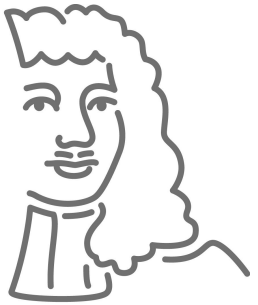
A physiologically based population pharmacokinetic model describing the non-linear disposition and blood distribution of indisulam

Anthe Zandvliet, Sanae Yasuda, Jan Schellens, Jos Beijnen, Alwin Huitema

Slotervaart Hospital



NKI-AVL

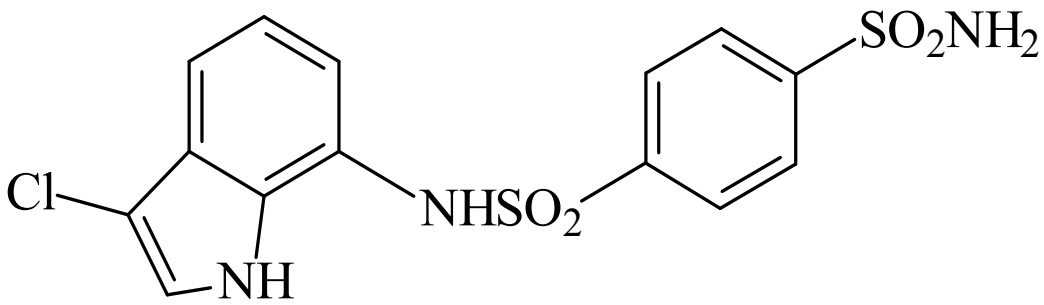
The Netherlands Cancer Institute
Antoni van Leeuwenhoek Hospital

Overview of presentation

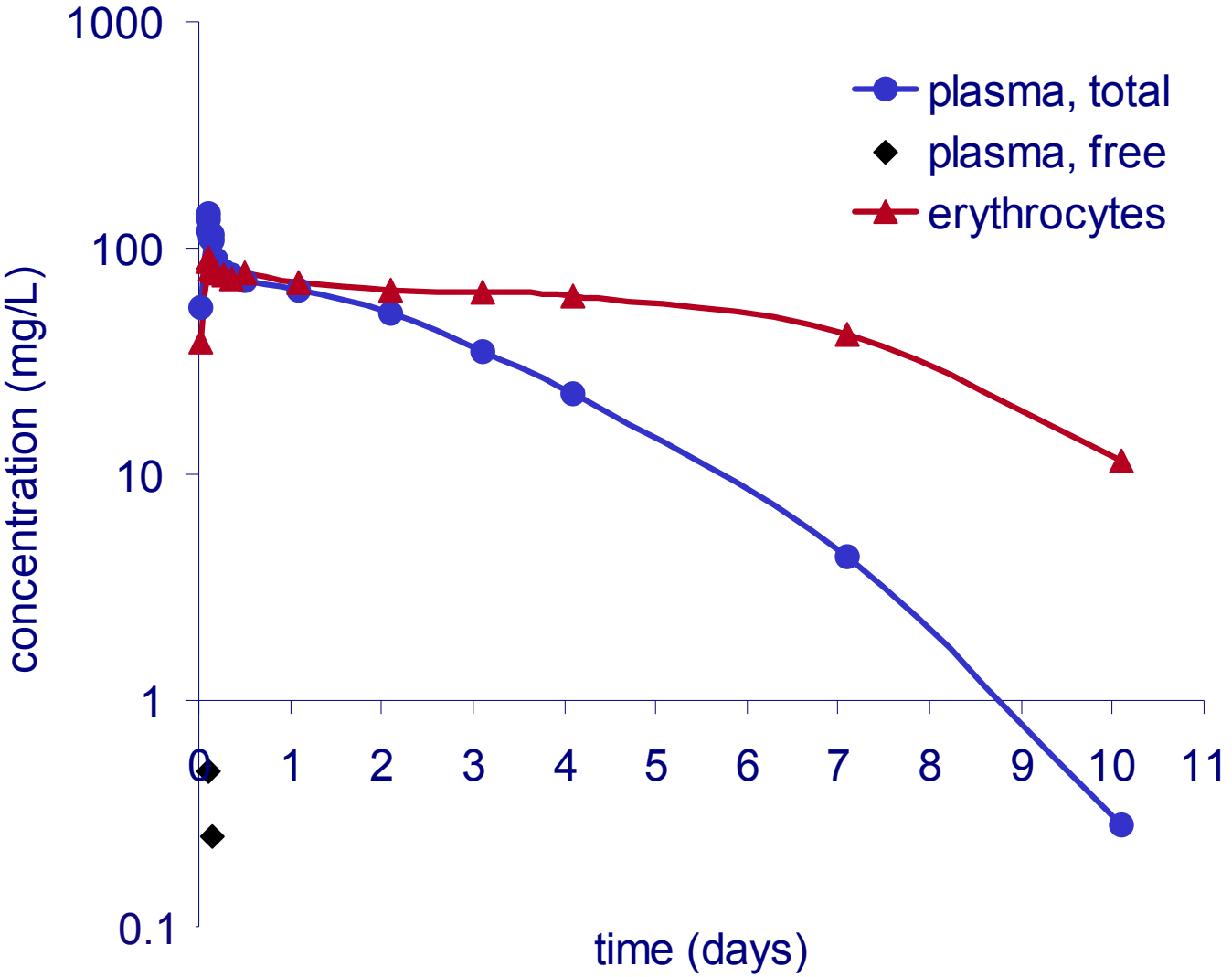
- Introduction indisulam
- Objectives
- Data
- Physiological model
  - Protein binding
  - Distribution to red blood cells
  - Tissue distribution
  - Elimination
- Implications for pharmacodynamic studies
- Conclusions

Indisulam

- Sulphonamide anticancer agent
- Inhibition of G1/S transition
- Phase II clinical development
- Objective responses in patients with colorectal, breast and renal cell cancer



Non-linear pharmacokinetic profile



Objectives (1)

- To develop a physiological population pharmacokinetic model for indisulam describing time profiles of:

  a) free plasma concentrations

  b) total plasma concentrations

  c) erythrocyte concentrations

Objectives (2)

- To examine the role of plasma protein binding and distribution to erythrocytes in indisulam pharmacokinetics.

Phase I studies

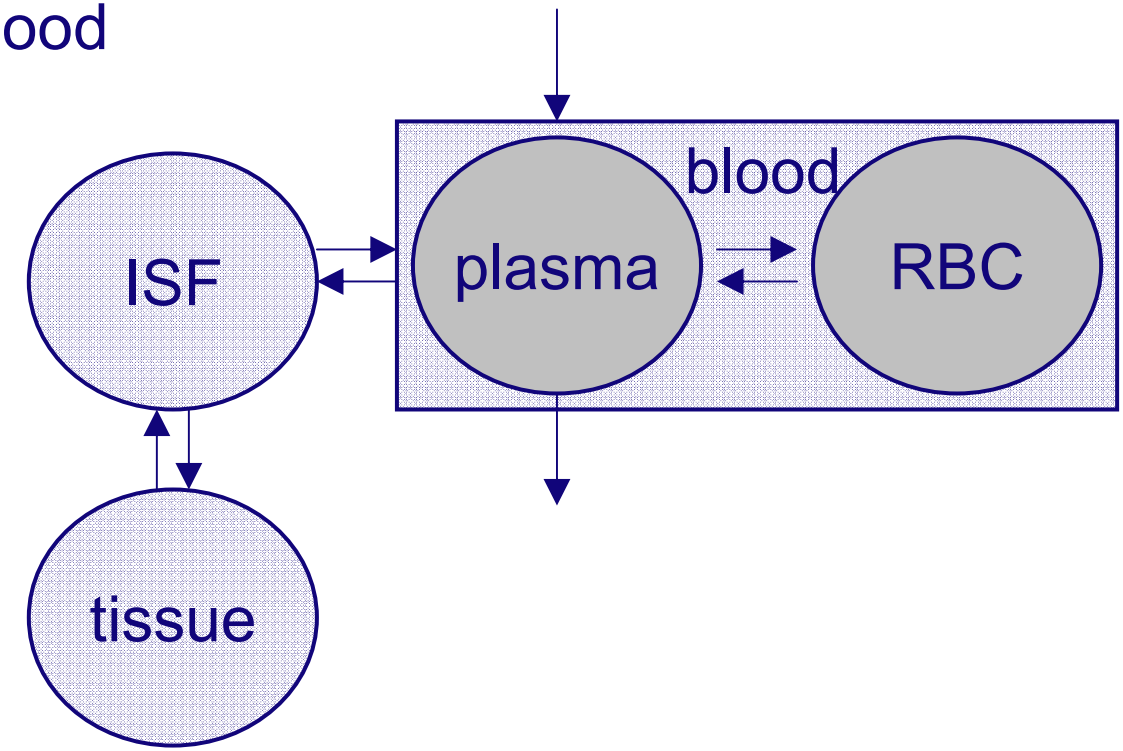
	regimen	dose (mg/m^2)	population	n
1.	daily x 1	50 - 1000	Caucasian	40
2.	daily x 5	10 - 200	Caucasian	35
3.	weekly x 4	40 - 500	Caucasian	43
4.	120-hour inf.	30 - 1000	Caucasian	25
5.	daily x 1	400 - 900	Japanese	21

Backbone of the physiological model

4 physiological compartments:

1. plasma
2. erythrocytes
3. interstitial fluid
4. tissue

blood

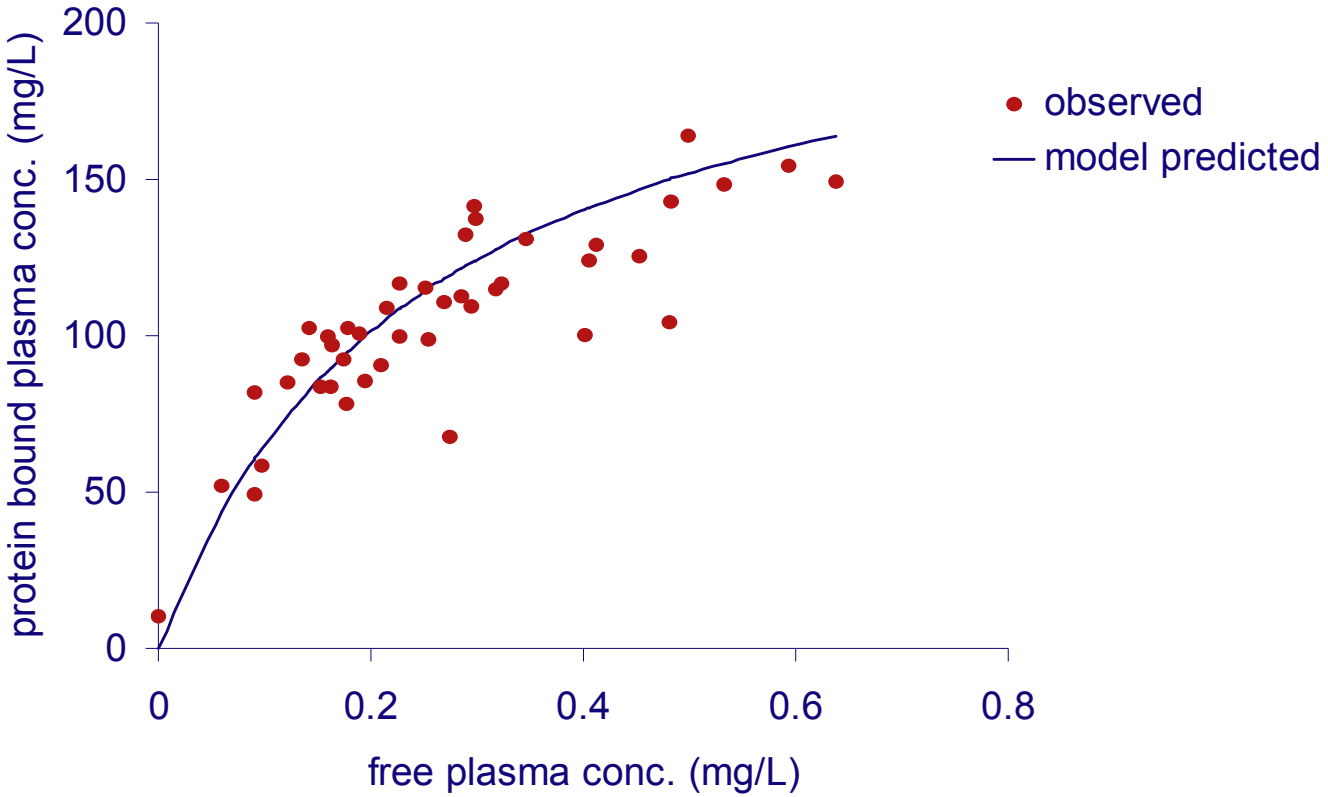


Distribution volumes

blood	♂	BL=(3.29*BSA-1.229)
	♀	BL=(3.47*BSA-1.954)
plasma		(1-HEMATOCRIT)*BL
erythrocytes		HEMATOCRIT*BL
interstitial fluid		4/27*WT

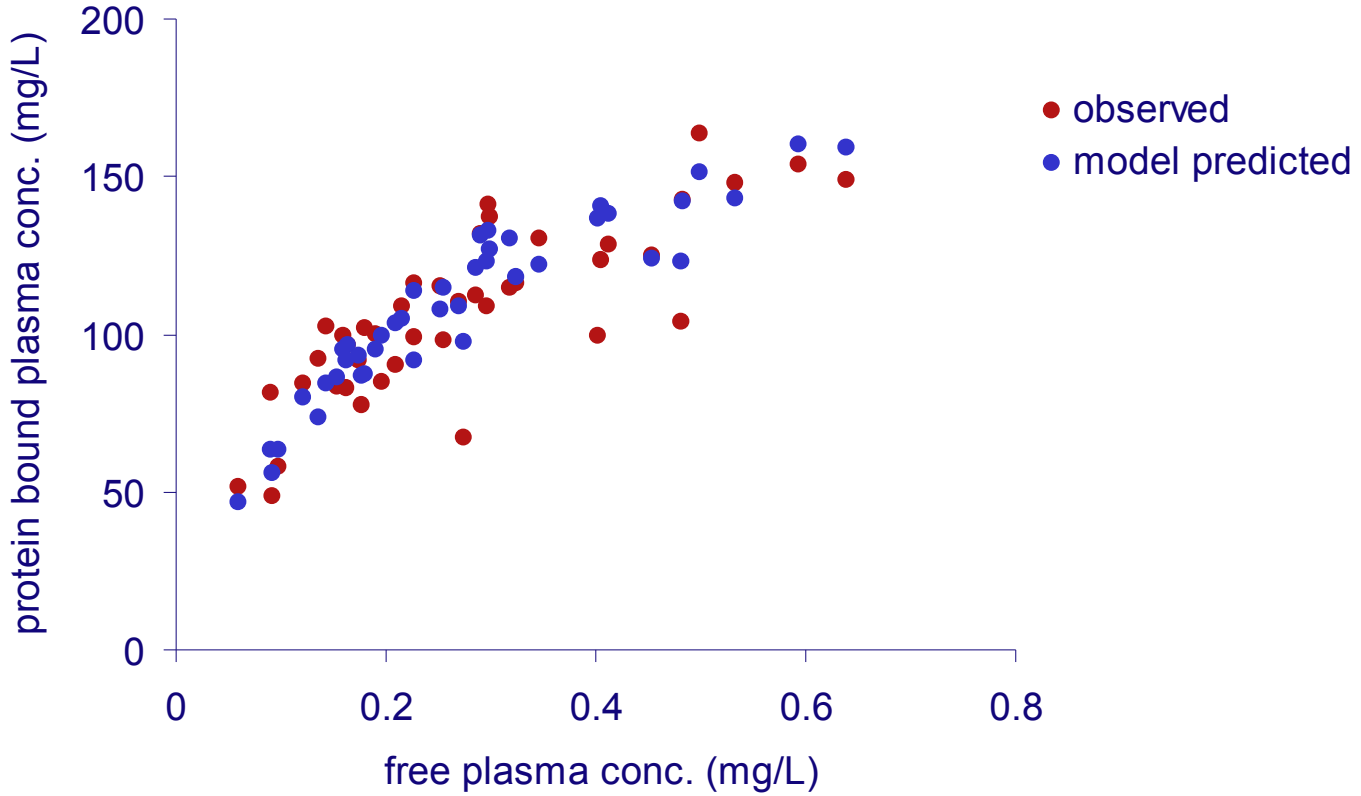
Ref: Surg Gynecol Obstet 1957; 104(2):183-189.

Saturable plasma protein binding



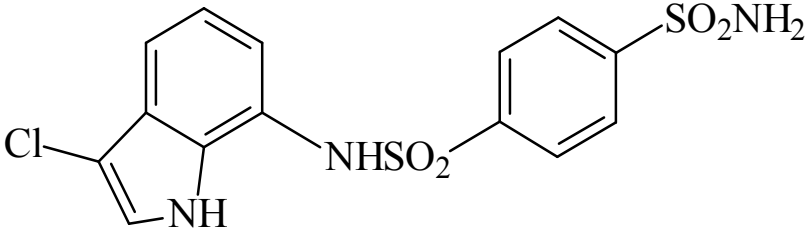
Langmuir model $$C_{plasma,bound} = B_{max} * \frac{C_{plasma,free}}{(C_{plasma,free} + K_D)}$$

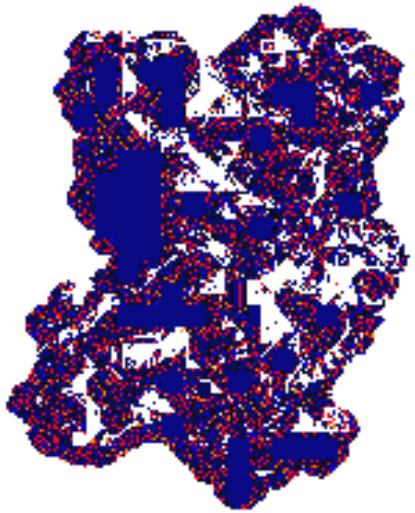
Saturable plasma protein binding



$$C_{plasma,bound} = [albumin] * \frac{C_{plasma,free}}{(C_{plasma,free} + 0.25\ mg/L)}$$

Saturable plasma protein binding



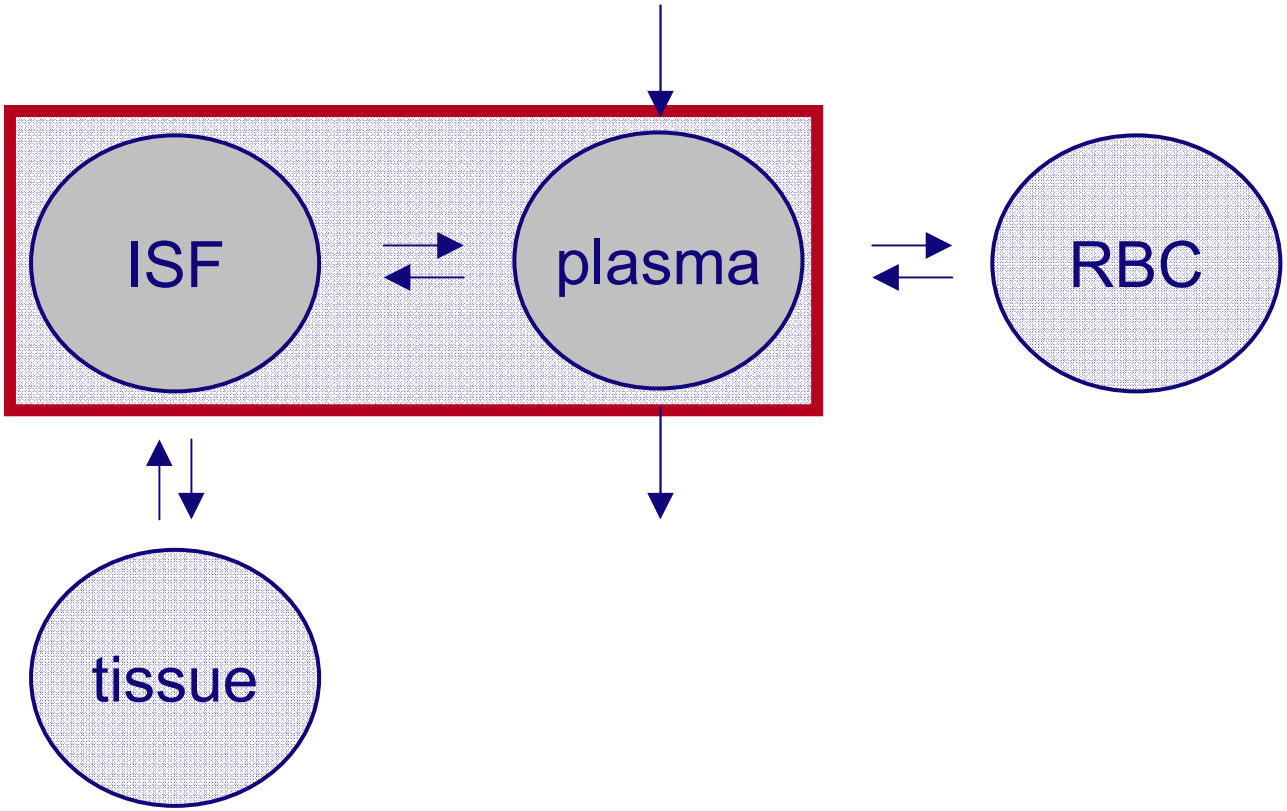


indisulam albumin

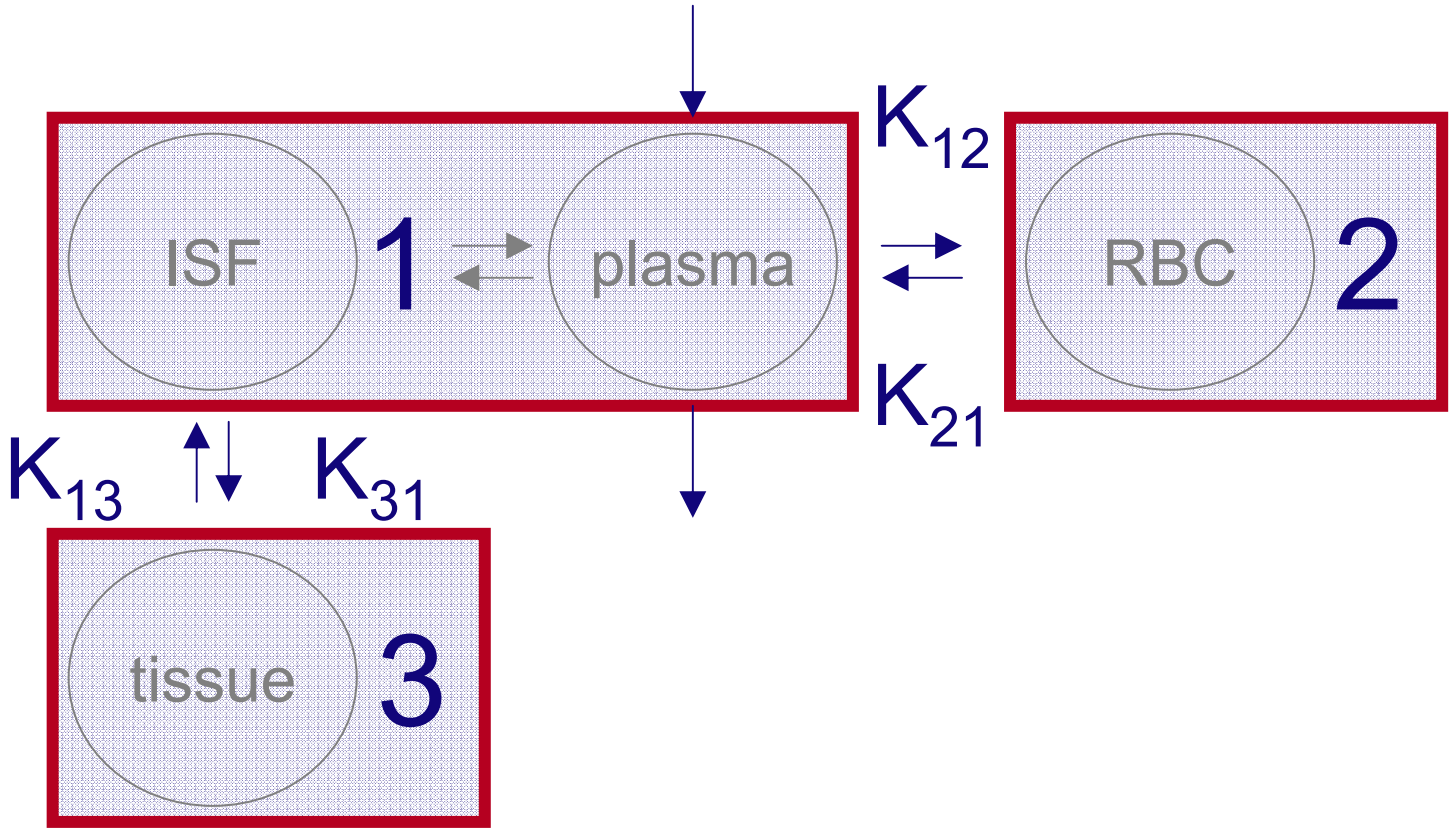
1:1 binding complex

B_{max} = [albumin] (g/L) * $MW_{indisulam}$ / $MW_{albumin}$ * 1000 mg/L

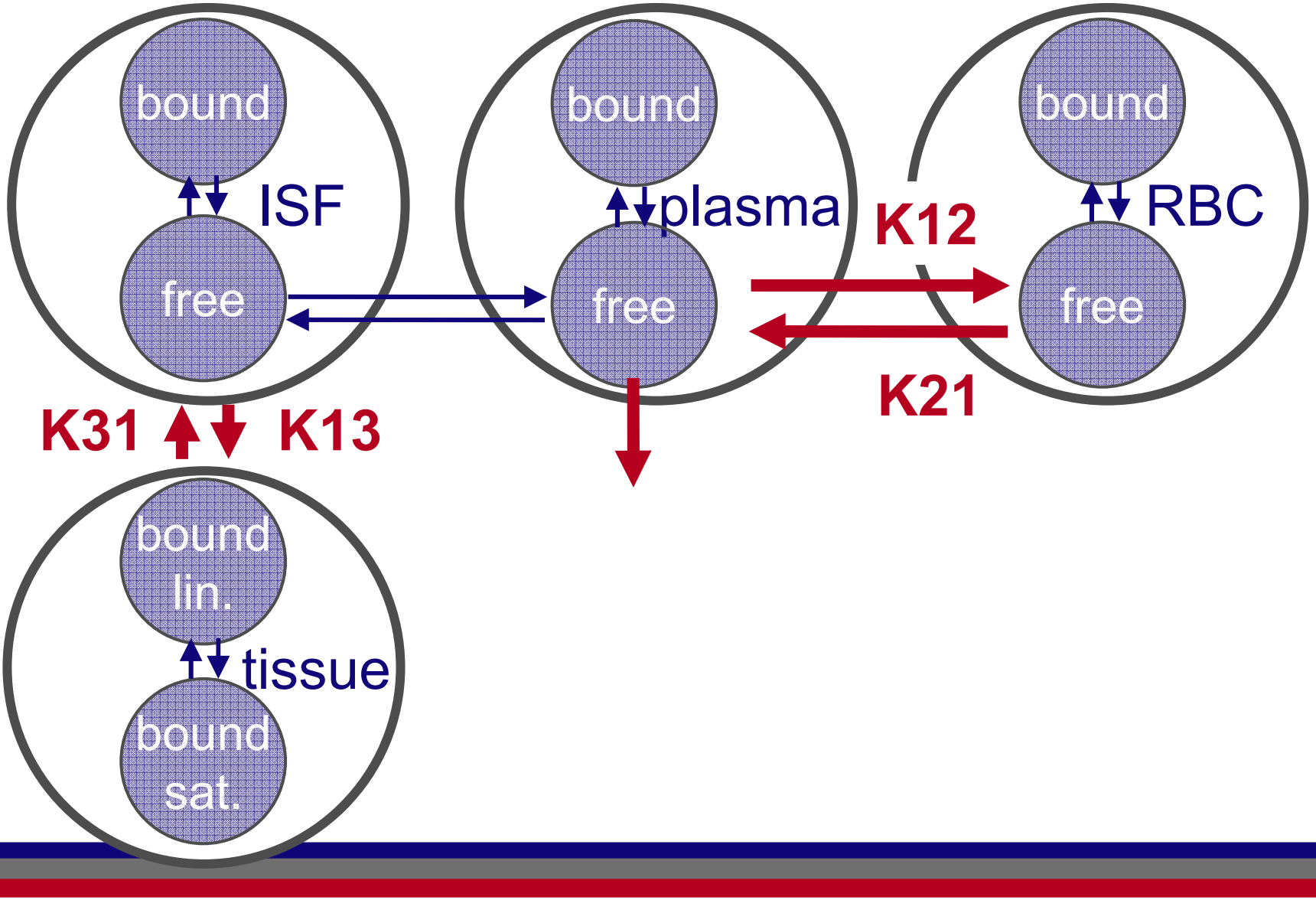
Central compartment



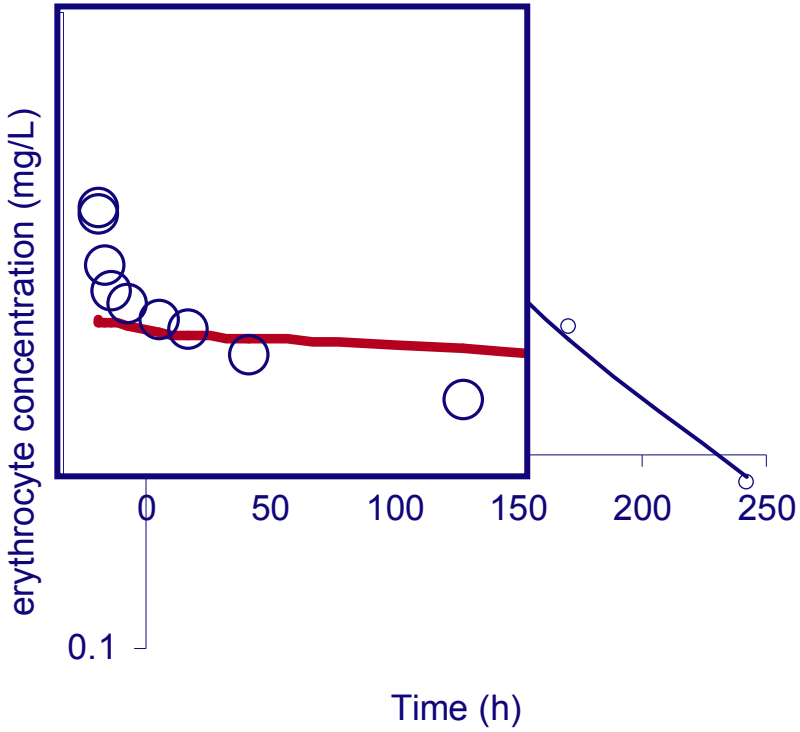
Three compartment model



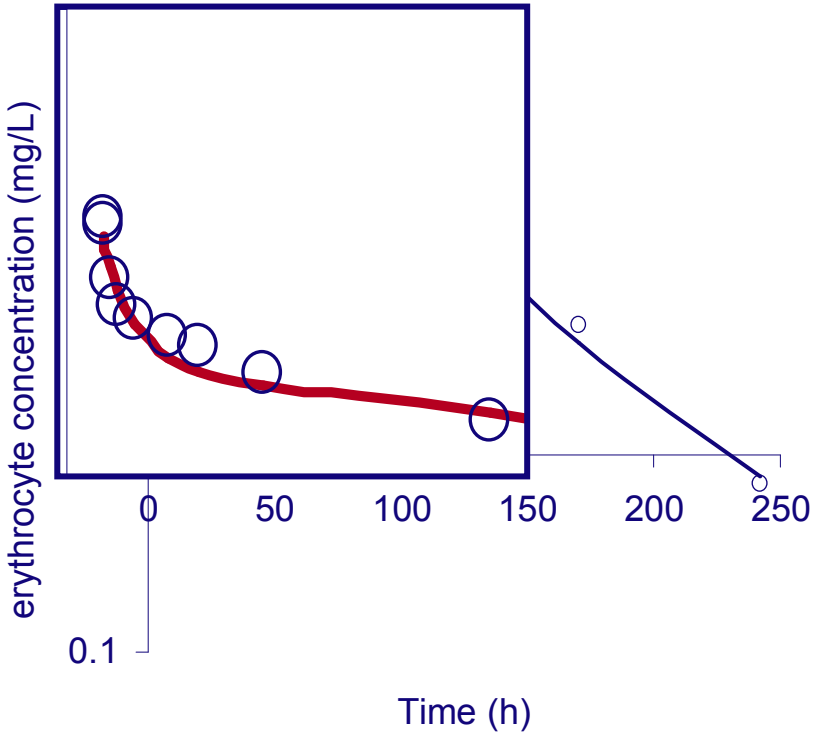
Three compartment model



Distribution to erythrocytes



One site binding model
saturable



Two site binding model
saturable + non-specific

Binding in erythrocytes

$$C_{erythrocytes,bound} = B_{max\ erythrocytes} * \frac{C_{erythrocytes,free}}{(C_{erythrocytes,free} + K_{D\ erythrocytes})} + N_{erythrocytes} * C_{erythrocytes,free}$$

saturable

non-specific

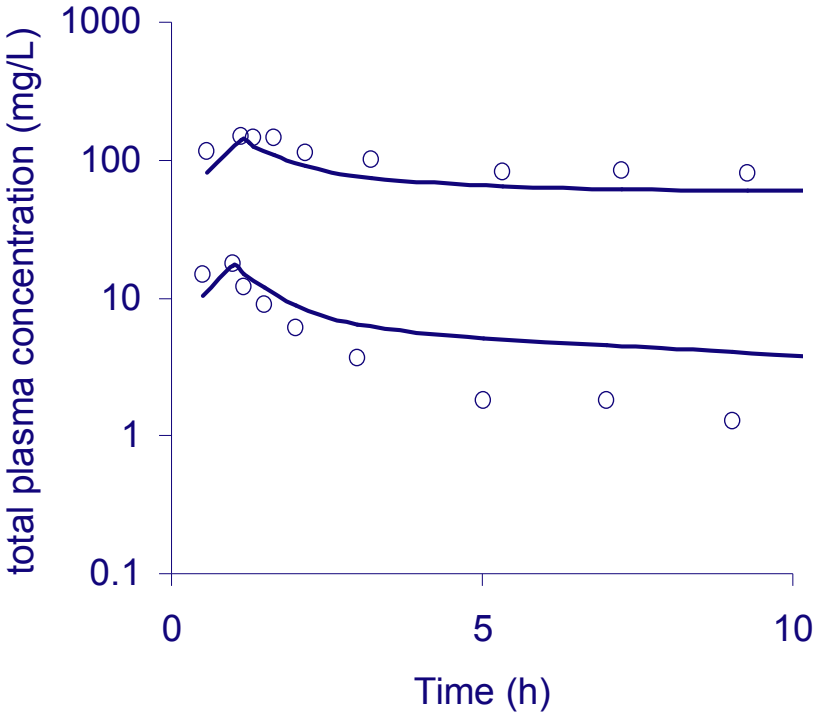
$B_{max\ erythrocytes}$ = 59.0 mg/L (±7.1%) = 153 uM

$K_{D\ erythrocytes}$ = 0.00251 mg/L (±7.9%)

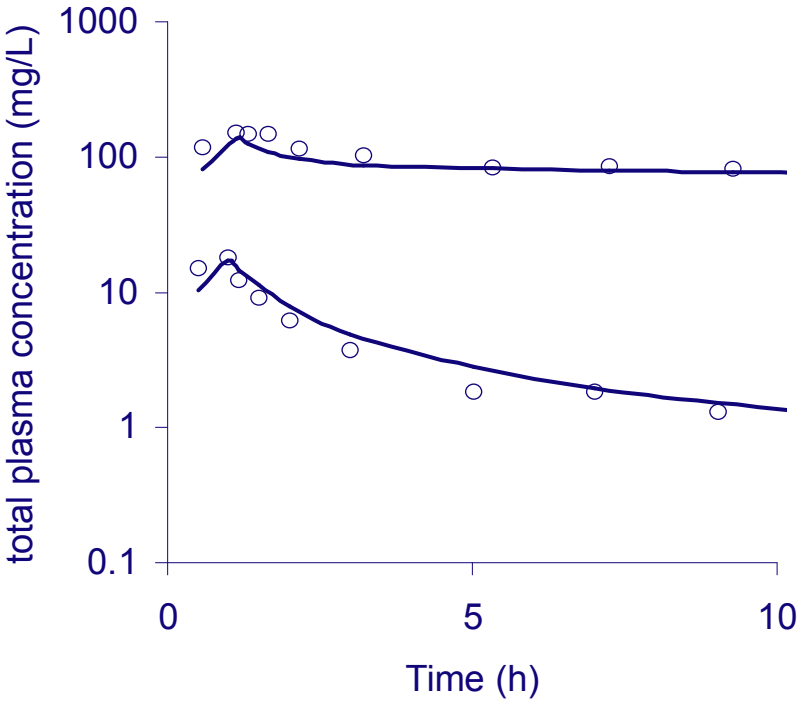
$N_{erythrocytes}$ = 85.5 (±8.7%)

Carbonic anhydrase conc. in erythrocytes 133-186 uM

Tissue distribution

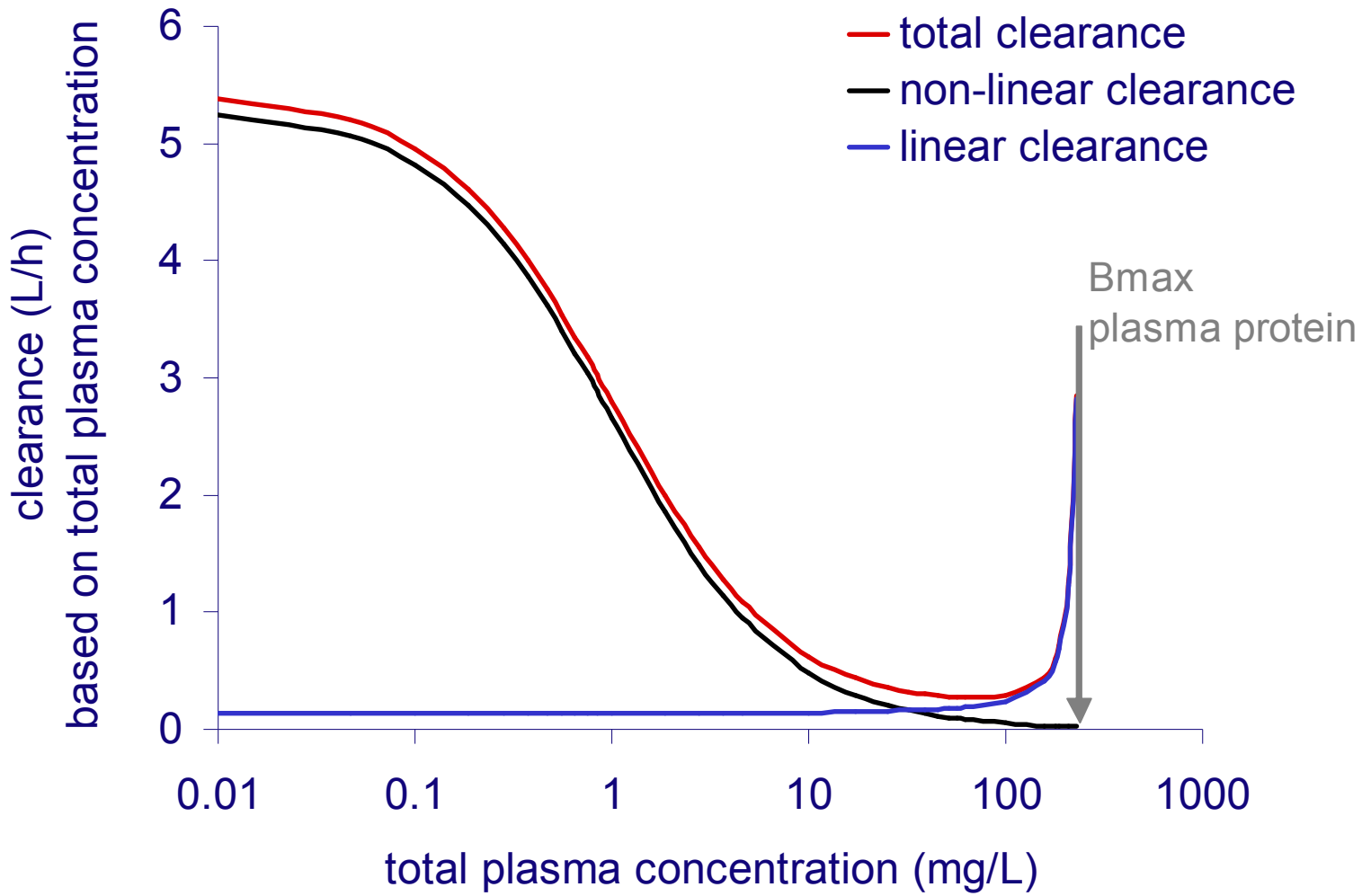


Linear distribution

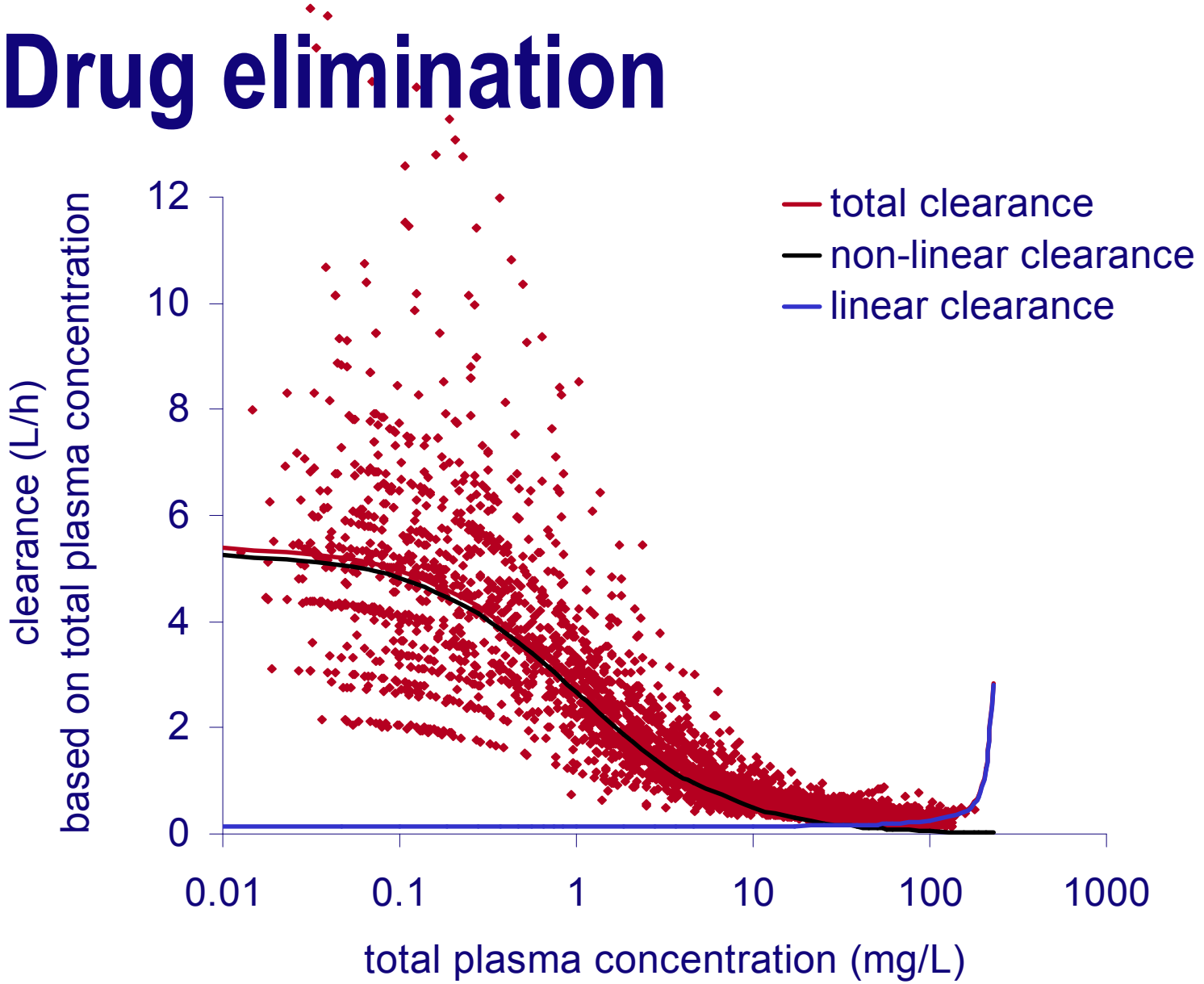


Linear and saturable distribution

Drug elimination



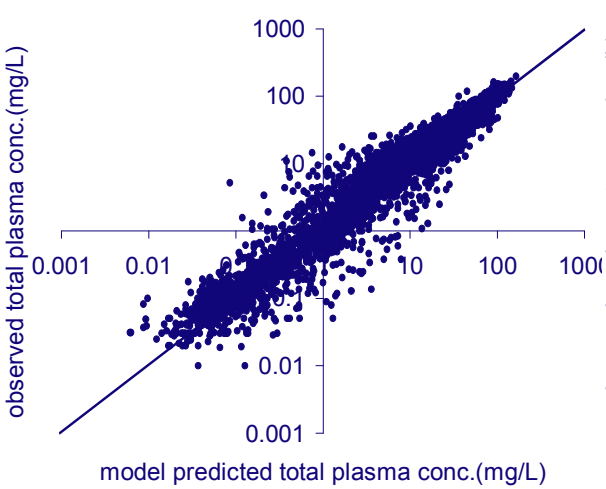
Drug elimination



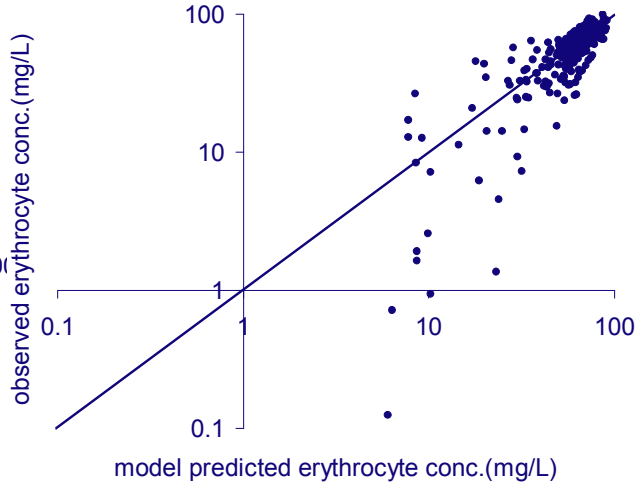
Goodness of fit

The model adequately described the data.

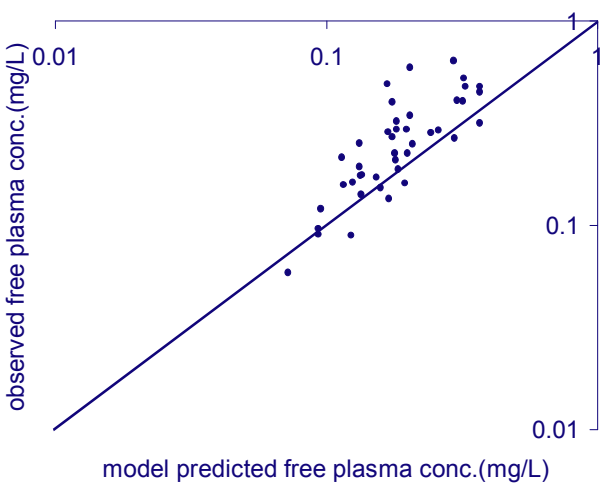
DV vs PRED



plasma

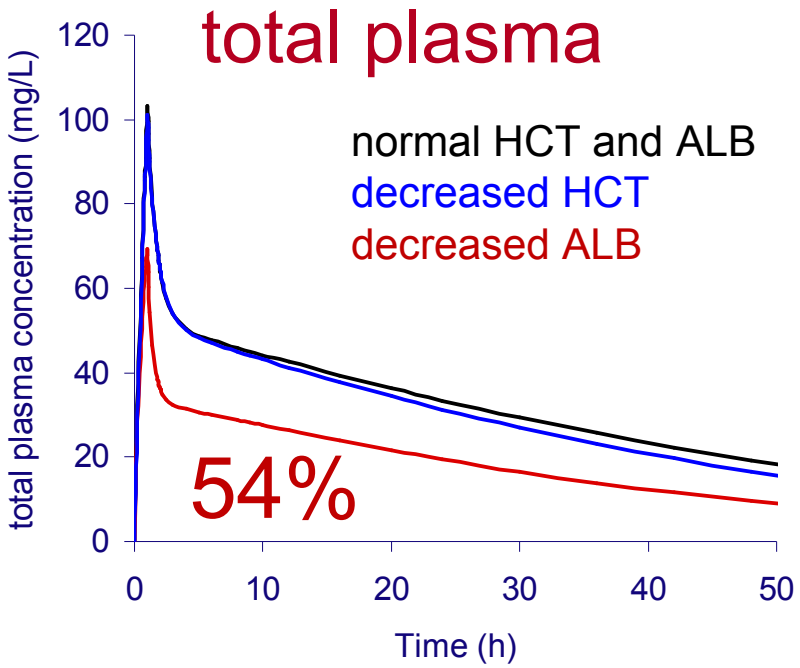


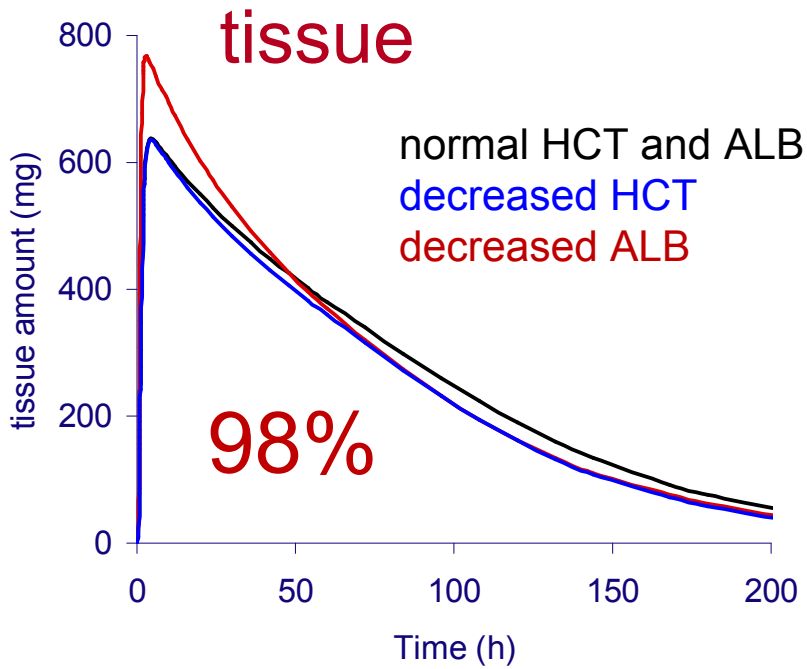
RBC



plasma ultrafiltrate

Impact of hematocrit & albumin





Albumin (g/L)	Hematocrit	Dose (mg/m^2)	AUC (mg*h/L) plasma, total	AUC (g*h) tissue
40	0.4	700	2352 (100%)	58.6 (100%)
40	0.2	700	2118 (90%)	53.5 (91%)
20	0.4	700	1272 (54%)	57.5 (98%)

Discussion

- Total plasma concentrations may not be a preferable target in pharmacodynamic studies of indisulam.

- Improved insight into the disposition of indisulam may facilitate the establishment of new PK-PD relationships.

Conclusions

- The physiological model adequately described indisulam pharmacokinetics in the monitored compartments.

- The model has elucidated the important impact of plasma protein level on indisulam disposition.

Acknowledgments

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