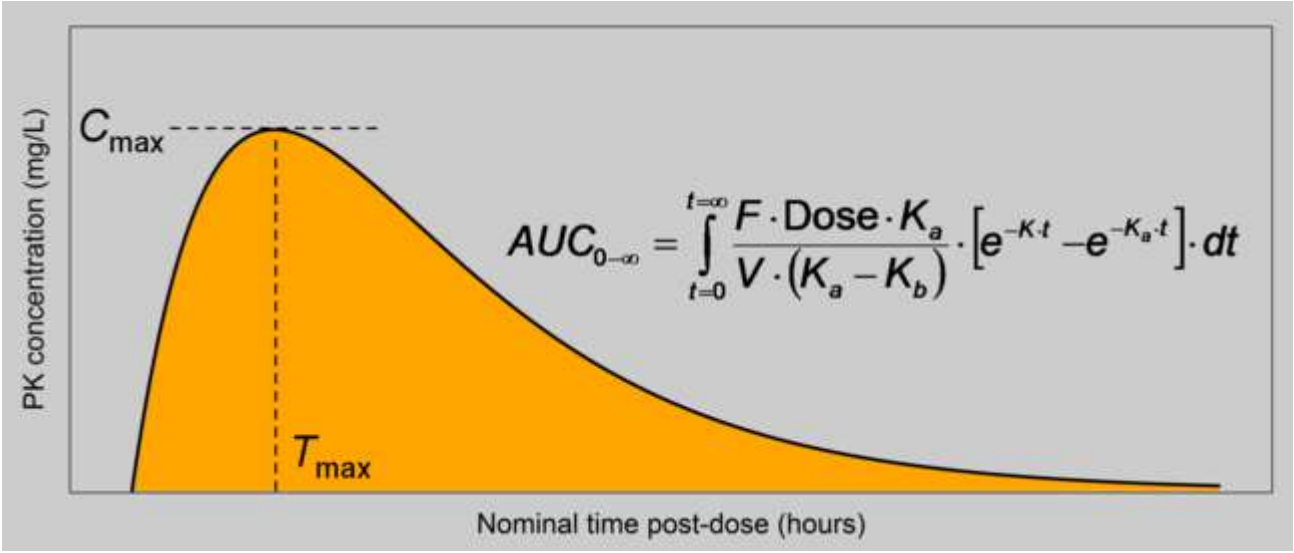
천식환자에서의 테오필린 (theophylline)의 혈중농도와 호기량 (FEV)의 관계.

Pharmacokinetics (PK) & Pharmacodynamics (PD)

- Clinical Pharmacokinetics
  - Design individualized dosage regimens
  - Optimize therapeutic response of a medication
  - Minimizing the chance of an adverse drug reaction
  - How?
    - By finding the intra- and inter-subject variability which can explain the difference of drug concentration among the patients
    - By establishing the relationship between PK parameter and confounding factor (covariates – e.g., WT, age, gender)

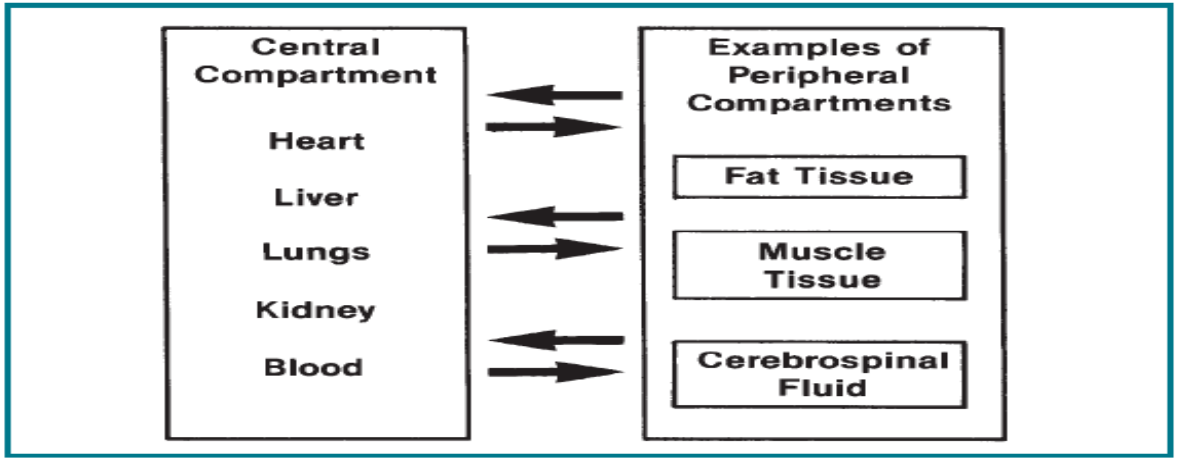
Concept and application of PK/PD M&S - NCA (PK model)

- Non-compartmental analysis (NCA)
  - Do not assume a body model (compartment)
  - Highly dependent on estimation of total drug exposure which is calculated by trapezoidal rule called Area under curve (AUC)
  - AUC, C_{max}, T_{max}, Volume of distribution, Clearance can be calculated by NCA
  - Only provide limited information



Concept and application of PK/PD M&S - Compartmental analysis (PK model)

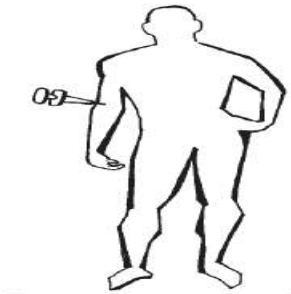
- Compartmental analysis
  - Model dependent analysis
  - Simplify complicated drug change in the body using 'compartment'



Concept and application of PK/PD M&S - Compartmental analysis (PK model)

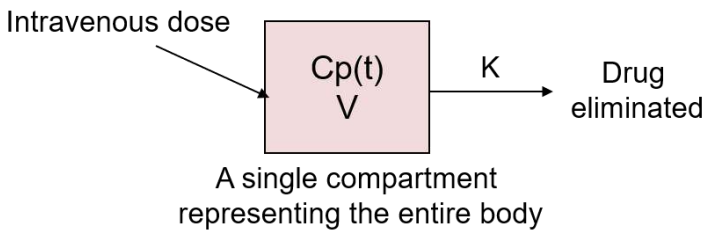
- Compartmental analysis
  - View the body as comprising kinetic compartments between which drug distributes and from which elimination occurs

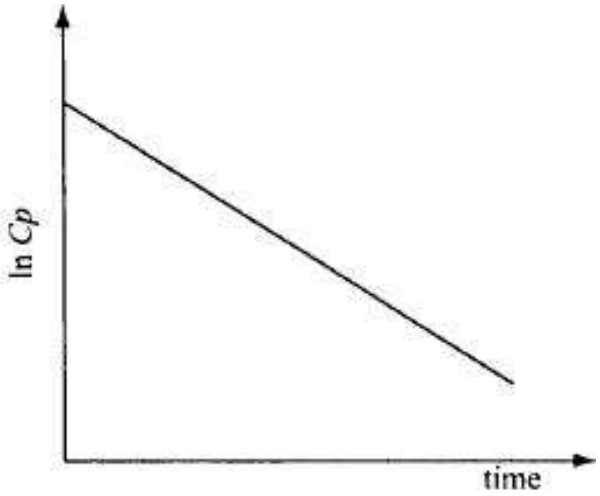
- One compartment model



One-compartment model before administration

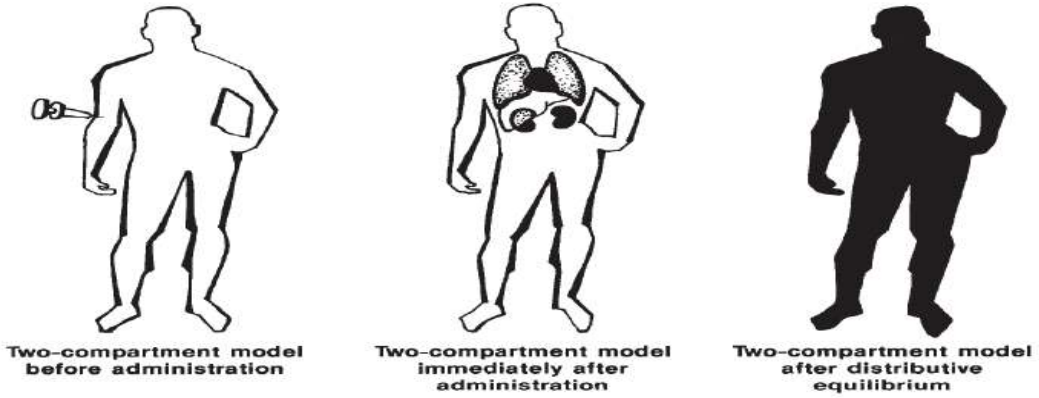
One-compartment model immediately after administration

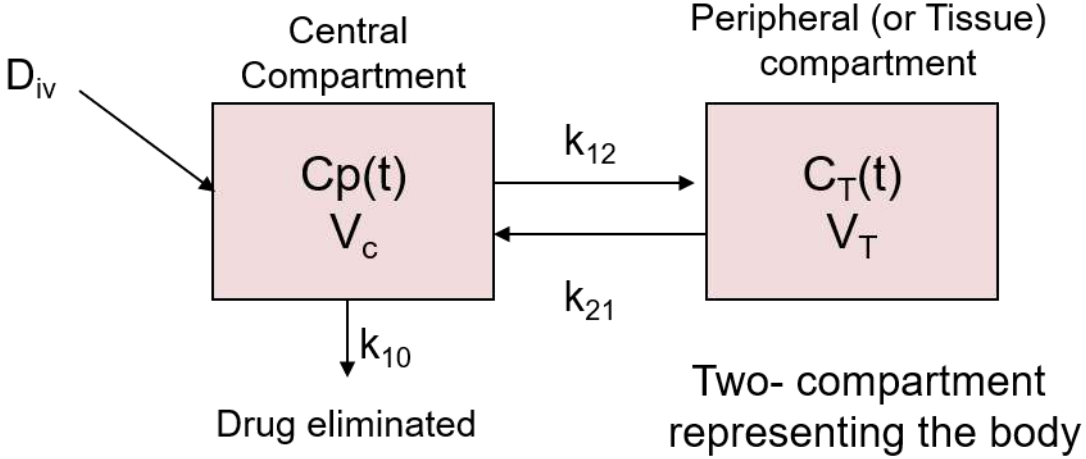


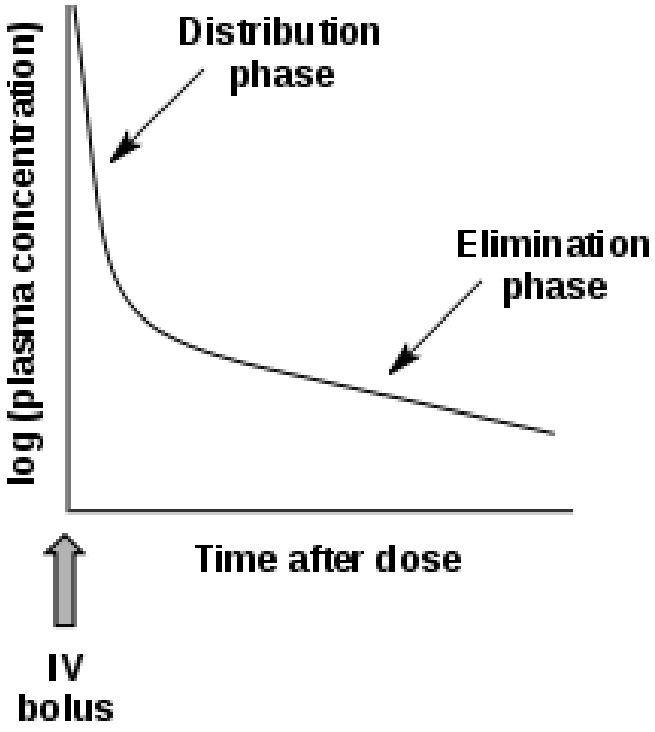


Concept and application of PK/PD M&S - Compartmental analysis (PK model)

- Two compartment model

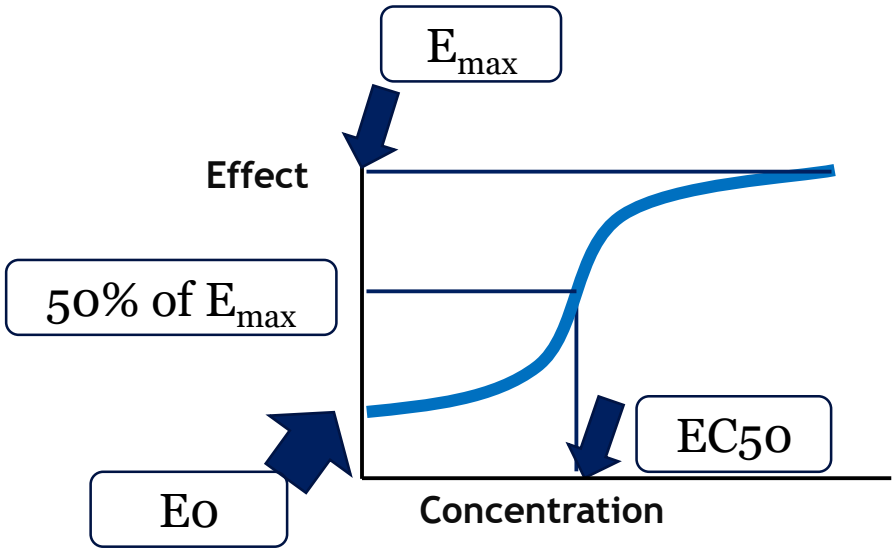






Concept and application of PK/PD M&S - PD model

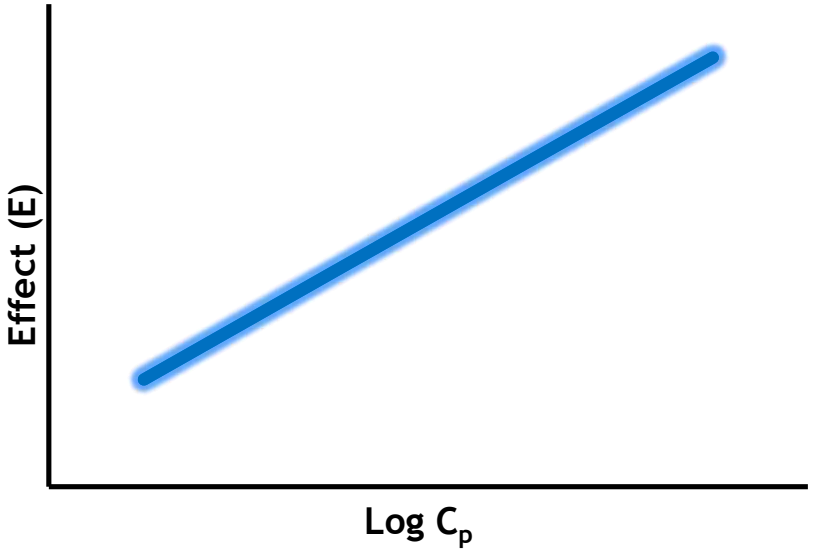
- Linear model
- Log-linear model
- E_{max} model
- Sigmoid E_{max} model
- Inhibitory E_{max} model



Concept and application of PK/PD M&S - PD model

- Log-linear model
  - 약물의 혈중 농도 (log transformation)와 약효가 linear한 관계
    - 약물 농도가 EC_{50}보다 낮은 경우 약효와의 관계를 설명
    - Disease progression model

  - $E = S \times C + E_0$
  - $E = S \times \log C + E_0$



Concept and application of PK/PD M&S - PD model

- Emax model

$$E = \frac{E_{max} \times C}{EC_{50} + C}$$

- Sigmoid Emax model

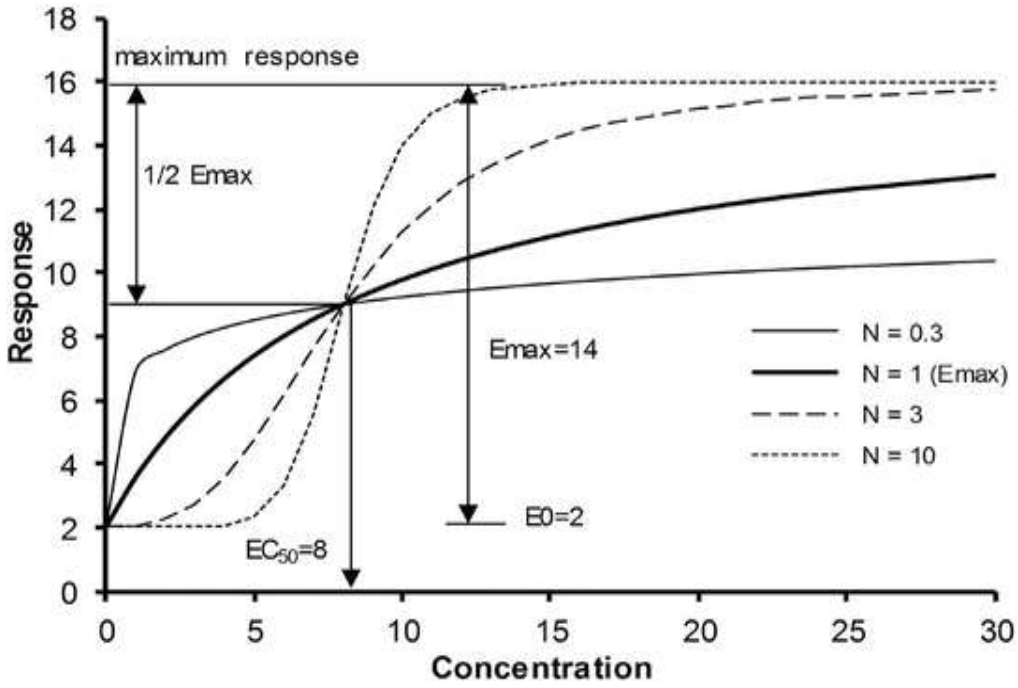
$$E = \frac{E_{max} \times C^{\gamma}}{EC_{50} + C^{\gamma}}$$

- Baseline effect model

$$E = E_0 \pm \frac{E_{max} \times C^{\gamma}}{EC_{50} + C^{\gamma}}$$

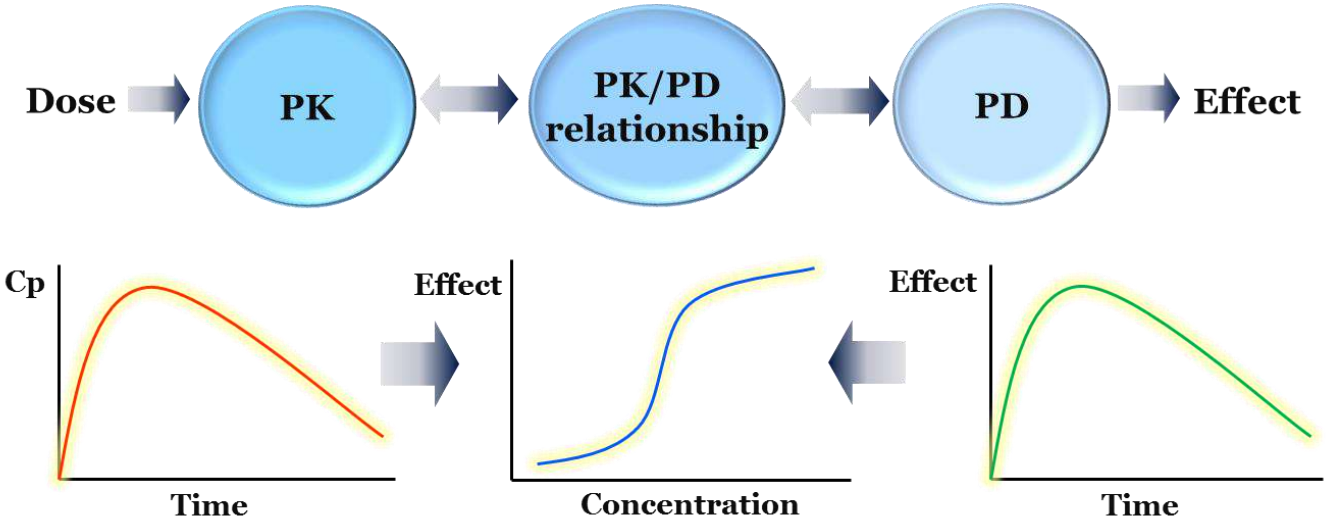
- Threshold model

$$E = \frac{E_{max} \times (C - C_0)^{\gamma}}{(EC_{50} - C_0)^{\gamma} + (C - C_0)^{\gamma}}$$



PK/PD model & simulation

- Definition:
  - 약물 투여 후 실험으로부터 얻어진 PK 및 PD data를 특정한 system 또는 공식에 따라 해석하여 data 해석의 신뢰성을 높이고 해석을 객관화하며, data가 존재하지 않는 부분의 값 을 추정하고 투여환경이 변화된 상태의 simulation이 가능하게 하는 것.



PK/PD model & simulation

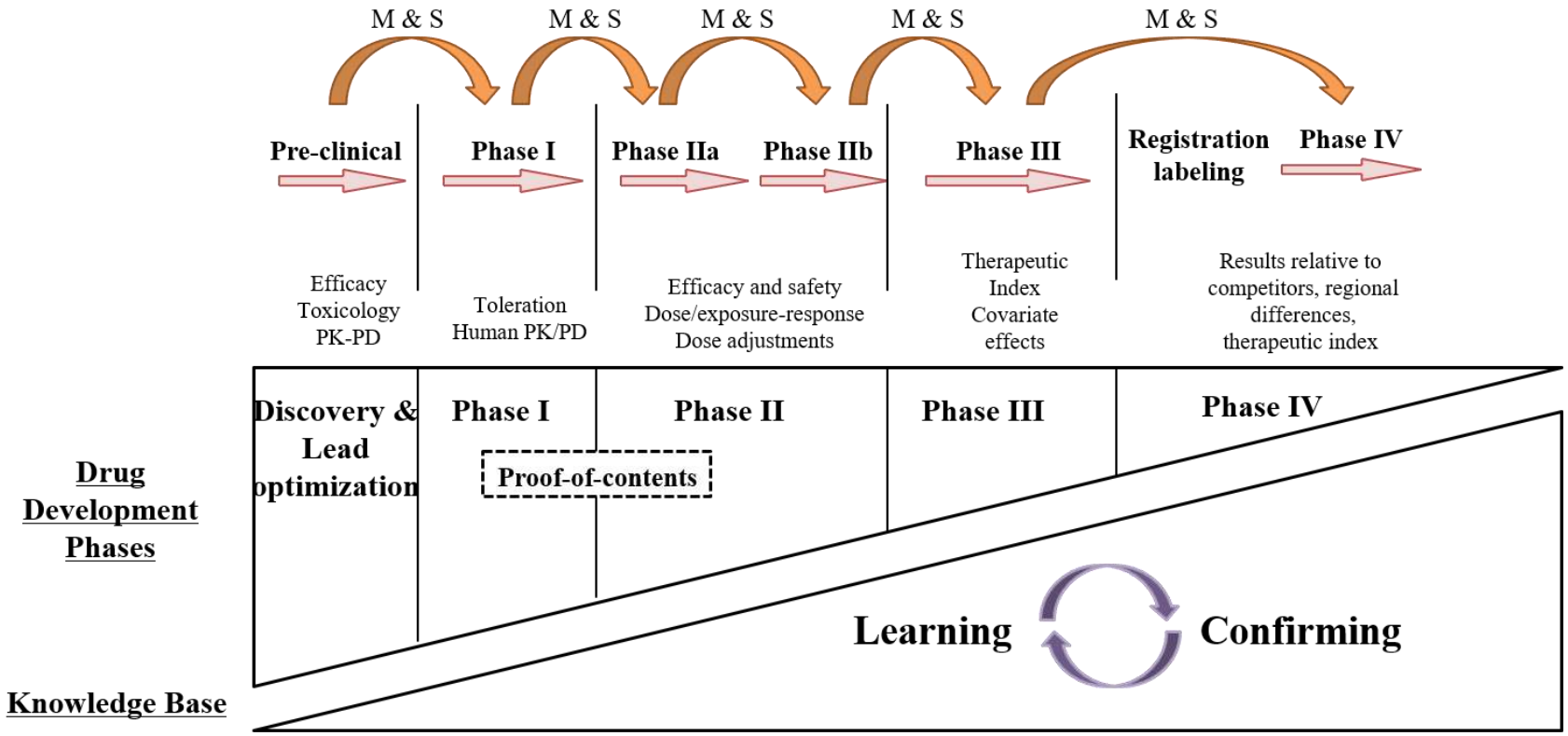
- Estimation of inter relationship between **dose-efficacy** in drug development (critical path)
- **Prediction** of experimental result of **new dosing method (simulation)**
- Estimation of action mechanism of drug **(mechanism based modeling)**
- **Qualification of new biomarker** (clinical validation)
- Tool of **translational research**
- Objective interpretation of experimental result and **decision making** (go, no go decision)
- Prediction of dose-efficacy correlation to control dosing regimen (**personalized medicine**)

PK/PD model & simulation

- Critical path
  - FDA report to improve the system of new drug development
  - The scientific process through which a potential human drug can be developed efficiently.
    - Predict whether a product candidate will be safe and effective, so can decide which candidates to move to each successively more rigorous phase of testing
    - Assess whether a product candidate is safe and effective, once the potential product is moved into human testing
    - Manufacturing large amount of the product, and assess the quality of the finished product

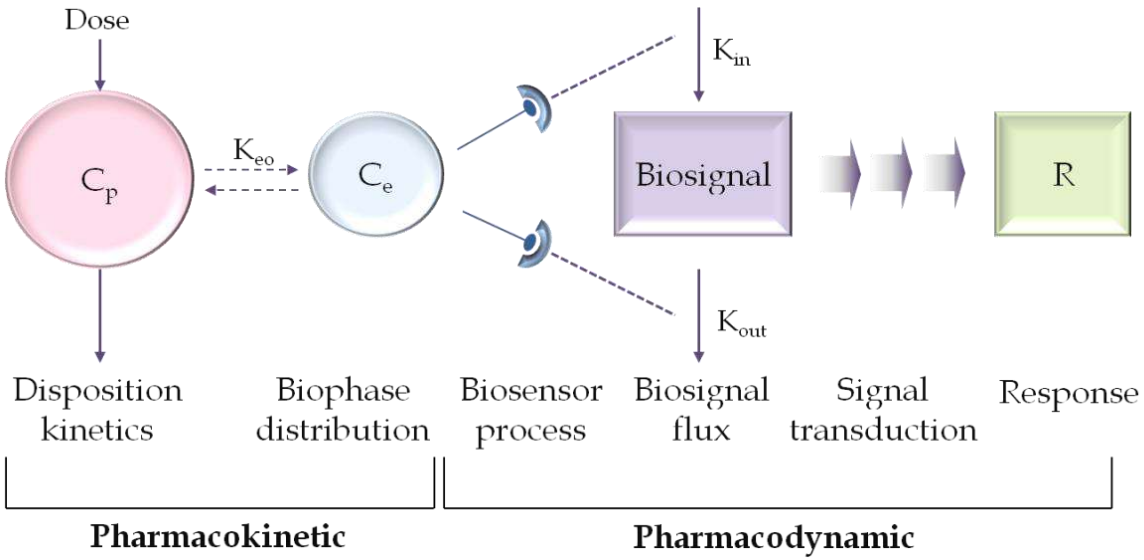
- **Critical path tools**: Animal models of human disease, Biomarker, PK/PD modeling & Clinical trial design, quality assessment technology

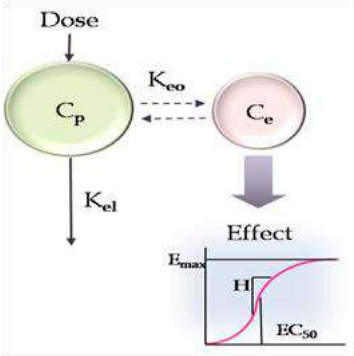
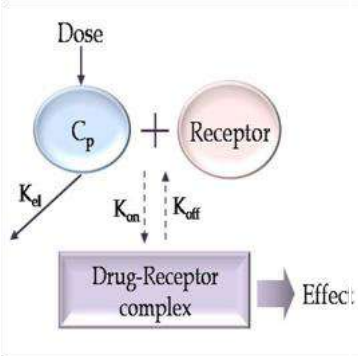
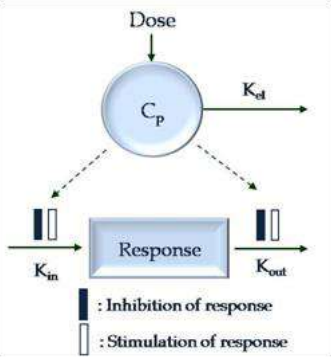
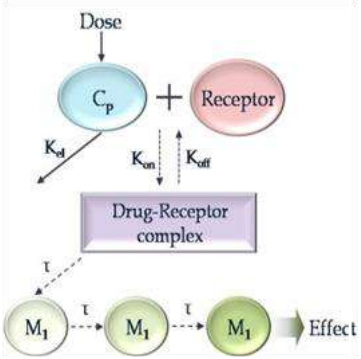
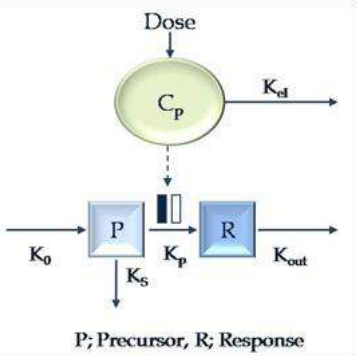
PK/PD model & simulation



- Effective implementation of **learning and confirming** requires timely application of **modeling and simulation** tools

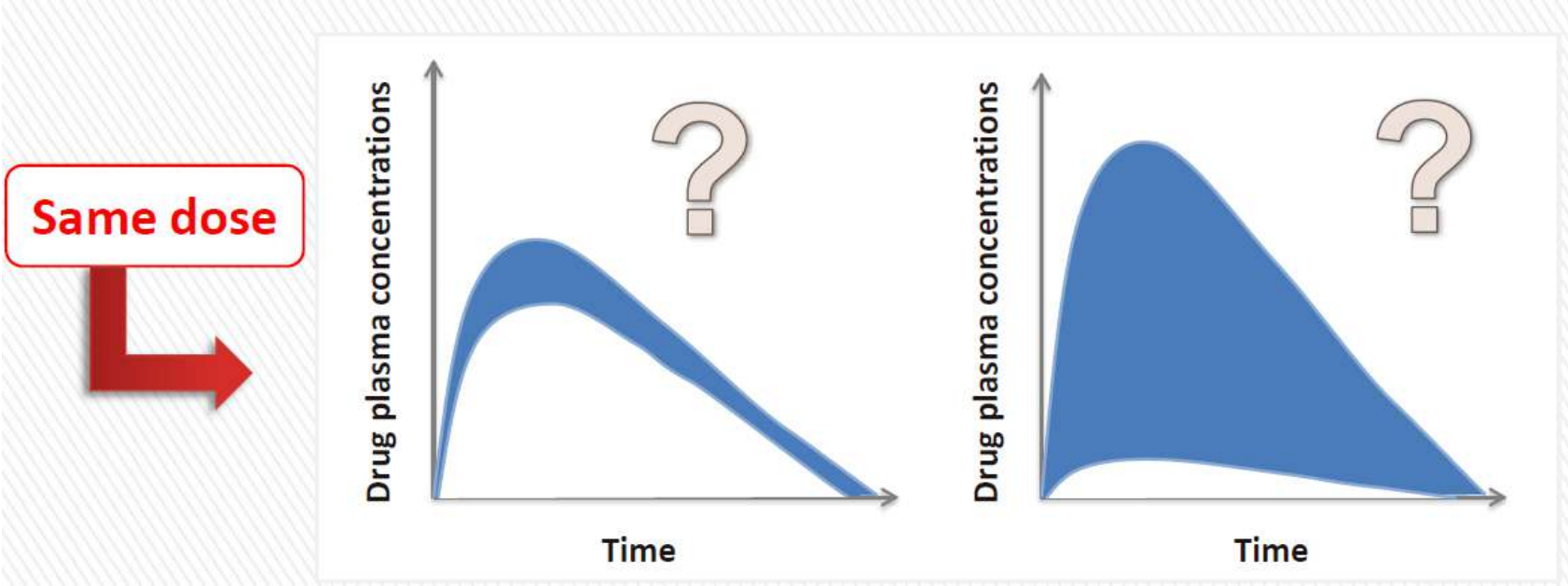
PK/PD model & simulation



Biophase model	Slow receptor binding model	Indirect response model	Signal transduction model	Precursor pool deletion
				

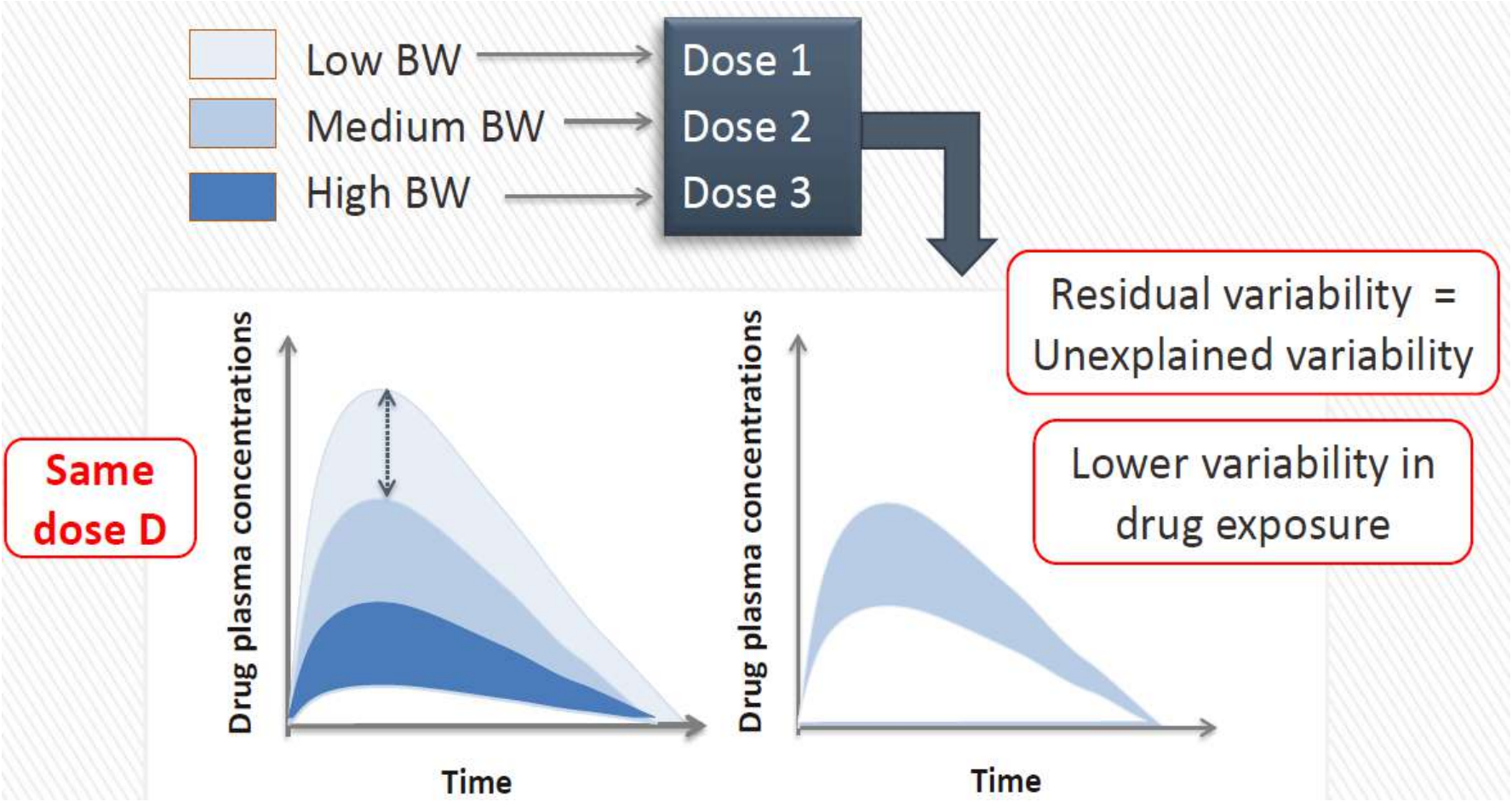
PK/PD model & simulation

- To quantify the PK variability in the target population under the real conditions of drug use



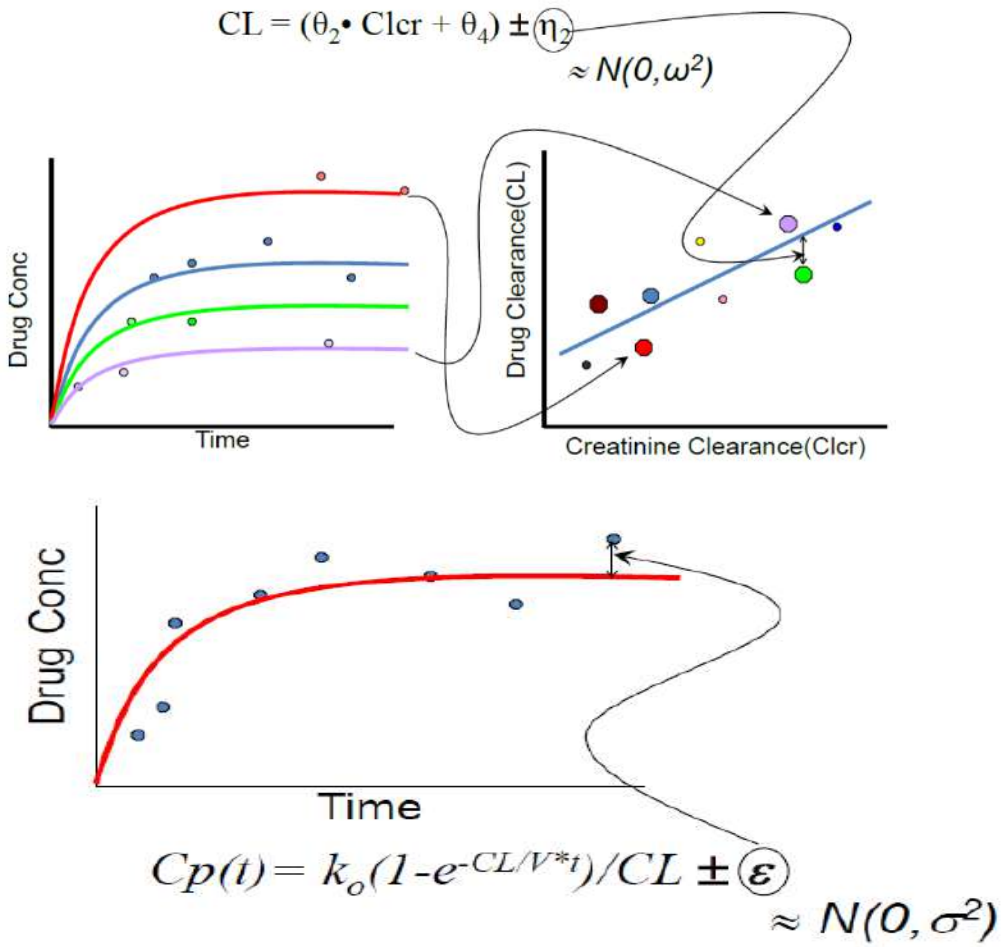
PK variability	Small	Big
Adjust dose?	No	Yes, depending on therapeutic window

- To explain this variability with covariates when it is sufficiently large to justify a dose adjustment



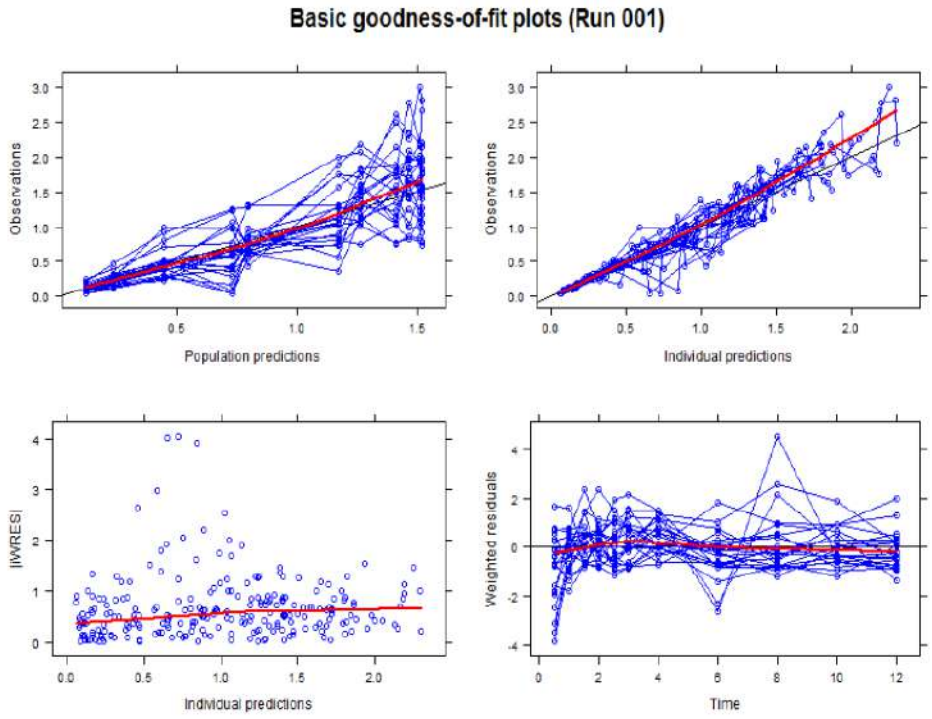
PK/PD model & simulation

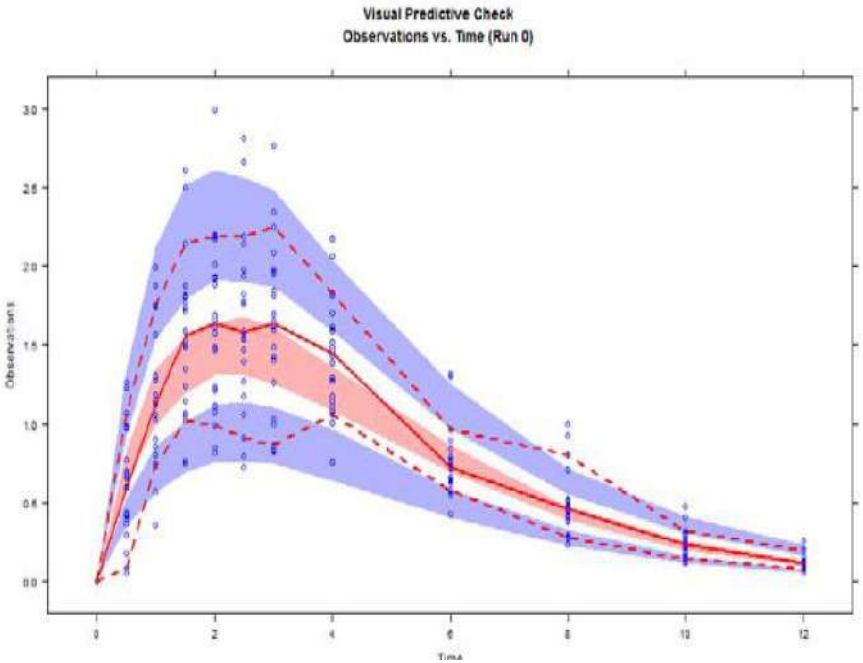
- Finding appropriate covariate which could affect PK parameters and its response



PK/PD model & simulation

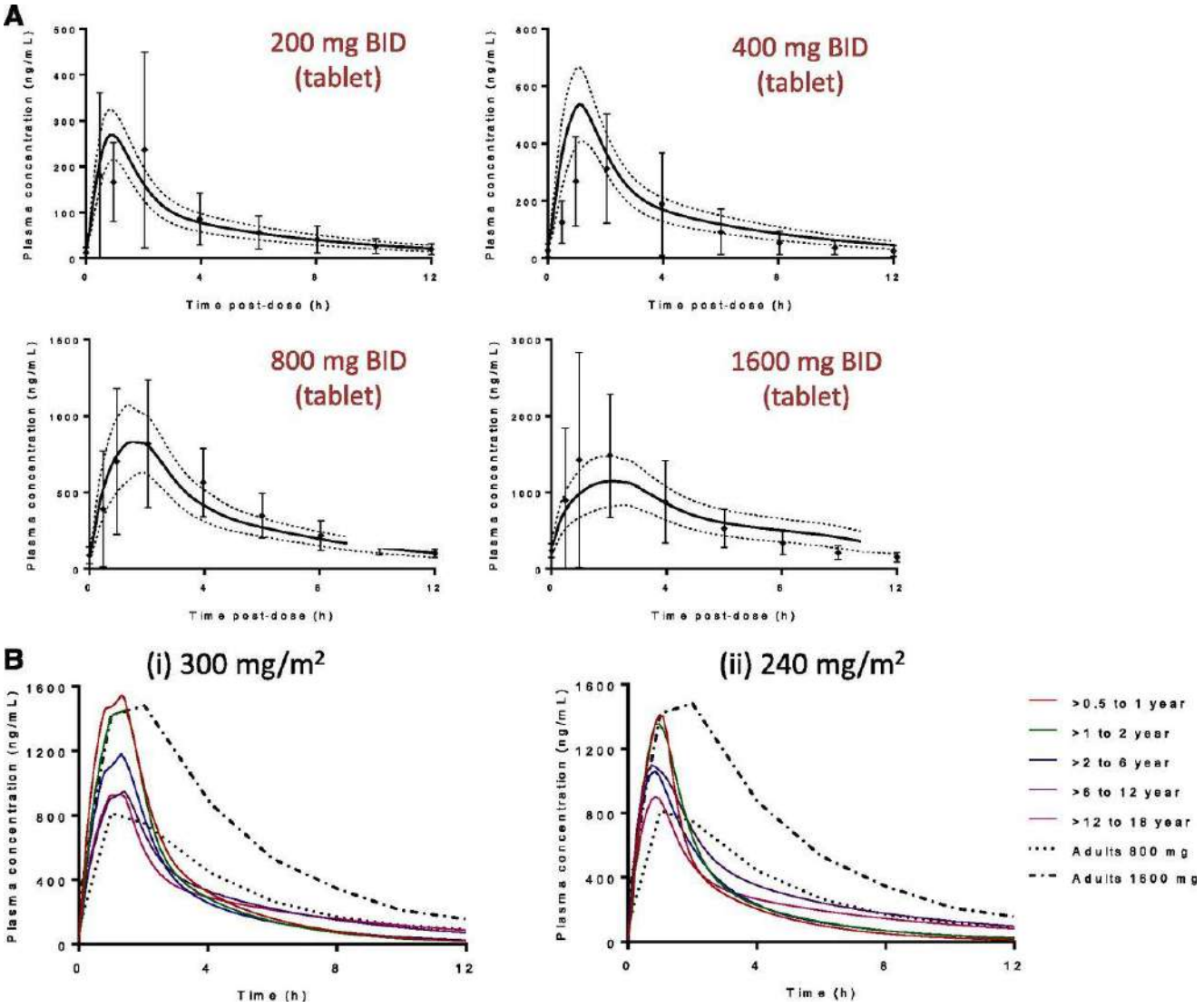
- Model evaluation





PK/PD model & simulation

- Simulation



Case I

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2012.04260.x

Population PK/PD analysis of metformin using the signal transduction model

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Keywords
antihyperglycaemic effect, metformin, PK/PD, signal transduction model, simulation

Received
7 February 2011

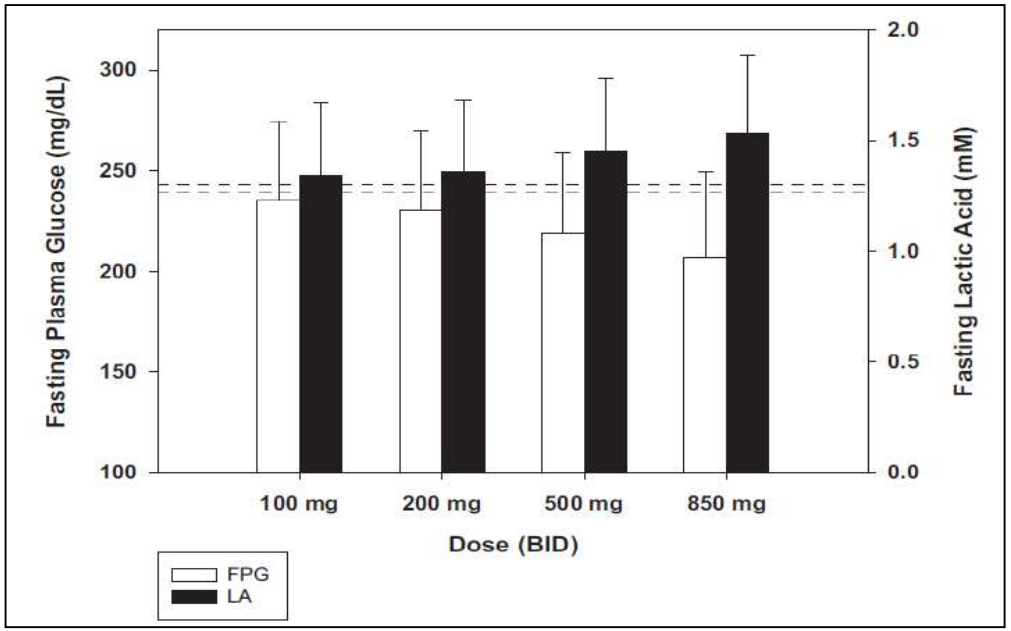
Accepted
24 February 2012

Case I

- Metformin
  - A biguanide glucose lowering agent which commonly is used to manage type 2 diabetes
  - MOA
    - Not clearly identified, but mainly assumed due to **turnover of biomarker such as glucose and signaling pathways or translocation of glucose transporters**
- Aims
  - To develop a population PK/PD model for metformin (500 mg) using the signal transduction model in healthy volunteers, and predict the PK/PD profile in patients with type 2 diabetes

Case I

Disease	Biomarker	Surrogate endpoint
Diabetes mellitus (Biguanides)	***Fasting plasma glucose concentration***	***Fasting plasma glucose concentration***
	HbA1C	***HbA1C***
	Plasma insulin concentration	Plasma insulin concentration
	Insulin resistance value (HOMA-IR, OGTT)	-
	C-reactive protein	-



➢ ***Fasting plasma glucose (FPG) concentration***

- The FPG of patients with diabetes > 126 mg/dL.
- The 2 hr postprandial glucose of patients with diabetes > 200 mg/dL

Ying. H, Population Exposure-Response Modeling of Metformin in patients with Type 2 diabetes Mellitus. Quantitative Clinical Pharmacology. 48, 696-707 (2008)

Case I

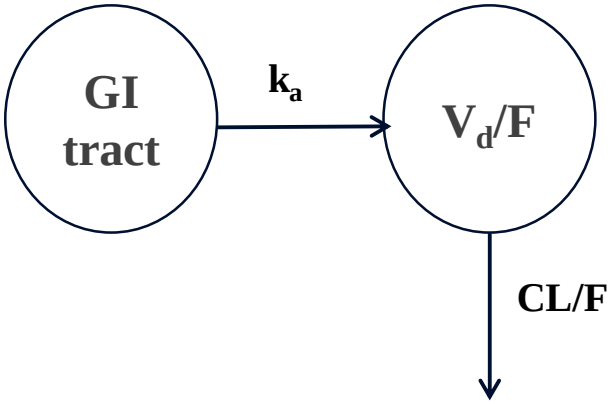
- Metformin tablet 500 mg one time.
- Sampling time : 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 hr
- PK - plasma concentrations of metformin using LC-MS/MS
- PD - plasma glucose concentrations using glucose-oxidase/UV
- Demographic and data characteristics

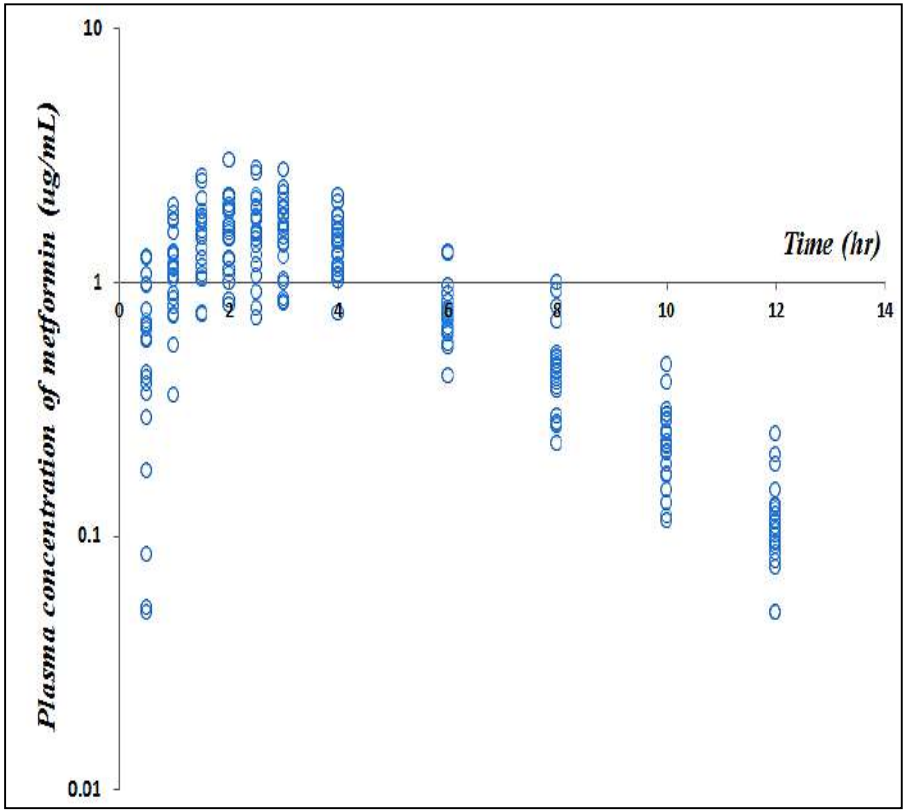
	Mean (SD)	Median	Range
Number of healthy humans	42		
Number of observations (PK/PD)	1008 (504/504)		
Age (years)	26 (4)	27	21–31
Weight (kg)	69 (8)	69	61–78
Height (m)	1.8 (0.1)	1.7	1.6–1.8
FPG (mg dl^{-1})	98 (7)	98	92–105
CL_{cr} (ml min^{-1})	107 (16)	106	90–123
TBIL (mg dl^{-1})	1.1 (0.3)	1.1	0.8–1.6
Hb (g dl^{-1})	16 (0.8)	16	15–17

Jung-woo Chae. Population PK/PD analysis of metformin using the signal transduction model. British journal of clinical pharmacology. 74 (5): 815-823. (2012)

Case I

- ***Final Pharmacokinetic model of metformin***

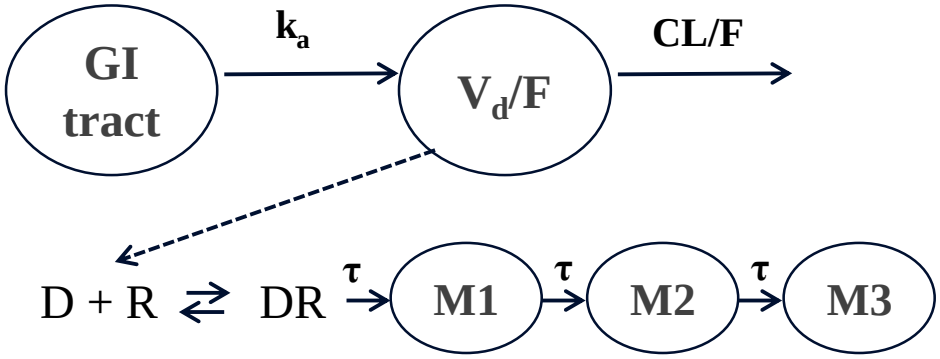




- K_a (hr^{-1}) = 0.4
- V_d/F (L) = 113
- CL/F (L/hr) = 52.6 · $(CL_{CR}/106.5)^{0.782}$

Case I

- ***Signal transduction model***



- $DR = {(E_{max} \cdot (Conc)^r)}/{((Conc)^r + (EC_{50})^r)}$
- $\frac{dM1}{dt} = {(DR - M1)}/{\tau}$
- $\frac{dM2}{dt} = {(M1 - M2)}/{\tau}$
- $\frac{dM3}{dt} = {(M2 - M3)}/{\tau}$
- Response = M3

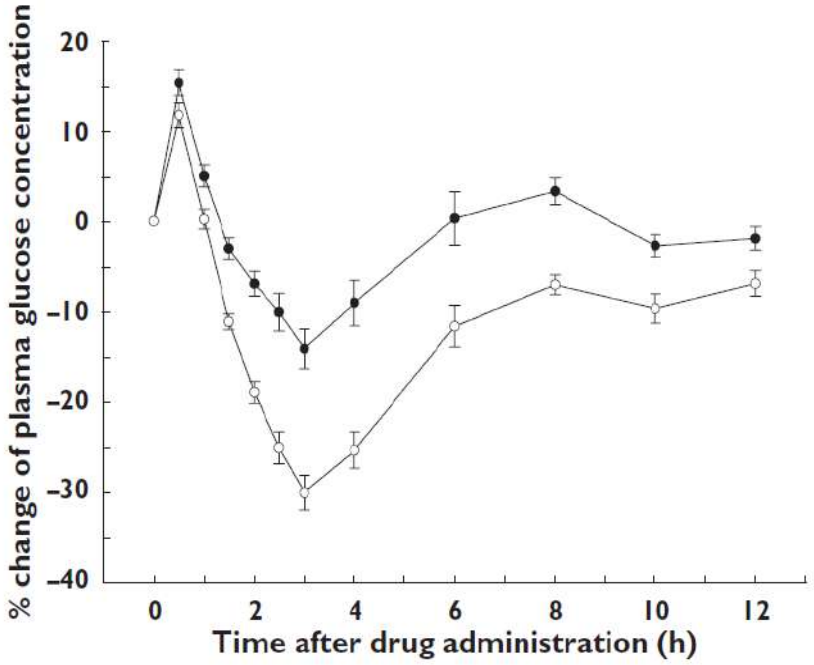


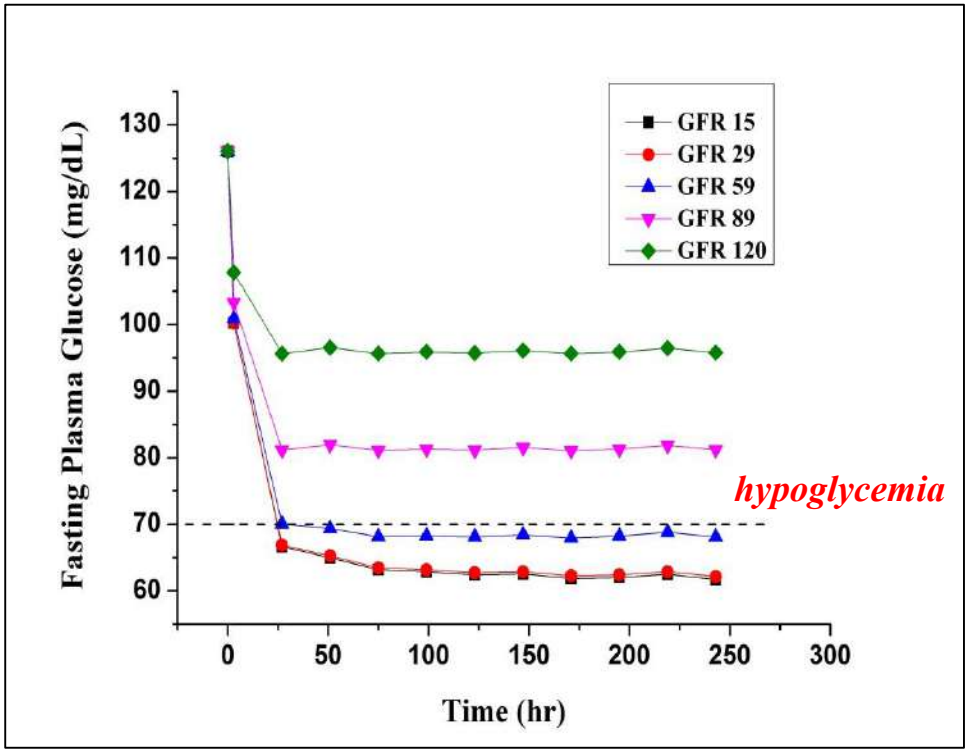
Figure 1

Time course of the percent change in plasma glucose concentration from baseline (mean ± SE, $n = 42$). Black circles are the control group (–●–), and white circles are the metformin group (–○–). All volunteers consumed 12 g of sugar 20 min after drug administration and abstained from food until 4 h after the administration

Case I

- Metformin is cleared from the body by renal elimination and excreted unchanged form in the urine.
- Stage in chronic kidney disease patients
  - CL/F (L/hr) = 52.6 · ($\mathbf{CL_{CR}}$/106.5)$^{0.782}$

CKD STAGE	STATE	GFR level (mL/min/ 1.73 m^2)
STAGE 1	Slightly diminished function	>89
STAGE 2	Mild reduction in GFR	60-89
STAGE 3	Moderate reduction in GFR	30-59
STAGE 4	Severe reduction in GFR	15-29
STAGE 5	Kidney failure or end stage renal disease	<15



National Kidney Foundation (2002). "K/DOQI clinical practice guidelines for chronic kidney disease". Retrieved 2008-06-29.

Case II

Cancer Chemother Pharmacol (2016) 78:623–632
DOI 10.1007/s00280-016-3104-9

ORIGINAL ARTICLE

BSA and *ABCB1* polymorphism affect the pharmacokinetics of sunitinib and its active metabolite in Asian mRCC patients receiving an attenuated sunitinib dosing regimen

Jung-woo Chae[1,2] · Yi Ling Teo[2] · Han Kiat Ho[2] · Jaeyeon Lee[1] · Hyun-moon Back[1] · Hwi-yeol Yun[1] · Mats O. Karlsson[4] · Kwang-il Kwon[1] · Alexandre Chan[2,3]

Received: 18 March 2016 / Accepted: 6 July 2016 / Published online: 2 August 2016

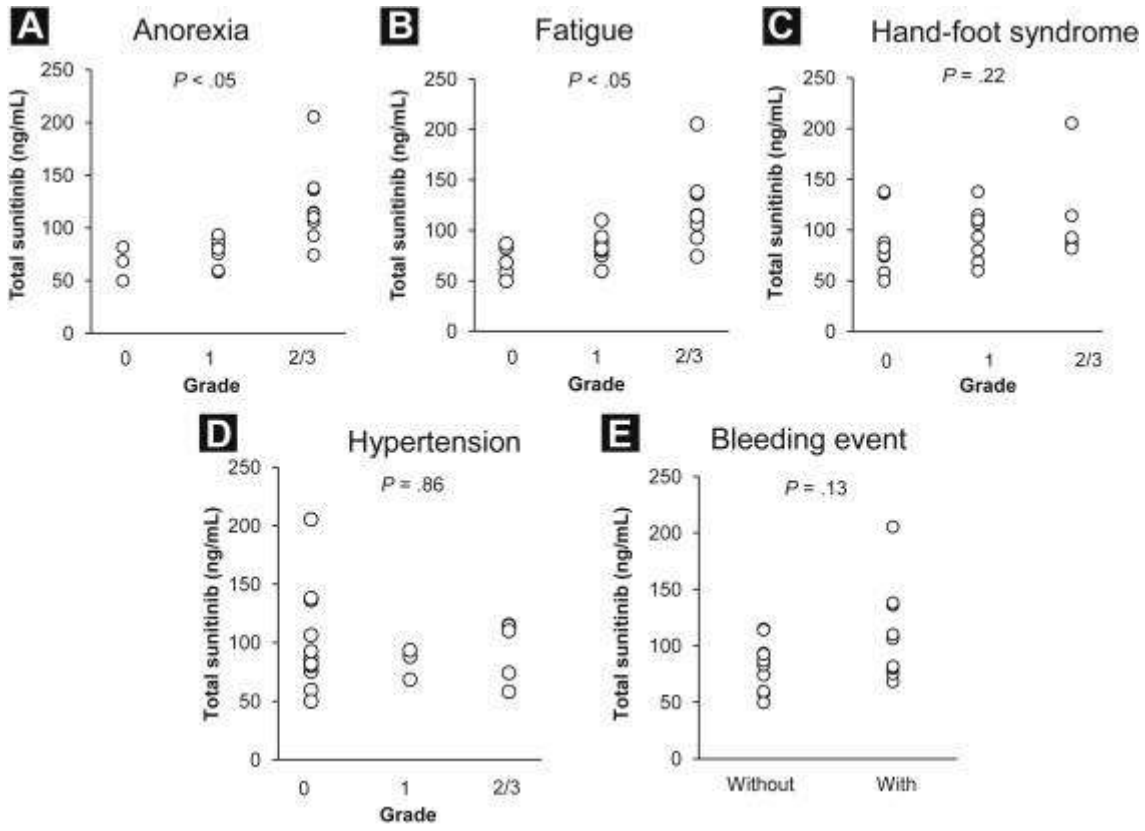
Case II

- Sunitinib malate
  - Standard treatment option of metastatic renal cell carcinoma (mRCC)
  - Sunitinib 50 mg daily for 4 weeks, 2 weeks off therapy
  - Side effects
    - Fatigue, diarrhea, nausea, anorexia, hypertension, a yellow skin discoloration, hand-foot skin reaction, and stomatitis
  - Active metabolite (SU12662) mainly metabolized in liver

Parameter	Contents
Protein binding	95%
Metabolism	Hepatic(CYP3A)
Half-life	40~60 hours
Excretion	Fecal (61%) and renal (16%)

Case II

- The **total trough level (TTL)** of sunitinib and SU12662, the active metabolite, between 50 and 100 ng/mL was proposed as the target range for efficacy and safety



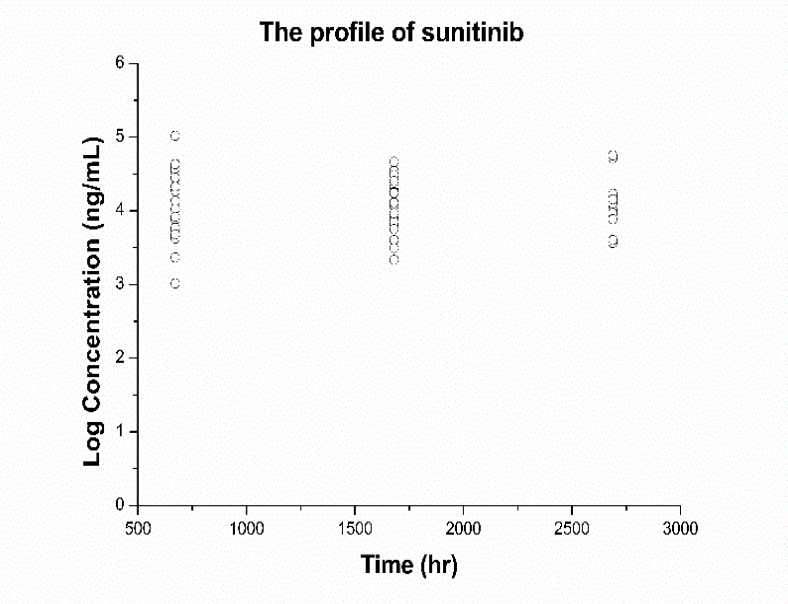
Case II

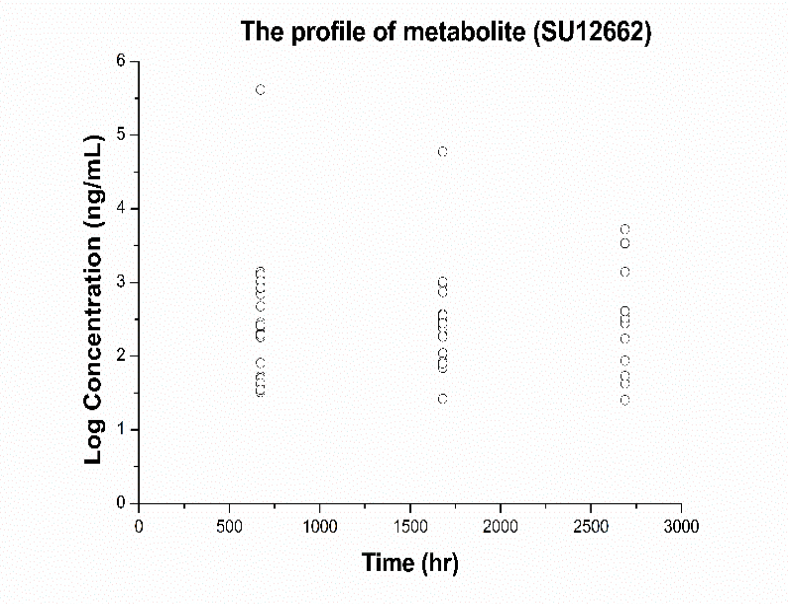
- Introduction
  - ***An attenuated dosing (AD) sunitinib regimen of 37.5 mg daily*** has been suggested to reduce the toxicity

- Aim
  - To characterize the population PK properties receiving AD regimen and to ascertain significant covariates influencing PK parameters

Case II

- Sunitinib 37.5 mg daily for 4 weeks, 2 weeks off therapy for 3 cycles
- A blood sample was collected on day 29 of each treatment





Case II

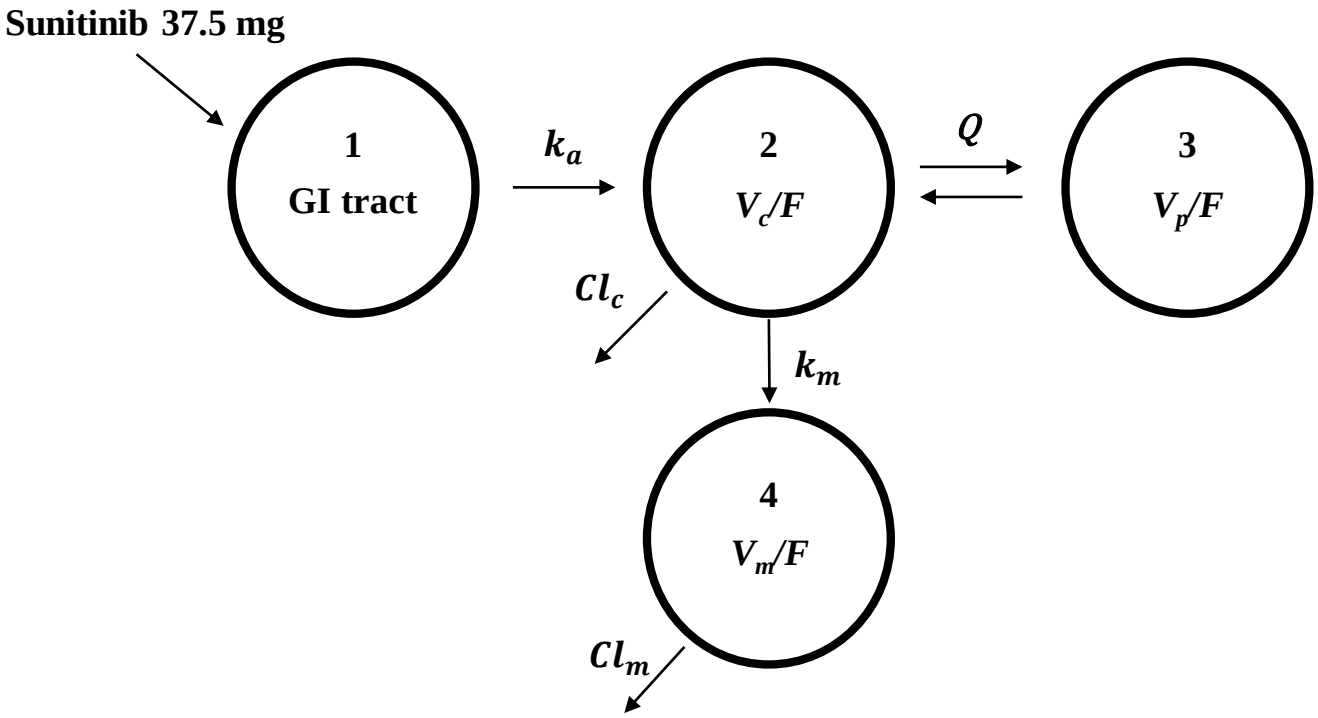
- Demographic data

Characteristics	n (%)
Age, year (SD)	58.8 (9.8)
Weight, kg (SD)	65.9 (13.4)
Gender	
Male	26 (83.9)
Female	5 (16.1)
Ethnicity	
Chinese	27 (87.1)
Malay	2 (6.5)
Indian	2 (6.5)
Presence of comorbidities	21 (67.7)
Previous nephrectomy	22 (71.0)
Body Surface Area (BSA, Mean±SD)	1.73±0.2

Characteristics	n (%)
Site of metastasis	
Lung	24 (77.4)
Bone	9 (29.0)
Brain	3 (9.7)
Liver	3 (9.7)
Others	1 (3.2)
ABCB1 polymorphism	
CC (Wild genotype)	9 (36)
CT/TT (Mutant genotype)	16 (64)
CYP3A5	
*1*1	5 (20)
*1*3	10 (40)
*3*3	10 (40)

Case II

- PK model development which describe simultaneously sunitinib and its metabolite



Case II

- $CL/F_{sunitinib}(L/hr) = 16.9 \times BSA(effect) \times ABCB1(effect)$
- **Final model에서 산출된 sunitinib과 대사체(SU12662)의 약동학 파라미터는 아래와 같음.**
  - $Cl_c/F = 16.9 \longrightarrow$ *12.1 (BSA=1.6 m²), 27.7 (BSA=2.0 m²)*
  - $Cl_c/F = 16.9 \longrightarrow$ *8.9 (ABCB1 Wild type), 16.9 (ABCB1 Mutant type)*

Estimates of sunitinib

Parameter	Estimate (%RSE)	IIV (CV%) (%RSE)	IOV (CV%) (%RSE)
k_a (hr^{-1})	0.2	-	-
V_c/F (L)	1720	-	-
CL_c/F (L/hr)	16.9 (9.1%)	35.7 % (17.6%)	19.7% (40%)
BSA on CL_c/F	3.71 (23%)	-	-
ABCB1 polymorphism on CL_c/F	-0.476 (20%)	-	-
Q	21.2	-	-
V_p/F (L)	893	-	-
k_{cm} (hr^{-1})	0.0044 (30%)	-	-
Proportional error	0.147 (29%)	-	-

Estimates of metabolite (SU12662)

Parameter	Estimate (%RSE)	IIV (CV%) (%RSE)	IOV (CV%) (%RSE)
V_m/F (L)	1410	-	-
CL_m/F (L/hr)	42.7 (23%)	56.1 % (35%)	-
Proportional error	0.323 (30%)	-	-

Abbreviations: IIV, Inter-individual variability; IOV, Inter-occasion variability; RSE, Relative standard error; OFV, Objective function value

Case II

RR (95% CI)	CYP3A5 *1*1/ *1*3 (n = 15) vs *3*3 (n = 9)		ABCB1 CC (n = 8) vs CT/TT (n = 16)	
	All-grade	Grade 2 and above	All-grade	Grade 2 and above
Dermatological toxicity[a]	0.98 (0.72–1.32)	0.86 (0.52–1.41)	1.23 (0.97–1.56)	1.09 (0.65–1.83)
Dry skin	1.00 (0.56–1.79)	1.20 (0.27–5.29)	1.20 (0.69–2.08)	2.00 (0.52–7.77)
HFSR	1.32 (0.68–2.55)	1.20 (0.61–2.38)	1.20 (0.69–2.08)	1.33 (0.74–2.40)
Rash	0.90 (0.35–2.35)	0.30 (0.03–2.86)	3.00 (1.17–7.67)	1.00 (0.11–9.44)
Pruritus	NA	NA	2.00 (0.52–7.77)	NA
Hematological toxicity[b]	NA	1.20 (0.61–2.38)	NA	0.73 (0.34–1.57)
Anemia	0.47 (0.27–0.80)	0.60 (0.15–2.36)	0.67 (0.32–1.41)	0.40 (0.06–2.88)
Leucopenia	2.70 (0.74–9.81)	3.00 (0.41–21.76)	0.44 (0.12–1.59)	1.00 (0.23–4.35)
Neutropenia	0.96 (0.45–2.04)	2.10 (0.55–7.99)	0.36 (0.11–1.26)	0.57 (0.15–2.15)
Thrombocytopenia	0.90 (0.35–2.35)	1.20 (0.13–11.43)	1.33 (0.52–3.41)	4.00 (0.42–37.78)
Hepatotoxicity[c]	1.00 (0.31–3.22)	NA	2.00 (0.67–5.98)	2.00 (0.14–27.99)
Transaminitis[d]	0.80 (0.23–2.79)	NA	2.67 (0.78–9.15)	NA
Increase in TB	0.60 (0.04–8.46)	NA	2.00 (0.14–27.99)	NA
Increase in ALT	0.60 (0.10–3.55)	NA	2.00 (0.34–11.70)	NA
Increase in AST	0.40 (0.08–1.96)	NA	3.00 (0.62–14.49)	NA
Gastrointestinal				
Mucositis	0.94 (0.59–1.50)	1.00 (0.56–1.79)	1.60 (1.10–2.34)	2.00 (1.23–3.27)
Constitutional				
Fatigue	0.83 (0.56–1.21)	0.60 (0.10–3.55)	0.92 (0.58–1.47)	N.A.
Cardiac				
Increase in BP	1.14 (0.88–1.49)	2.00 (0.77–5.18)	1.08 (0.93–1.25)	1.67 (0.88–3.14)
Neurology				
Altered taste	0.68 (0.42–1.08)	1.00 (0.31–3.22)	1.09 (0.65–1.83)	0.29 (0.04–1.94)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BP, blood pressure; CI, confidence interval; HFSR, hand–foot skin reaction; RR, relative risk; TB, total bilirubin. [a]Includes dry skin, HFSR, rash and pruritus. [b]Includes anemia, leucopenia, neutropenia and thrombocytopenia. [c]Includes elevation of TB, ALT and AST. [d]Includes elevation of ALT and AST.

Case II

- **Simulation scenario(n=1,000)**
  - 최종 모델을 이용하여 아래 scenario에 따라 simulation을 수행함.
  - 용량 : 12.5, 25, 37.5, 50, 62.5 mg
  - 최종 모델에서 공변량으로 선택된 BSA 와 ABCB1 type에 따른 최적의 용량을 제안하고자 함.

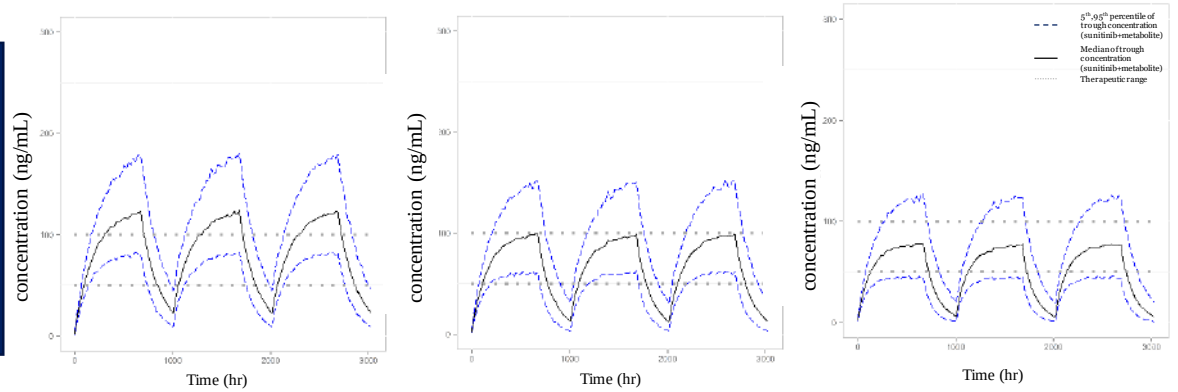
Body surface area (BSA)	ABCB1 polymorphism	
	Wild	Mutant
Low (1.6 m^2)	Scenario 1	Scenario 4
Middle (1.8 m^2)	Scenario 2	Scenario 5
High (2.0 m^2)	Scenario 3	Scenario 6

Case II

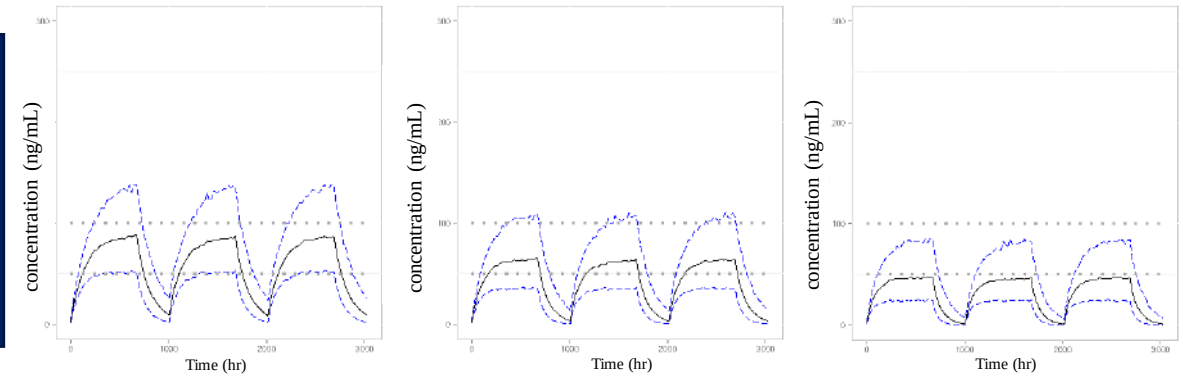
- **AD regimen의 적절성을 평가하기 위한 simulation을 수행함.**

BSA 1.6m² | **BSA 1.8m²** | **BSA 2.0m²**

ABCB1 Wild type



ABCB1 Mutant type



The results of NPC*

ABCB1 Polymorphism	BSA 1.6m²	BSA 1.8m²	BSA 2.0m²
Wild (NPC, %)	28.8	**47**	46.8
Mutant (NPC, %)	**48.3**	39.5	20.6

* NPC(Numeric predictive check): 치료영역 내 들어오는 subject 비율(%)

Case II

- **Optimized dose following BSA**
  - 현재 sunitinib의 indication에는 BSA에 따른 용량 조절이 권고되고 있지 않으나, BSA에 따라 약물의 농도가 현저하게 변하는 것을 확인할 수 있었음.
  - 본 연구에 의해 확립된 모델을 활용해 BSA 및 ABCB1 type에 따른 환자에서의 적정 용량을 아래와 같이 제시함.

Body surface area (BSA)	ABCB1 polymorphism	
	Wild (npc)	Mutant (npc)
Low (1.6 m^2)	25 mg (53.0%)	37.5 mg (48.4%)
Middle (1.8 m^2)	37.5 mg (47.0%)	50 mg (44.2%)
High (2.0 m^2)	37.5 mg (46.9%)	62.5 mg (41.4%)