PIPET

Q-fitter

주요 *in vivo* 정보와
이를 활용한 인간 약동학 예측 이론

So Jin Lee, PharmD
Researcher / Team leader

Q-fitter

분당서울대병원 헬스케어 혁신파크 2019.04.25
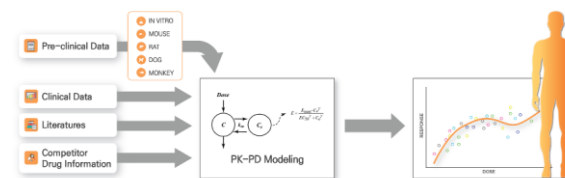
Contents

1. Dallphin 에서 사용하는 in vivo 정보

2. In vivo 정보를 통한 PK parameter 예측
- Basic info – "fraction unbound"
- Distribution – "allometry"
- Elimination – "human CL"

3. Allometry
- General allometric approaches (V, CL)
- Dallphin allometric approach (V)

4. Examples
- Various allometries (V, CL)
- Dallphin CL vs. allometry CL predictons

What is Dallphin-AtoM

- **D**rugs with

- **ALL**ometry and

- **PH**ysiology

- **IN**side

- **A**nimal **to**

- Hu**M**an
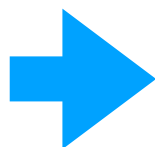
PBPK software for human PK parameters prediction

using physicochemical properties, in vitro and animal PK data

Dallphin: Inputs & Outputs

Input

In vitro data
- LogP
- Cb/Cp
- fu
- pKa
- Papp
- CLmet

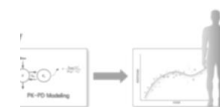**Animal in vivo PK**
- CLh
- Vc
- Vp
- CLr
- Q

Output

Human PK parameter
- Clearance (CL)
- Central volume (Vc)
- Peripheral volume (Vp)
- Intercompartment clearance (Q)
- Absorption rate constant (Ka)
- Bioavailability (F)

→ Vss

Major PK parameters Dallphin predicts

- [Absorption] Ka
- [Distribution] Vd (Vss, Vc, Vp), and Q
- [Elimination] CL
- [Absorption] F (if drug follows first-order kinetics)

In vivo data provides···

✓ Allometric methods to predict Vd, Q
✓ One of the methods to predict CLh & Fh (ex vivo data)
✓ Two methods to predict CLr

Dallphin methods: Clearance & F

$$CL_{hepatic} = \frac{Q_H \cdot fu \cdot CLint}{Q_H + fu \cdot CLint}$$

CL total = CL hepatic + CL renal

Microsome
1. MPPGL
2. Rat IVIV ratio
3. PS
4. PS(logD)

Hepatocyte
1. Human hepatocyte

1. CL renal_rat
2. CL renal_dog
3. CL renal_user input

$$CLr_{Human} = CLr_{Species} \times \frac{fu_{Human}}{fu_{Species}} \times \frac{KBF_{Human}}{KBF_{Species}}$$

$$Fh = 1 - \frac{CL_{hepatic}}{Q_H}$$

F total = Fh x Fa

Microsome
1. MPPGL (CLint)
2. Rat IVIV ratio
3. PS
4. PS(logD)

Hepatocyte
1. Human hepatocyte

1. Fa_Caco
2. Fa_PSA

CLint: intrinsic metabolic or hepatic clearance
Fh: hepatic availability
Fa: fraction absorbed from intestinal tract
PS: permeability surface area coefficient
Q_H: hepatic blood flow
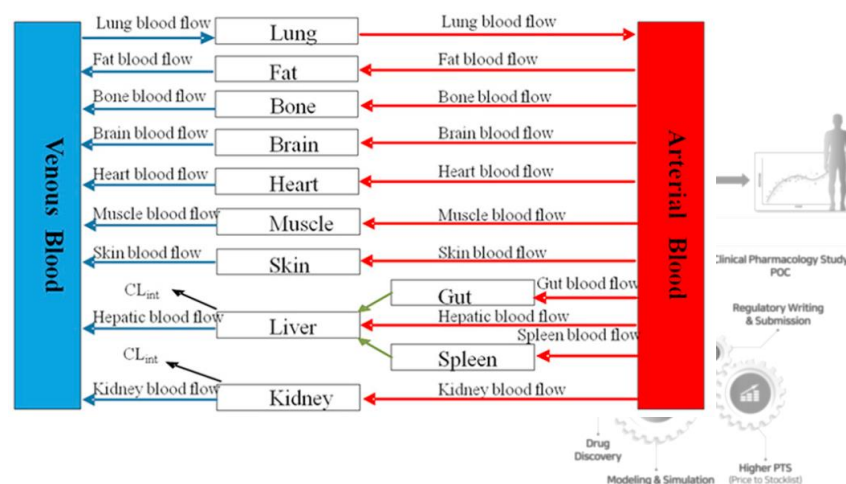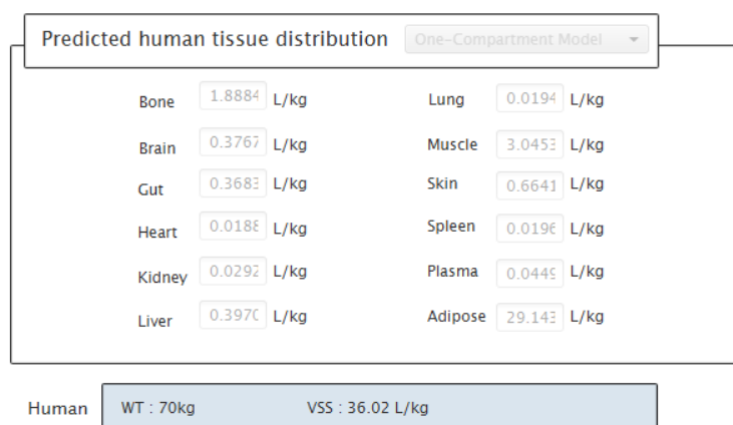PSA: dynamic polar molecular surface area

Dallphin methods: Vd & Q

Allometric approaches

1. Vss: 1-compartment model
2. Vss, Vc, Vp, Q: 2-compartment model

PBPK approach[12,13]

1. Vss: 1-compartment model (Vc:well-perfused organs)

PBPK approach

1. Dallphin 에서 사용하는 in vivo 정보

- [Basic info] Plasma protein binding (ex-vivo data)
- Rat fraction unbound => human hepatic CL(2), hepatic availability(2), human renal CL
- Dog fraction unbound => human renal CL
- Human fraction unbound => human hepatic CL (1)-(4), hepatic availability (1)-(4)
- Blood to plasma ratio

- [Distribution] Allometric approaches: Animal IV PK parameters
- Weight, Q, Volume of distributions (Vss, Vc, Vp)

- [Elimination] Microsome:
- CLint,rat_initial, observed in vivo => human hepatic CL(2), hepatic availability(2)
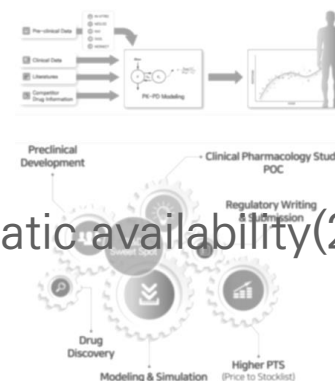
2. Input parameter for human PK prediction[1,2]

- [Basic info] Plasma protein binding
1. fu_Rat => CL hep_rat_pred -> CL rat_iviv_ratio -> CLh_hum_iviv_cor ->
              human hepatic CL CL hep_rat
              -> human bioavailability Fh_hum_iviv_cor
         => human renal CL CLr (rat to human prediction)

$$CL\ hepatic, rat = \frac{Q_{H,B} \cdot fu_B \cdot CLu_{int,H}}{Q_{H,B} + fu_B \cdot CLu_{int,H}} \times CLh, rat, IVIV\ ratio \left(= \frac{CLint, rat\ (in\ vivo\ observed)}{CLint, rat\ (in\ vitro\ predicted)}\right)$$

2. fu_Dog => human renal CL CLr CLr (dog to human prediction)

$$CLr_{Human} = CLr_{Species} \times \frac{fu_{Human}}{fu_{Species}} \times \frac{KBF_{Human}}{KBF_{Species}}$$

[Basic info]

- Plasma protein binding
  – fu_Rat
  – fu_Dog

CL renal[2]

- Three animal scaling techniques for the prediction of human CL renal:

1. Direct correlations between CLr in man and each of the two main preclinical species (rat and dog)

$$CLr_{Human} = CLr_{Species} \times \frac{fu_{Human}}{fu_{Species}} \times \frac{KBF_{Human}}{KBF_{Species}}$$

2. Simple allometry

$$CLr = a(W)^b$$

$$CLr_{Predicted\ total} = CLr_{Predicted\ unbound} \times fu_{Human}$$

3. Mahmood's renal clearance scaling method

$$SSF = \frac{(Glomerular\ filtration \times kidney\ blood\ flow)}{(body\ weight \times kidney\ weight)} \qquad Correction\ factor = \frac{SSF_{Species}}{SSF_{Human}}$$
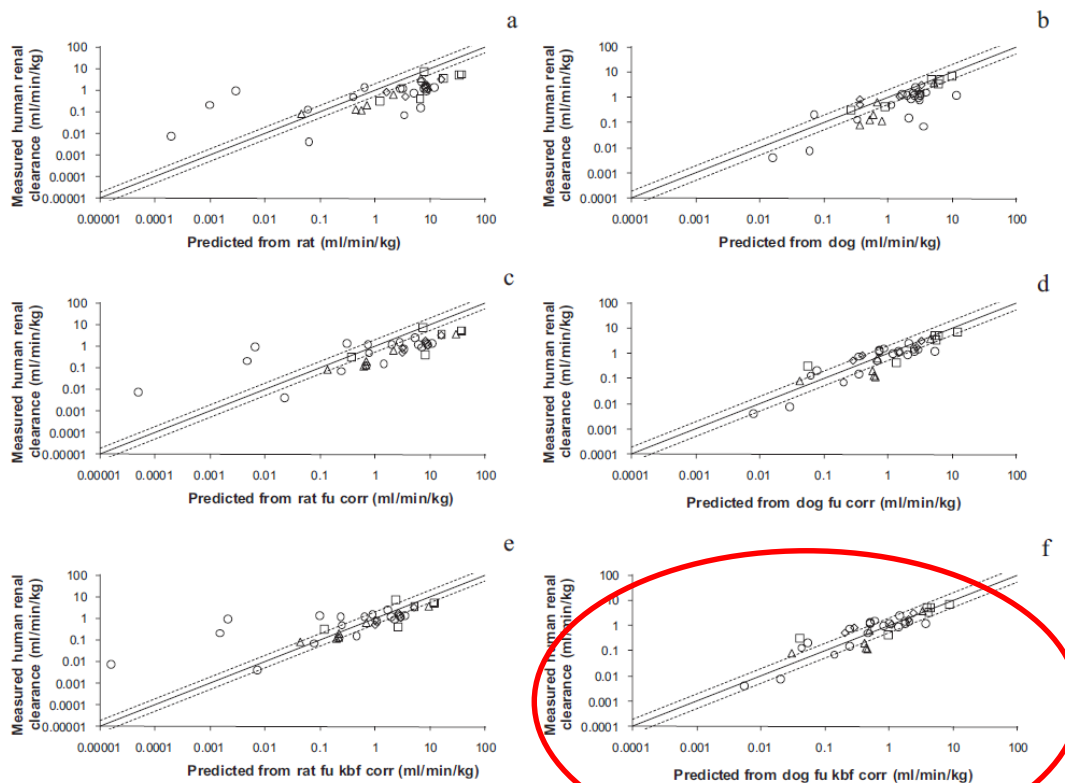
CL renal[2]

Fig. 2. Measured human renal clearance versus measured renal clearance from rat (a), dog (b), rat corrected (corr) for fu differences (c), dog corrected for fu differences (d), rat corrected for both KBF and fu differences (e), and dog corrected for both KBF and fu differences (f). Circles, acids; squares, bases; triangles, neutrals; diamonds, zwitterions.

- Most accurate prediction: 1. Direct correlation with the dog renal clearance with PPB and KBF corrections (R^2 = 0.84)

Theories and Practices for Human Pharmacokinetics Prediction Using Non-clinical Information

2. Input parameter for human PK prediction[1,2]

- [Elimination] Microsome

1. CL int_ini Rat => CL int Rat –> CL hep_rat_pred –> CL hep_rat_iviv ratio –>
   –> human hepatic CL CL h_rat
   –> human bioavailability Fh (CLh_rat)

$$Human\ CLh, rat = \frac{Q_{H,B} \cdot fu_B \cdot CLu_{int,H}}{Q_{H,B} + fu_B \cdot CLu_{int,H}} \times CLh, rat, IVIV\ ratio$$

$$CLh, rat, IVIV\ ratio\ = \frac{CLh, rat\ (in\ vivo\ observed)}{CLh, rat\ (in\ vitro\ predicted)}$$

$$CLh, rat\ (in\ vitro\ predicted) = \frac{Q_{H\ rat} \cdot furat \cdot CLint_{,rat}}{Q_{H,rat} + fur_{at} \cdot CLint_{,rat}}$$

$$CL_{int,rat} = CL_{int\ ini,rat} \cdot MPPGLrat \cdot Liver\ wtrat$$

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[Elimination]

- Hepatic Clearance (CLh)

Microsome
- CL int_ini Rat (ul/min/mg protein)
- Observed in vivo (L/h)

- Renal Clearance (CLr)
- CLr_Rat (ml/min/kg)
- CLr_Dog (ml/min/kg)

Theories and Practices for Human Pharmacokinetics Prediction Using Non-clinical Information

2. Input parameter for human PK prediction [Distribution]

- Mouse, rat, monkey, dog 총 4종의 정보 입력 가능
- 각 종 별 Weight
- Model structure – 1 compartment vs. 2 compartment
- Model 을 통해 구한 각 종 별 Vss 또는 Q, Vss (Vc, Vp)

- [Prediction] 을 통해 Allometric scaling 수행 =〉
  70 kg-human Q, Vc, Vp, Vss 구함

[Distribution]

- Animal data available ? YES
  - One-compartment model
  - Two-compartment model

- [Prediction]

- Allometric scaling result
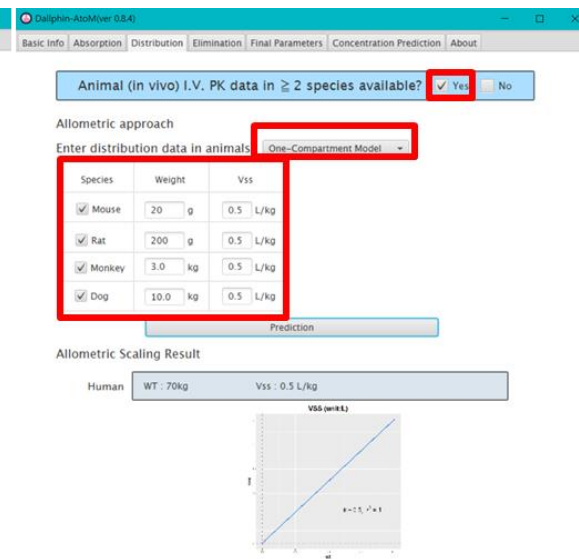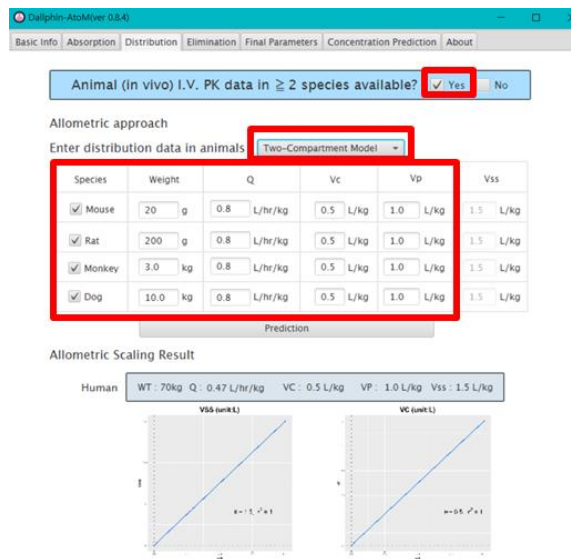
Volume of distribution

- Allometric scaling as choice of method to predict human Vd

- Plasma protein binding should be considered[3]

- Multiple methods available for prediction of volume of distribution[3,4,6]
  - ✓ Simple allometric scaling
  - ✓ Allometry with correction factors
  - ✓ Average fraction unbound tissue
  - ✓ Proportionality (dog–human)
  - ✓ QSAR

Volume of distribution[3,4]

- Simple allometric scaling
- Allometry with correction factors*
- Average fraction unbound tissue*
- Proportionality (dog−human)*
- QSAR

*Pertains plasma protein binding data as an essential element

Table 4. Methods for prediction of volume of distribution (V_d).

Method	Equation		Comment*	Ref.
Simple AS	$V = a(W)^b$	(93)	The prediction of V_d is well predicted equally with using two species in AS	[108]
Average fraction unbound in tissue [1]	$V = V_{Plasma}\left(1 + R_{E/I}\right) + f_u \cdot V_P\left(\frac{V_E}{V_p} - \frac{V_R \cdot f_u}{\alpha_R}\right)$	(94)	It is useful to analyze and predict an alteration in apparent V_d then identify the cause of alteration. It is particularly useful for drugs with low V_d (<15 L or 0.2 L/kg)	[119]
Proportionality	$V_{human,pred} = \dfrac{V_{animal} \cdot f_{u,human}}{f_{u,animal}}$	(95)	It is assumed that the volume of distribution at a steady state of free drug is identical between species	[120]
One species AS	$V_{human,pred} = -0.35V_{rat}^{0.91}$	(96)	Statistical modeling is applied in this model	[121]
QSAR	$\begin{aligned}\log(Vd_{ss,human}) = {}& 0.1859 \\ & \cdot \log(Vd_{ss,rat}) \times \log(Vd_{ss,rat}) \\ & - 0.3887 \\ & \cdot \log(Vd_{ss,rat}) \times \log(MW) \\ & + 0.3089 \\ & \cdot \log(Vd_{ss,dog}) \times \log(MW) \\ & + 0.003306 \cdot \log(MW) \times c\log P \\ & + 1.71\end{aligned}$	(97)	$Vd_{ss,\,human}$ (mL/kg) is predicted by QSAR modeling with quadratic term descriptors	[122]

* Each comment corresponds to all the equations within each major section of the table defined by horizontal lines.

[1] Where V_d is apparent volume of distribution, V_{plasma} is plasma volume, V_E is extracellular space minus the plasma, V_R is physical volume into which the drug distributes minus the extracellular space, f_u is the fraction unbound in plasma, and $R_{E/I}$ is the ratio of distributed albumin in the extravascular space to that in the intravascular space. It is 1.4. α_R equals to C_u/C_R where C_u is unbound drug concentration at distribution equilibrium and C_R is concentration in V_R.

3. Allometry[5,6]

- "Study of size and its consequences"
- Based on the assumption that there are <u>anatomical, physiological, and biochemical similarities</u> among animals which can be described by simple mathematical models
- Choice of method for projection to human PK

- Possible with in vivo IV PK data from 2 species, but $\geq$ 3 species provide more accurate prediction
- Plasma protein binding data in two or more species and human should be emphasized
- Completed after each species modeling to predict human PK parameters, which is used for simulations
- Different allometric approaches available

For which PK parameter prediction?
- Human Vd
- Human CL
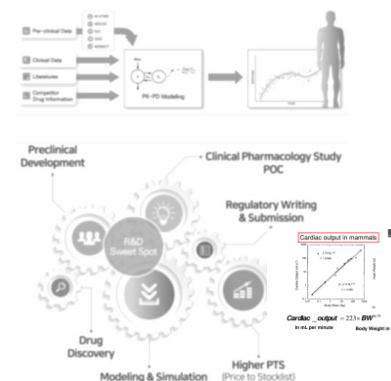
General allometric approaches[3,4,5]

- Simple allometry $\quad Y = a(BW)^b \qquad logY = \log(a) + b \cdot \log(BW)$

- Allometry with standard correction factors for Vd − PPB (plasma protein binding)

$$\log(VD) = \log(a) + b \cdot \log(BW)$$

$$VD_{free} = \frac{VD_{total}}{f_u}$$

- Allometry with standard correction factors for CL − MPL (product of maximum life−span), brain weight

$$Clearance = aBW^b$$

$$Clearance \times MLP = aBW^b$$
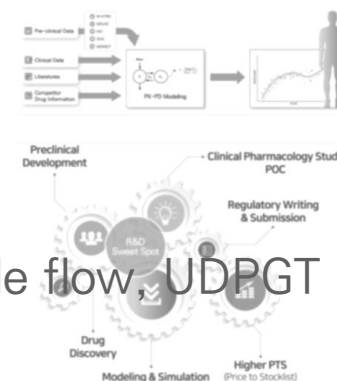
$$Clearance \times BrainWeight = aBW^b$$

cf) Correction factors for renally/biliary excreted drugs3 − GFR/bile flow, UDPGT

$$Clearance / GFR = aBW^b$$

$$Cl \times Bile\_flow = aBW^B$$

$$Cl \times UDPGT = aBW^b$$

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Different allometric approaches for CL[10]

- Simple allometry
- Rule of exponents
- Correction factor – MLP, brain weight
- Two-term method
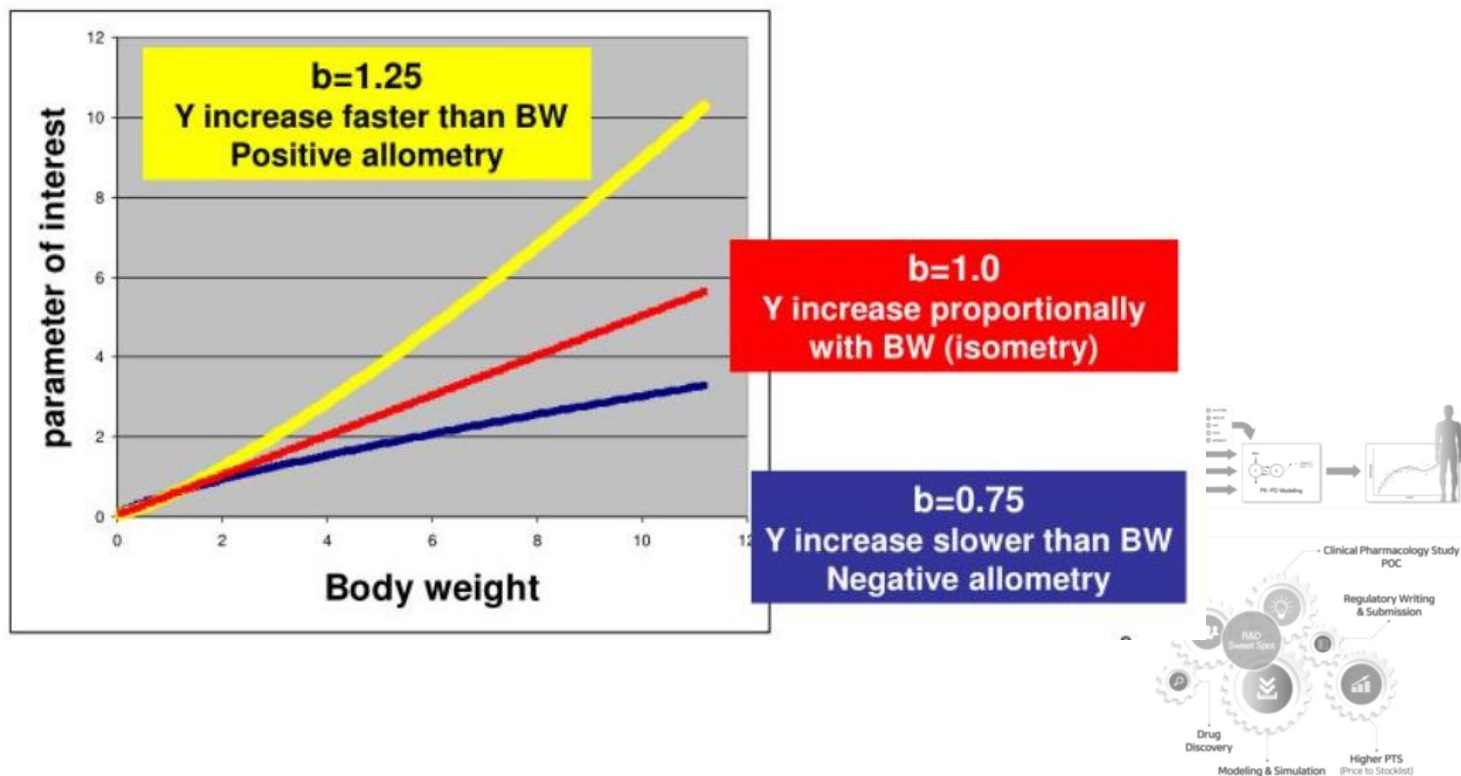- Multiexponential
- Normalized

Different allometric approaches for CL[4]

Table 3. Methods for prediction of clearance (CL) using allometric scaling (AS).

Method	Equation		Comments *	Ref.
Simple AS	$CL = a(W)^b$	(74)	Select a proper equation by the rule of exponent (ROE) W and BW represent body and brain weight, respectively	-
AS with MLP [1]	$CL \cdot MLP = a(W)^b$	(75)		-
AS with BW	$CL \cdot BW = a(W)^b$	(76)		[89]
Rule of exponent	If the exponent is 0.55 to 0.7, then use the simple AS, Equation (74)			[90]
	If the exponent is 0.71 to 1, then use the MLP, Equation (75)			
	If the exponent is more than 1, then use the BW, Equation (76)			
Two-term method	$CL = \theta(W)^a \cdot (BW)^b$	(77)	θ is a constant, which is determined by multiple regression analysis	[91]
Multiexponential	$CL_{human} = aW^b + \left[\left(\frac{1 - \frac{3}{2}b}{1 - \frac{1}{2}b}\right)\right]aW^{0.9}$	(78)	The unit of CL is mL/min	[92]
Normalized AS	$CL_{animal}\frac{CL_{int,human}}{CL_{int,animal}} = a(W)^b$	(79)	CL_{int} refers the unbound CL_{int} in microsomes or hepatocytes in species and humans	[93]

One species AS	$CL_{human} = CL_{animal} \cdot (\frac{W_{human}}{W_{animal}})^b$	(80)	The exponent b is a constant 0.75, which is physiologically relevant value (e.g., blood flow, filtration, etc.)	[94,95]
One species AS	$CL_{pred} = 0.152 \cdot CL_{rat} \cdot (\frac{W_{human}}{W_{rat}})$	(81)	Predict the CL of bound drug	[90]
	$CL_{pred} = 0.41 \cdot CL_{dog} \cdot (\frac{W_{human}}{W_{dog}})$	(82)		
	$CL_{pred} = 0.407 \cdot CL_{monkey} \cdot (\frac{W_{human}}{W_{monkey}})$	(83)		
Two species AS	$CL_{pred} = a_{rat-dog} \cdot W_{human}^{0.628}$	(84)	Predict the CL of bound drug	
	$CL_{pred} = a_{rat-monkey} \cdot W_{human}^{0.650}$	(85)		
Hepatic liver method	$CL_{pred} = CL_{animal} \cdot (\frac{Q_{H,human}}{Q_{H,animal}})$	(86)		[96]
FCIM [2]	$CL = 33.35 \times (\frac{a}{Rf_u})^{0.77}$	(87)	Rf_u is the f_u ratio between rats and humans and a is the coefficient form AS The unit of CL is mL/min	[97]
QSAR [3]	$LogCL_{pred} = 0.433 \cdot \log(CL_{rat})$ $+ 1.0 \cdot \log(CL_{dog})$ $- 0.00627 \cdot MW + 0.189 \cdot Ha$ $- 0.00111 \cdot \log(CL_{dog}) \cdot MW$ $+ 0.0000144 \cdot MW^2$ $- 0.0004 \cdot MW \cdot Ha - 0.707$	(88)	The unit of ...	[99]

* Each comment corresponds to all the equations within each major section of the table defined by horizontal lines.
[1] The maximum life-span potential (MLP) is calculated by the equation MPL (years) = 185.4BW^0.636W^-0.225[100].
[2] Fraction unbound intercept correction method
[3] Quantitative structure activity relationship (QSAR) consist of physicochemical properties, such as molecular weight (MW), partition coefficient (cLogP), and number of hydrogen-bound acceptors (Ha).

Simple allometry[5]

- $Y = a(BW)^b$
- Log-log transformation
- Dallphin's choice for Vd (exponents fixed)
- Easily done with Excel linear regression
- When a midpoint species (e.g. dog) is the source of the error, the change is primarily in the intercept rather than the slope
- Fixed exponents...

Simple allometry:
the log-log transformation

The scaling exponents

- $Y = a(BW)^b$
- Scaling exponent (b) (i.e. the slope) defines the type of scaling relationship

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Allometry with correction factors for CL

- Simple allometry vs. corrected allometry
- The rule of exponents provides an idea of which standard correction factor to select[7,8]

Simple vs. corrected allometry (MLP): Cefazolin clearance in man

Cefazolin $y = 5.3801x^{0.7826}$
$R^2 = 0.9982$

cefazolin MLP $y = 3.7432x^{1.1068}$
$R^2 = 0.9906$
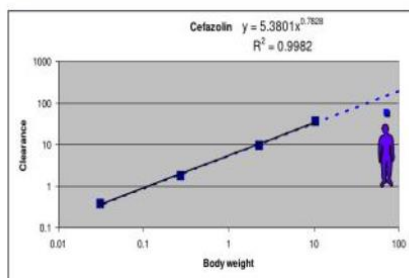
Simple allometry
Predicted: 141 mL/min
Actual: 61 mL/min
Error: 131%
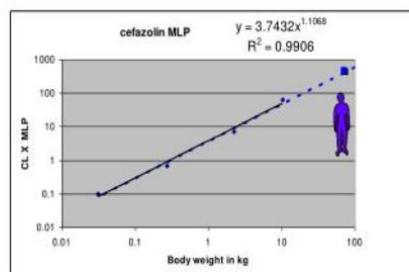
Allometry with MLP as a correcting factor
Predicted: 50.55mL/min
Actual: 61mL/min
Error:17.1%

The rule of exponents to predict human CL

1. $0.55 \le b < 0.71$: no correction factor is necessary

2. $0.71 \le b < 1.00$ MLP should be incorporated into scaling method

3. $B > 1.00$ Brain weight should be incorporated into the scaling method

Methods	% Mean absolute error (MAE)
Simple allometry	106
CL x MLP	40
CL x brain Weight	49
Rule of exponents	**25**

How to use Dallphin allometric approach?

- 각 종별 PK modeling*을 선행적으로 수행해야함
- Model structures: 기본 1-comp or 2-compartment model
- 모든 종에서 동일한 model structure 를 사용

*PK modeling: General workflow
1. Model structure 정하기
2. Model optimization
3. Model diagnosis – GOF, individual plots
4. Model validation – VPC , (bootstrap for human data)
5. PK parameter estimation & extrapolation

Dallphin allometric approach (Vd, Q)

- For 2 compartment model:
  Vss = Vc + Vp, Q
- Exponents fixed to 1 and 0.75
  $V = a(WT)^1$
  $Q = a'(WT)^{0.75}$

Two-compartment open model, IV injection.

k_{12}

k_{21}

k

1   2

$Q = K_{12}*V_1$
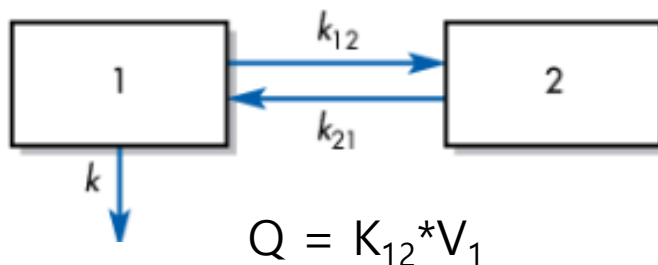
Dallphin-AtoM(ver 0.8.4)

Basic Info | Absorption | Distribution | Elimination | Final Parameters | Concentration Prediction | About

Animal (in vivo) I.V. PK data in ≧ 2 species available?   ☑ Yes   ☐ No
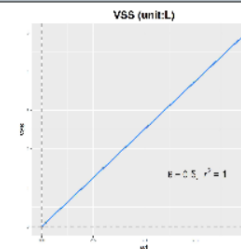
Allometric approach

Enter distribution data in animals   Two-Compartment Model ▾

Species	Weight		Q		Vc		Vp		Vss	
☑ Mouse	20	g	0.8	L/hr/kg	0.5	L/kg	1.0	L/kg	1.5	L/kg
☑ Rat	200	g	0.8	L/hr/kg	0.5	L/kg	1.0	L/kg	1.5	L/kg
☑ Monkey	3.0	kg	0.8	L/hr/kg	0.8	L/kg	0.5	L/kg	1.3	L/kg
☑ Dog	10.0	kg	0.6	L/hr/kg	1	L/kg	1.0	L/kg	2.0	L/kg

Prediction

Allometric Scaling Result

Human   WT : 70kg   Q : 0.37 L/hr/kg   VC : 0.98 L/kg   VP : 0.96 L/kg Vss : 1.94 L/kg

VSS (unit:L)   VC (unit:L)

Drug Discovery   Modeling & Simulation   Higher PTS (Price to Stocklist)
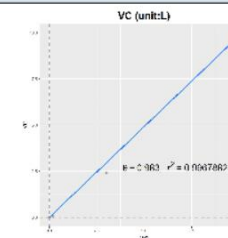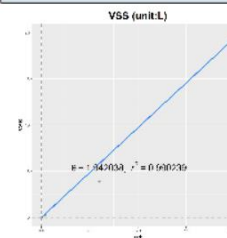
Dallphin allometric approach (Vd, Q)

- For 1 compartment model:
  Vss only (Q, Vc, Vp)
- Exponents fixed to 1
  $V = a(WT)^1$
  Q = a'(WT)$^{0.75}$

One-compartment open model, IV injection.

*Note: when using 1-compartment model, in order to predict Ka,
Vss was used instead of Vc (as in 2-compartment model)[13],
which may provide potential discrepancy in predicting human Ka.

Dallphin's allometric approach example (Vd)

- Excel 데이터분석의 회귀분석과 같은 결과
- Natural scale 그래프로 제시, 상수는 0 을 사용 ((0,0) 을 지나가는 직선)
- Vc = 0.9833(WT) (R^2 = 0.9967), Vss = 1.9420(WT) (R^2 = 0.9902)
- 다음 버전에는 scaling exponent 를 예측하도록 update 될 예정

4. Examples

1. Simple allometry using monkey data
2. Simple allometry using 4 species data (mouse, rat, monkey, dog)
3. Allometry with correction factor (brain weight)
4. Modified allometry with correction factor

Simple allometry example (1)

- 실제 수행된 모델링 프로젝트에서의 simple allometry
- Scaling 3-kg monkey to 70-kg human for mAb[9]
- Scaling CL (non-specific CL), Vc, Vp, Q, and Vmax, Km (target-specific CL)

	monkey	Unit	x 3 kg monkey	Unit	Human	allometry
CL	0.0005	L/h/kg		l/h		•CLh = CLm*(WTh/WTm)^0.85
V1	0.0423	l/kg		l		•V1 = V1m*(WTh/WTm)^1
V2	0.0181	l/kg		l		•V2 = V2m*(WTh/WTm)^1
Q	0.0011	l/h/kg		l/h		•Q h = CLm*(WTh/WTm)^0.85
Vmax	0.0173	mg/h/kg		mg/h		•Vmax = Vmaxmm*(WTh/WTm)^0.85
Km	0.5880	mg/l		mg/l		•Km 그대로
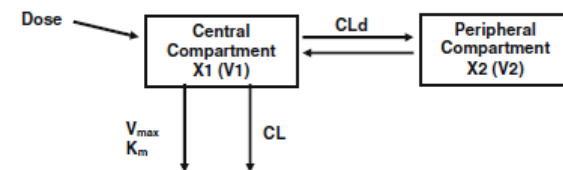
$$\frac{dX_1}{dt} = -\frac{CL}{V_1} \times X_1 - \frac{CL_d}{V_1} \times X_1 - \frac{X_1}{V_1} \times \frac{V_{max}}{K_m + \frac{X_1}{V_1}} + \frac{CL_d}{V_2} \times X_2$$

$$\frac{dX_2}{dt} = \frac{CL_d}{V_1} \times X_1 - \frac{CL_d}{V_2} \times X_2$$

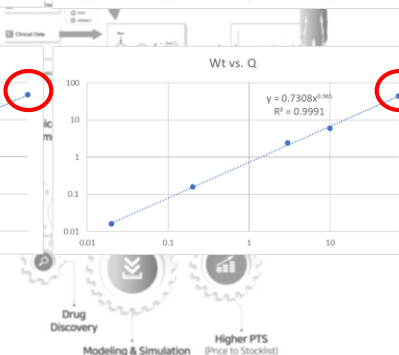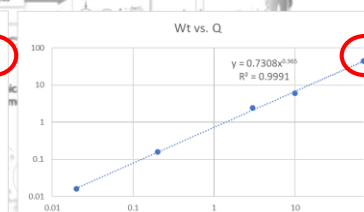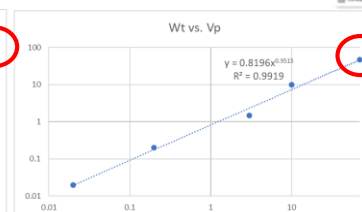Fig. 1 Two-compartment nonlinear PK model

Theories and Practices for Human Pharmacokinetics Prediction Using Non-clinical Information

Simple allometry example (2)

		kg	Vss (L/kg)	vc (L/kg)	vc (L)	vp (L/kg)	vp (L)	Q (L/h/kg)	Q(L/h)
		0			0		0		0
	mouse	0.02	1.5	0.5	0.01	1	0.02	0.8	0.016
	rat	0.2	1.5	0.5	0.1	1	0.2	0.8	0.16
	monkey	3	1.3	0.8	2.4	0.5	1.5	0.8	2.4
	dog	10	2	1	10	1	10	0.6	6
exp		70	1.84	1.17	81.96	0.67	46.69	0.63	44.09
dallphine				1.94	0.98		0.96		0.37

Two-compartment open model, IV injection.
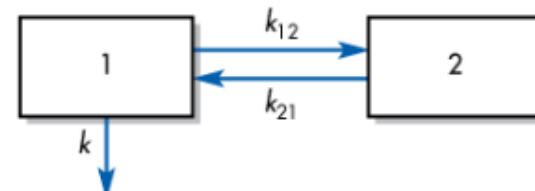
- 4 Species PK data
- Each species PK parameters estimated **from 2-compartment model**
- $Vd = a(WT)^b$, $Q = a(WT)^b$
- a, b estimated from regression line
- Extrapolation to predict PK in a 70-kg human

Theories and Practices for Human Pharmacokinetics Prediction Using Non-clinical Information
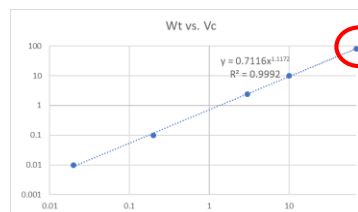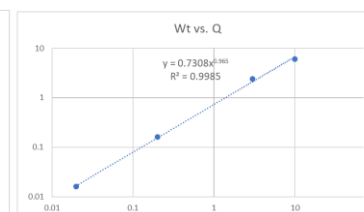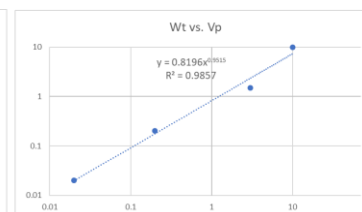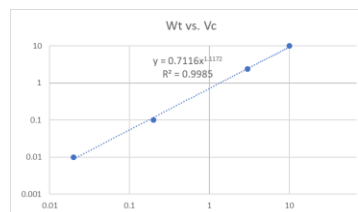
Allometry with correction factor example (3)

L/h	CL1	CL3	CL5	CL10
mouse				
rat				
monkey				
dog				
human				

BRAIN WT*					
KG	L/h	CL1*Br WT	CL3*Br WT	CL5*Br WT	CL10*Br W
0.00036	mouse				
0.0018	rat				
0.09	monkey				
0.08	dog				
1.4	human				
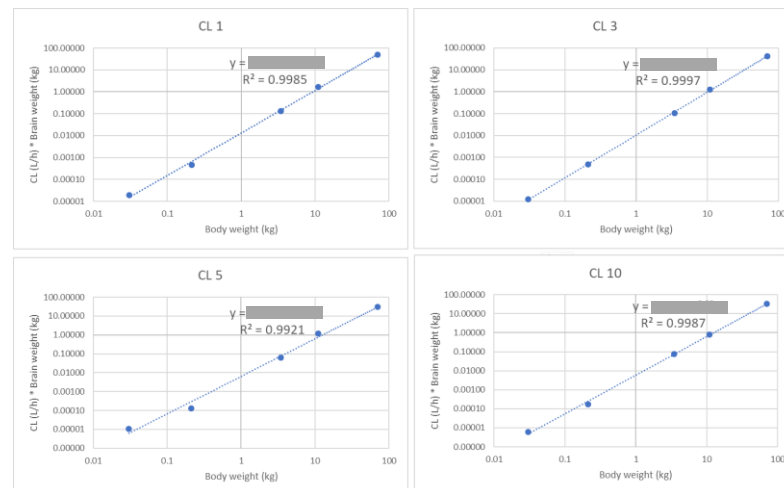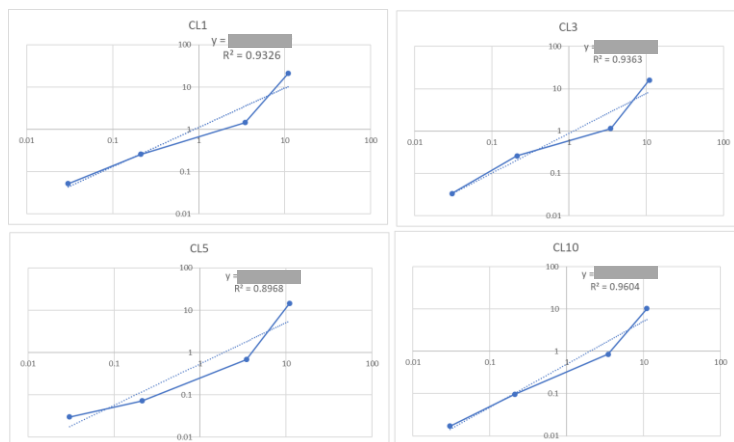
- $CL = a(BW)^b$ vs. $CL \times Brain\ Weight = a(BW)^b$

Modified allometry with correction factor example (4)

- 실제 수행된 모델링 프로젝트에서의 modified allometry
- Brain weight 를 correction factor 로 사용하여 human CL 예측 후, 용량에 따른 CL 변화를 수식으로 설명함
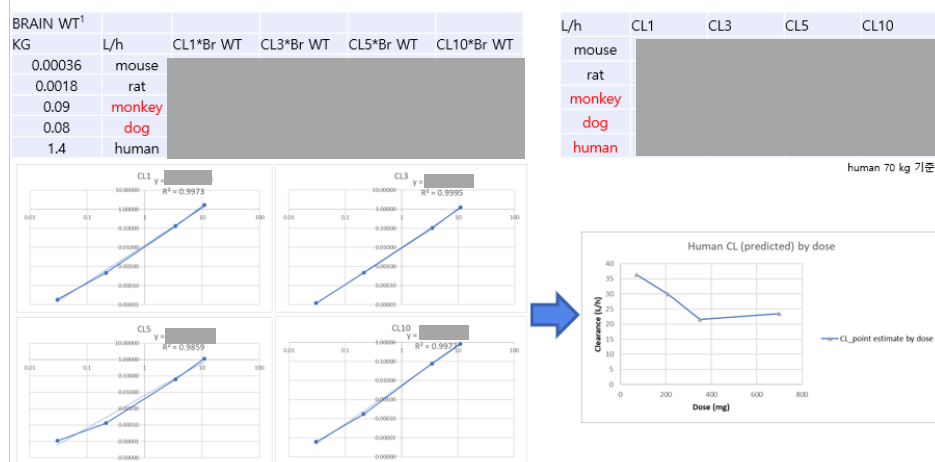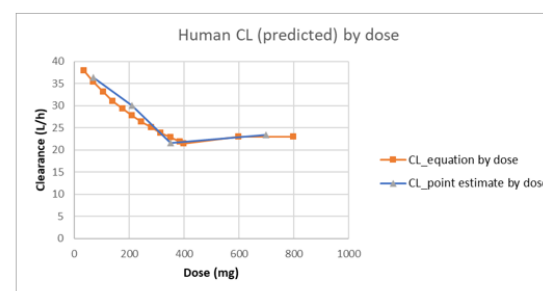
$$CL \times Brain\ weight = a \cdot f(Dose) \cdot (BW)^b$$

CL: allometry with standard correction factor (brain weight) (1)

BRAIN WT[1]					
KG	L/h	CL1*Br WT	CL3*Br WT	CL5*Br WT	CL10*Br WT
0.00036	mouse				
0.0018	rat				
0.09	monkey				
0.08	dog				
1.4	human				

L/h	CL1	CL3	CL5	CL10
mouse				
rat				
monkey				
dog				
human				

human 70 kg 기준

Human CL (predicted) by dose

- Brain weight 을 standard correction factor로 사용하여 CL 에 대해 각각의 용량 (1, 3, 5, 10 mg/kg)에 따른 interspecies scaling (모든 용량군의 R²~0.99) 을 수행하여 CL 를 구함 (CL_point estimate by dose)
- Clearance x BrainWeight = aBW^b

CL: allometry with standard correction factor (brain weight) (2)

Human CL (predicted) by dose

- 앞서 Mouse 에서 얻은 용량에 따른 CL 수식을 기반으로 이를 interspecies scaling 에 적용함, 400 mg 이하에서 수식을 적용하였으며, 400 mg 초과시 CL 는 일정하다고 가정함 -
  -400 mg 이하: CL*BrainWeight = a*(CLmax*(1-DOSE/(DOSE+CL50)))*BW^b
  (CLmax=   CL50=   , a=   b = 1 *상수 a 와 b 는 모델링을 통해 산출한 값임)
  -400 mg 초과: CL 는 용량에 따라 일정하다고 가정함
- 따라서, 용량에 따른 CL 변화를 BW 에 따라 나타낼 수 있으며, 용량과 BW 정보가 있다면 이젠 CL 산출이 가능해짐
- 이를 기반으로 70kg 사람에서의 CL 를 산출한 결과는 위와 같음(CL_equation by dose), 이를 앞의 각각 용량별 interspecies scaling 결과(CL_point estimate by dose)와 비교하였음

CL prediction: Allometry vs. in vitro data[11]

- Allometry vs. IVIVE methods

- Allometry: fu intercept method and two-species-based allometry (rat-dog) were best
- IVIVE: Using microsomes (incorporating both plasma and microsomal binding) and hepatocytes (not incorporating binding) resulted in better prediction

$\Rightarrow$ Allometry slightly more accurate than predictions based on in vitro data
$\Rightarrow$ Dallphin uses only in vitro data for CL prediction
- 다음 버전에는 allometry(in vivo data)를 통해 CL 예측이 가능하도록 update 될 예정

Final parameters

- Hepatic CL: CL h_rat
- Renal CL:
- –CLr (Rat to human prediction)
- –CLr (Dog to human prediction)

- Vss
- Vc ➡ Ka
- Q

- Fh (CL h_rat)

Theories and Practices for Human Pharmacokinetics Prediction Using Non-clinical Information

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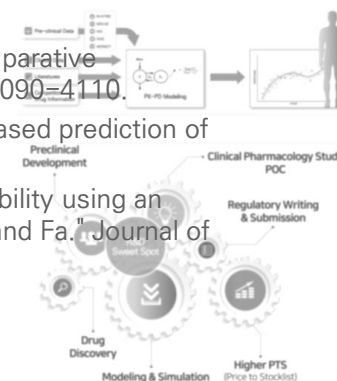
경청해 주셔서 감사합니다.

주요 *in vivo* 정보와
이를 활용한 인간 약동학 예측 이론