

Development of a Whole-Body Physiologically Based Pharmacokinetics Model for Children with Severe Malnutrition

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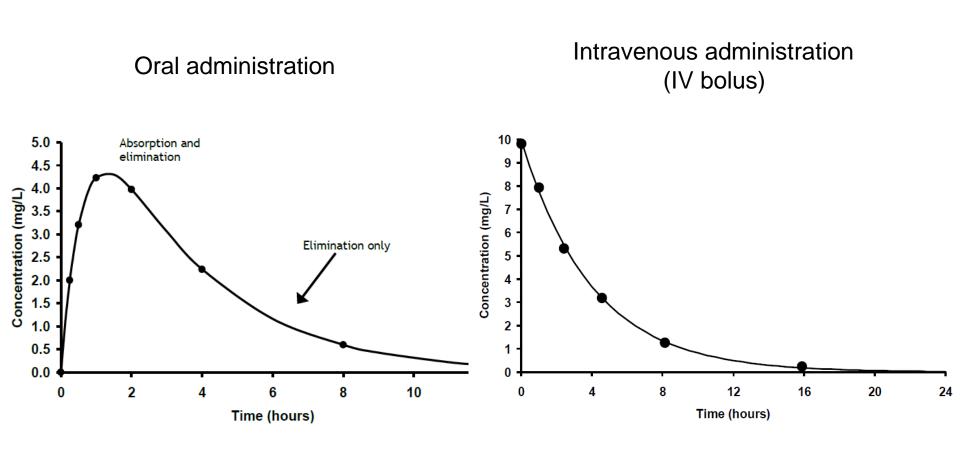


Pharmacokinetics (PK)

- Describes the movement of drugs in and out of the body through the following processes:
 - i. <u>Absorption</u>: the movement of drug from the site of oral or extravascular administration into the systemic circulation
 - ii. <u>Distribution</u>: the reversible transfer of drug between the systemic circulation and the tissues
 - iii. <u>Elimination</u>: the removal of drug from the body by processes such as renal excretion or hepatic metabolism



Concentration-time profile





 Hypothetical structures used to describe and predict the disposition of drugs

For example:

If the desired target range of Drug X is 10-20 mg/L

- What loading dose should be used to achieve a serum concentration of 15 mg/L?
- What is the maximum concentration if an oral loading dose of 1000 mg is given?
- What concentration would you expect to measure 8 hours after the dose?



UPPSALA How to develop PK models?

• PK models can be developed by two approaches:

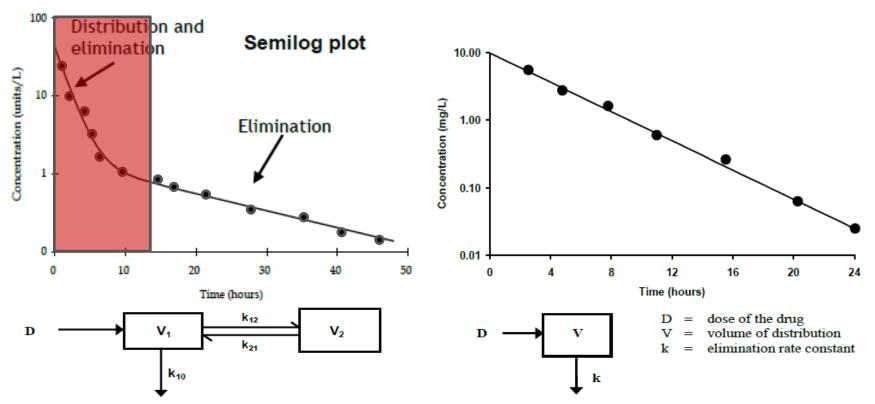
i. Empirical approach (traditional method)

ii. Mechanistic approach



Empirical approach

• Compartmental model e.g. one- and two-compartment models

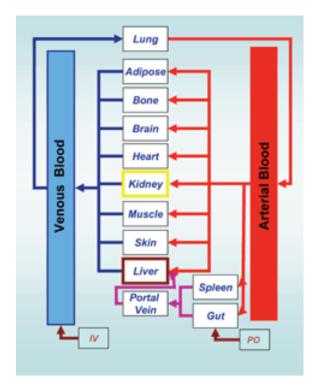


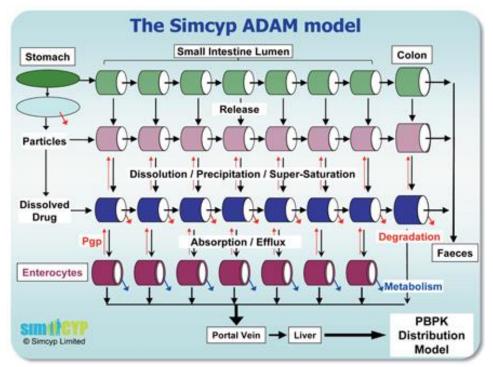
- · Simple but the models have no physiological meaning
- Derived from the experimental data (drug concentrations)
- · Complexity of the model depends on the data available



UPPSALA Mechanistic approach

- PK processes of drugs are described by physiologically realistic compartment (anatomy of organism).
- E.g. Whole-body physiologically based pharmacokinetic (PBPK) models, liver metabolism models, absorption model.



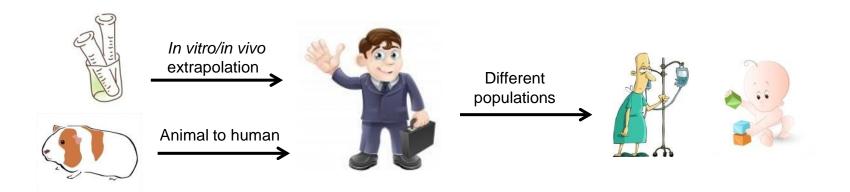


PBPK models implemented in Simcyp simulator (www.simcyp.com)



UPPSALA Mechanistic approach

- The main use is for predicting drug concentrations with the extrapolation techniques
 - i. Inter-species (e.g. rat to human)
 - ii. Inter-tissue (e.g. plasma to less accessible organs)
 - iii. Inter-route (e.g. IV to oral)
 - iv. Inter-drug (e.g. other drug in the same class)





Example

A whole-body physiologically based pharmacokinetic (WBPBPK) model for children with severe malnutrition



General method [1]

Input parameters

1. Drug specific

- Tissue:plasma partition coefficient (Kp)
- LogP, pKa
- Protein binding (R, fu)
- Solubility, Permeability
- Rate and extent of absorption
- Clearance
- Dosage form, particle size

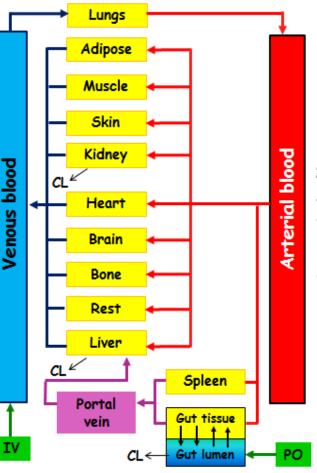
2. Species specific

- Organ volume
- Organ blood flow

Trial design

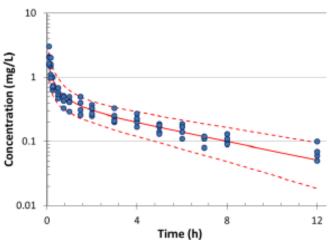
- Dosing regimen
- *n* doses
- n subjects
- Demographic data

PBPK model



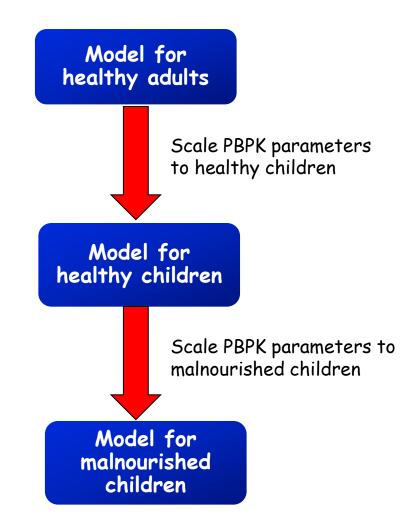
Output

- Incorporate uncertainty and variability
- Simulate *n* times to obtain median and PIs





General method [2]

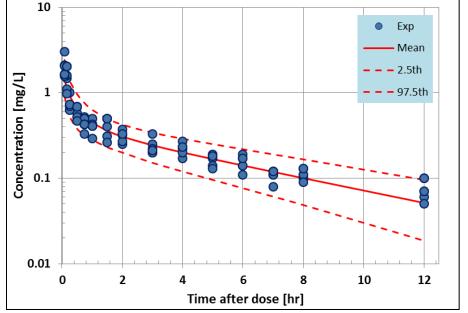




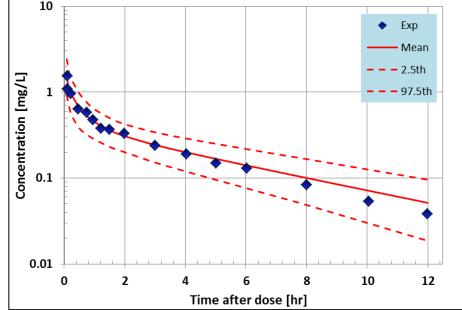
UPPSALA Results: healthy adults

1) IV bolus model (ciprofloxacin 100 mg)

- Observed data
 - Mean simulated data
- Prediction interval



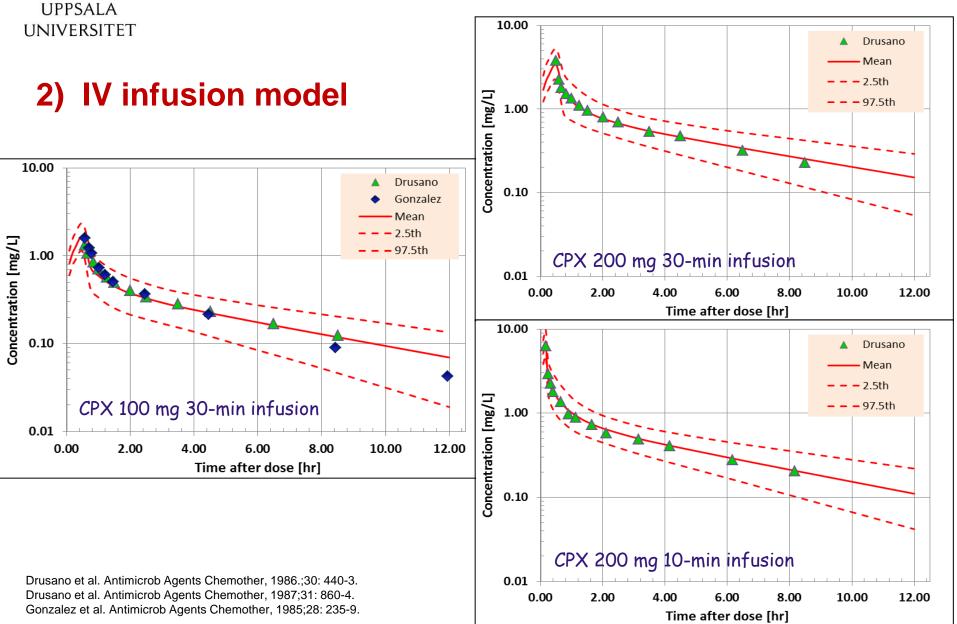
Wise et al. Pharmacokinetics of intravenously administered ciprofloxacin. Antimicrob Agents Chemother, 1984; 26:8-10.



Bergan et al. Pharmacokinetics of ciprofloxacin after intravenous and increasing oral doses. Eur J Clin Microbiol, 1986;5: 187-92.



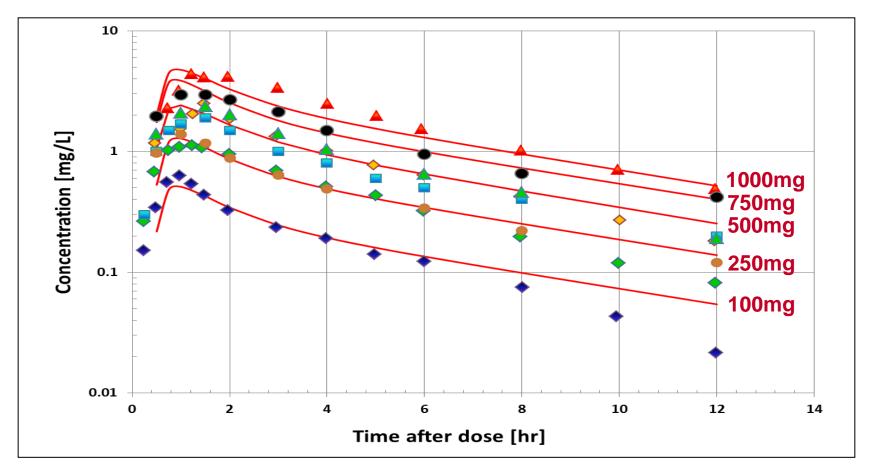
Results: healthy adults





UPPSALA Results: healthy adults

3) Oral model

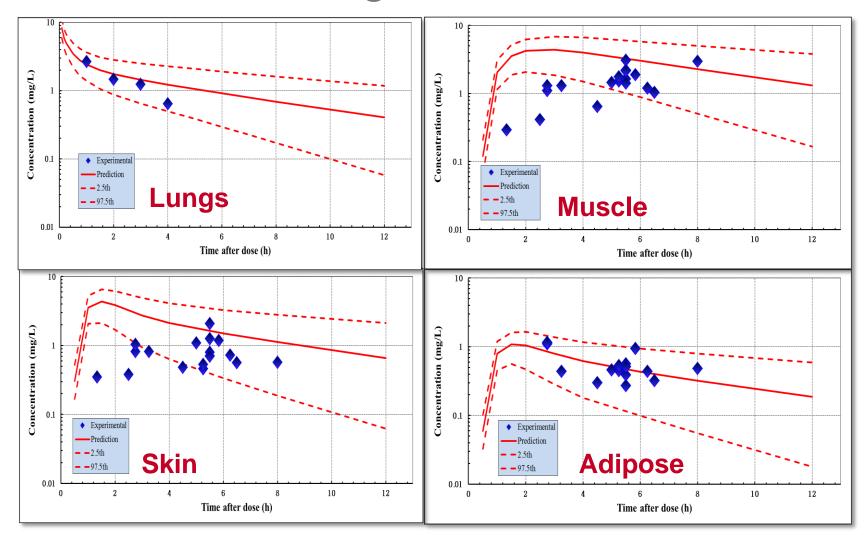


Bergan et al Pharmacokinetics of ciprofloxacin after intravenous and increasing oral doses. Eur J Clin Microbiol, 1986:5:187-92. Crump, et al Pharmacokinetics and tissue penetration of ciprofloxacin. Antimicrob Agents Chemother, 1983;24:784-6. Gonzalez et al Multiple-dose pharmacokinetics and safety of ciprofloxacin in normal volunteers. Antimicrob Agents Chemother, 1984;26:741-4.



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Results: organ concentrations

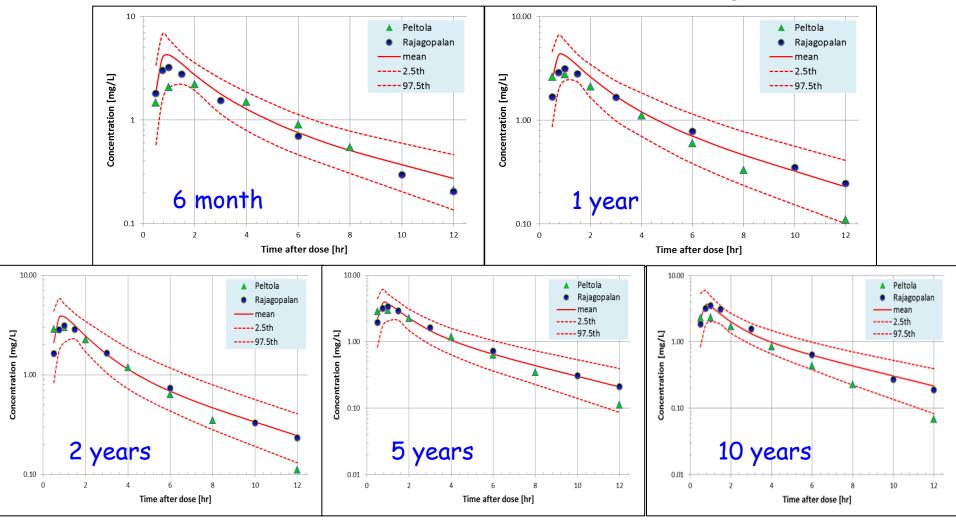


Aigner, K. R. & Dalhoff, A. 1986. Penetration activities of ciprofloxacin into muscle, skin and fat following oral administration. J Antimicrob Chemother, 18, 644-5. Schlenkhoff, D., Dalhoff, A., Knoff, J. & Opferkuch, W. 1986. Penetration of ciprofloxacin into human lung tissue following intravenous injection. Infection, 14, 299-300.



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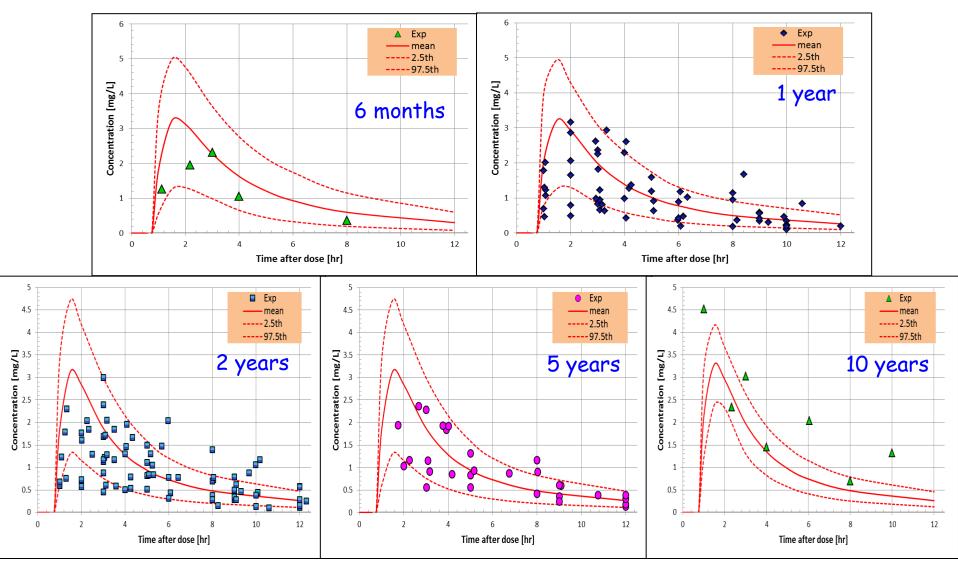
Results: oral model for healthy children UNIVERSITET



PELTOLA, H., UKKONEN, P., SAXEN, H. & STASS, H. 1998. Single-dose and steady-state pharmacokinetics of a new oral suspension of ciprofloxacin in children. Pediatrics, 101, 658-62. RAJAGOPALAN, P. & GASTONGUAY, M. R. 2003. Population pharmacokinetics of ciprofloxacin in pediatric patients. J Clin Pharmacol, 43, 698-710.



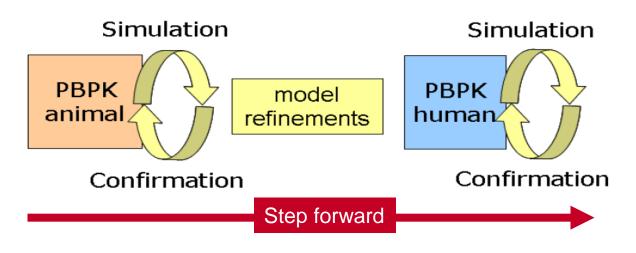
UNIVERSITET Results: oral model for malnourished children





Application

i. Drug discovery and development: "learn & confirm"



If the model prediction is adequate, then do step forward.

If the model prediction is inadequate, there are some systems that we do not know yet.

ii. Patient care

Predict drug concentrations, efficacy and toxicity for special populations



UNIVERSITET Program for PBPK simulation

Editor - C:\PBPK GUI\Ciprofloxacin.m				C:\PBPK GUI\samCO.							i← 🗆 🦻	
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This file uses Cell Mode. For information, see the <u>rapid code iteration</u> video, the <u>publishing</u> video, or <u>help</u> .				<pre>1 [function [f,ff,smp_BW,smp_C0] = samCO(mean,var) 2 - smp CO=[];</pre>								
580 %%ODE start				smp CO=[];	(360 36)							
581 - t=[0 0.083 0.17 0.25 0.5 0.75 1 1.5 2 3 4 5 6 7	8 121;			<pre>sum all=[];</pre>	(360,36)	,						
582 % t=[0:0.01:12];				ff=[];								
583 - [z, A, b]=matrix(p,n,dose);				while (mean>0)								
584 - [t,y]=ode23s('PKmodel',t,z);			7 - 1		= samBW	(mean,var);						
585 - Conc=y'; %transpose matrix			8 -			smp CO)/1.8;		<pre>%liver</pre>				
586 - kk=size(Conc); %return array dimension - kk= 1 1	4		9 -			mp_CO)/1.1228	407;	%gut (sma	ll+large intes	tine and s	tomach)	
587 - m=kk(1,2); %m=14			10 -			mp_CO)/0.1423		<pre>%spleen</pre>				
	<pre>%zint=y(:,m);</pre>			$11 - hh(4) = (f(7) \times 1.9 \times mp - C0)/0.2952381; \\ kidney$								
	<pre>Concsim=[Concsim; Conc];</pre>			12 - hh(5)=(f(8)*0.17*smp_CO)/27.857829; %muscle								
			13 -			mp_CO)/15.829		<pre>%adipose</pre>				
591 - Conceim; 592 - n comp=14;	Concsim;			14 - hh(7)=(f(10)*0.05*smp_C0)/2.9596892; %skin 15 - hh(8)=(f(11)*0.04*smp_C0)/0.3203883; %heart								
593 - ss=size(Concsim);						smp_CO)/0.320		<pre>%heart</pre>				
594 - ss1=ss(1,1);						smp_CO)/1.407		%brain				
595 - M=Concsim;			17 -		13)*0.05	*smp_CO)/2.76	38191;	<pre>%bone</pre>				
596			18 -	smp CO;								
597 - for j=1:n_comp			19 - 20 -	sum_all=su								
598 - 🕒 for i=j:n_comp:ss1			20 - 21 -	if (any (h elseif sum		- 60						
599 - if j==1			22 -	ko=1		p_co						
600 - sim.comp1=M(i,:);			23 -	else								
601 - <u>K1</u> =[K1; sim.comp1];			24 -		%ff are	organ blood	flow					
602 - elseif j==2 603 - sim.comp2=M(i.:);			25 -	break								
603 - sim.comp2=M(i,:); 604 - K2=[K2;sim.comp2];	,		26 -	end								
KZ=[KZ,SIM.COMP2],	🥠 pbpk											
Ciprofloxacin.m × pbpk.m × samCO.m ×	Design	– Drug paran	neters		-Кр-		Organ	n volumes		— — Orga	n BF (%CO)-	
A Start									014			
	Oral (mg) Oral (mg) 		.8 CV		Arterial	1	Arterial	3.6	CV 10	Arterial	100	
	IV bolus (mg)	Ka (/h) 2	.5 CV	/ 10	Lungs	5.1668	Lungs	0.4784	CV 10	Lungs	100	
/ritton using MATLAD soriet	IV infusion (mg/h) 🔘	Tlag (h) 0	.3 CV	/ 10	Venous	1	Venous	1.8	CV 10	Venous	100	
/ritten using MATLAB script	Dose (mg) 500	F (%) 0	.7 CV	/ 10	Liver	5.9010	Liver	1.8	CV 10	Liver	6.5	
iUI available					Gut	3.4868	Gut	1.8	CV 10	Gut	15	
ontained a library of drugs	Body weight	- Clearance			Spleen	4.4056	Spleen	0.1423	CV 10	Spleen	3	
, .	Mean 73	Renal (L/h)	15	CV 10	Adipose	0.5924	Adipose	15.8296	CV 10	Adipose		
mainly antibiotics) which is also	CV 10	Hepatic (L/h)	15	CV 10			11 .					
nked to therapeutic effects.					Muscle	3.5151	Muscle	27.8578	CV 10	Muscle	17	
•	Cardiac output	- Kp models			Skin	2.1362	Skin	2.9569	CV 10	Skin	5	
ossibly shared for academic uses	Mean 360	Poulin&Theil	ers&Rowland ()	Heart	3.3154	Heart	0.3203	CV 10	Heart	4		
	CV 10	Willmann	0		Bone	1.2514	Bone	2.7638	CV 10	Bone	5	
					Brain	1.3199	Brain	1.4077	CV 10	Brain	12	
Contact: Manchana Lingshelsen		hana Ungphakorr	n, University of S	Strathclyde	Kidney	6.4090	Kidney	0.2952	CV 10	Kidney	19	
Contact: Wanchana.Ungphakorn@f	armbio.uu.se											



Uppsala: Sweden's old capital city (~70 km from Stockholm)









UNIVERSITET Back up slides



Model equations

 Mass of the drug in each organ was calculated using Linear ordinary differential equations (LODE)

1) Non-eliminating organs:

$$V_{T,i} \frac{dC_{T,i}}{dt} = Q_{T,i} \times (C_A - \frac{C_{T,i}}{Kb_i})$$

2) Eliminating organs (kidney, liver, gut):

$$V_{T,i} \frac{dC_{T,i}}{dt} = \left[Q_{T,i} \times (C_A - \frac{C_{T,i}}{Kb_i}) \right] - CL_{int} \times \frac{C_{T,i}}{Kpu_i}$$

C = concentration (mg/L), Q = blood flow (L/h), Kb = tissue:blood partition coefficient, Kpu = tissue:plasma unbound partition coefficient, CLint = intrinsic clearance (L/h), V = volume (L), T = tissue, A = arterial blood, i = each organ in the model



UPPSALA in silico Kp prediction

 Based on in vitro data of i. drug lipophilicity (LogP_{O:W}), ii. protein binding (fu, R) and iii. tissue composition

	Tissue composition (fraction of tissue wet weight)									
Tissues	Water	Extracellular	Intracellular	Neutral	Neutral	Acidic				
		water	water	lipids	phospholipids	phospholipids				
Bone	0.45	0.074	0.0011	0.346	0.100	0.67				
Brain	0.78	0.051	0.0565	0.620	0.162	0.40				
Gut	0.76	0.0487	0.0163	0.475	0.282	2.41				
Heart	0.78	0.0115	0.0166	0.456	0.320	2.25				
Kidney	0.76	0.0207	0.0162	0.483	0.273	5.03				
Liver	0.73	0.0348	0.0252	0.573	0.161	4.56				
Lung	0.78	0.003	0.009	0.446	0.336	3.91				
Muscle	0.71	0.022	0.0072	0.630	0.079	2.42				
Skin	0.67	0.0284	0.0111	0.291	0.382	1.32				
Spleen	0.79	0.0201	0.0198	0.579	0.207	3.18				
Adipose	0.15	0.79	0.002	0.017	0.135	0.4				
Plasma	0.95	0.0032	0.0021	-	-	-				
Blood cells	0.63	0.0012	0.0033	0.603	-	0.57				



1) Poulin and Theil method

$$Kp = \frac{\left[P \cdot (V_{nl} + 0.3V_{ph}) + V_{w}/fu_{t} + 0.7V_{ph}\right]_{\text{-tissue}}}{\left[P \cdot (V_{nl} + 0.3V_{ph}) + V_{w}/fu_{p} + 0.7V_{ph}\right]_{\text{-plasma}}}$$

2) Rodgers and Rowland method

$$\begin{split} & \mathsf{Kpu}_{\mathsf{BC}} = \left[\frac{(\mathsf{Hct}-1)+\mathsf{R}}{\mathsf{fu}+\mathsf{Hct}}\right] \\ & \mathsf{X} = 10^{\mathsf{pKa}_{\mathsf{BASE}}-\mathsf{pH}_{\mathsf{iw}}} + 10^{\mathsf{pH}_{\mathsf{iw}}-\mathsf{pHa}_{\mathsf{ACD}}}; \ \mathsf{Y} = 10^{\mathsf{pKa}_{\mathsf{BASE}}-\mathsf{pH}_{\mathsf{p}}} + 10^{\mathsf{pH}_{\mathsf{p}}-\mathsf{pHa}_{\mathsf{ACD}}}; \ \mathsf{Z} = 10^{\mathsf{pKa}_{\mathsf{BC}}-\mathsf{pH}_{\mathsf{iw}}} + 10^{\mathsf{pH}_{\mathsf{iw}}-\mathsf{pHa}_{\mathsf{BC}}} \\ & \mathsf{Ka}_{\mathsf{AP}} = \left[\mathsf{Kpu}_{\mathsf{BC}} - \left(\frac{1\!+\!\mathsf{Z}}{1\!+\!\mathsf{Y}}\cdot\mathsf{V}_{\mathsf{iw},\mathsf{BC}}\right) - \left(\frac{\mathsf{P}\cdot\mathsf{V}_{\mathsf{nl},\mathsf{BC}} + (0.3\mathsf{P}\!+\!0.7)\cdot\mathsf{V}_{\mathsf{nl},\mathsf{BC}}}{1\!+\!\mathsf{Y}}\right)\right] \cdot \left(\frac{1\!+\!\mathsf{Y}}{\mathsf{AP}_{\mathsf{BC}}\cdot\mathsf{Z}}\right) \\ & \mathsf{Kpu} = \left[\left(\frac{1\!+\!\mathsf{X}\cdot\mathsf{V}_{\mathsf{iw}}}{1\!+\!\mathsf{Y}}\right)\!+\!\mathsf{V}_{\mathsf{ew}}\!+\!\left(\frac{\mathsf{Ka}_{\mathsf{AP}}\cdot\mathsf{AP}\cdot\mathsf{X}}{1\!+\!\mathsf{Y}}\right)\!+\!\left(\frac{\mathsf{P}\cdot\mathsf{V}_{\mathsf{nl}}\!+\!(0.3\mathsf{P}\!\!+\!0.7)\cdot\mathsf{V}_{\mathsf{ph}}}{1\!+\!\mathsf{Y}}\right)\right] \end{split}$$

 $P = P_{O:W}$ and $D_{VO:W}$ for lean and adipose tissues, respectively. $D_{VO:W}$ were estimated using linear regression and Henderson-Hasselbalch equations. Kp = Kpu-fu

3) Empirical method

$$V_{\rm SS} = V_{\rm plasma} + (V_{\rm BC} \cdot RBC_{\rm u} \cdot f{\rm u}) + \sum_{i=i}^{n} V_{\rm t,i} \times 10^{a_{t,i} \times \log K_{\rm pmuscle} + b_{\rm tissue,i} \times \log X_{\rm drug} + {\rm intercept}_{\rm tissue,i}}$$