Resisting Population PK – The Story of P-gp inhibition and Co-administered Chemotherapy

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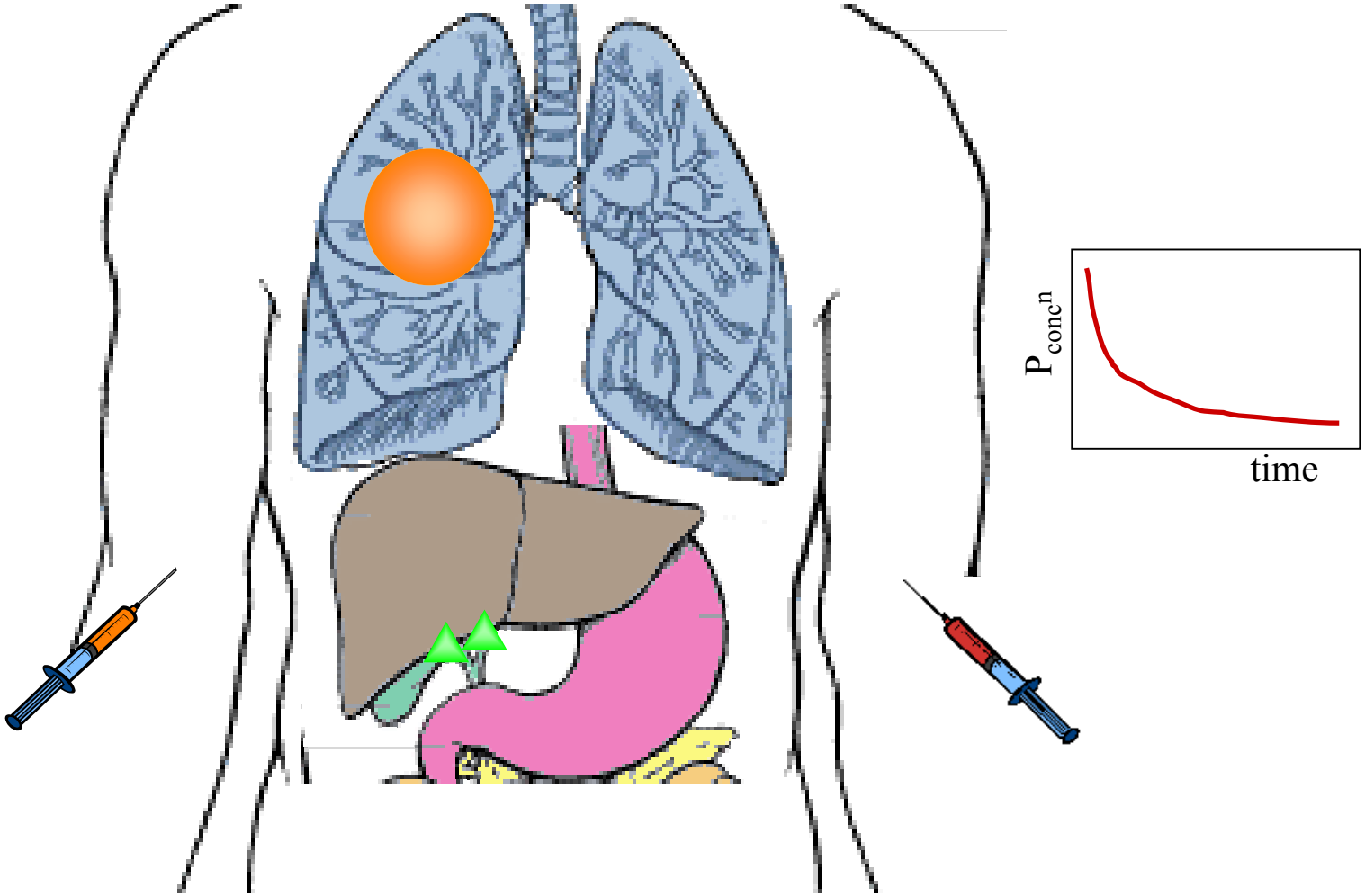
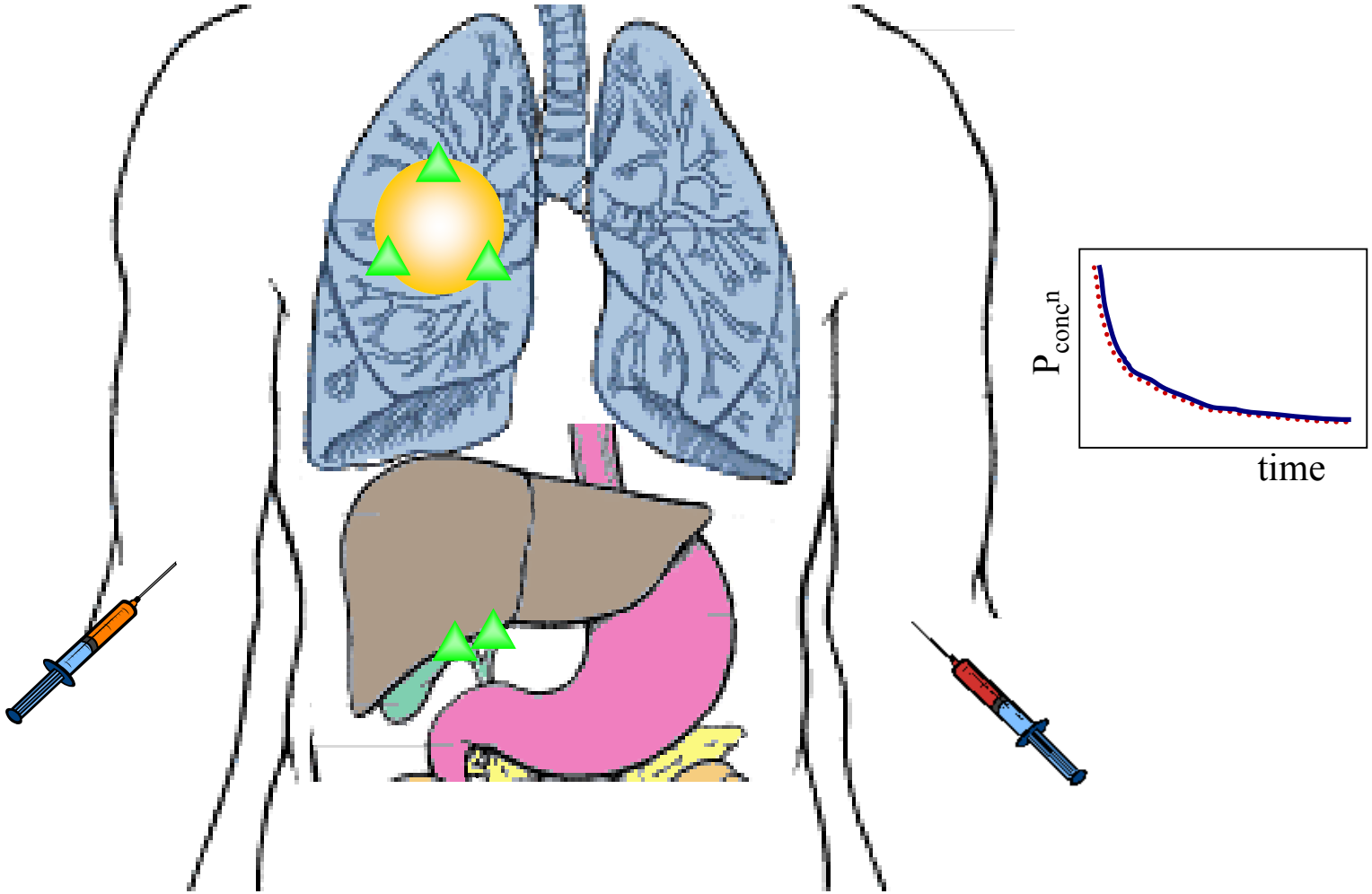
Lilly
Answers That Matter.

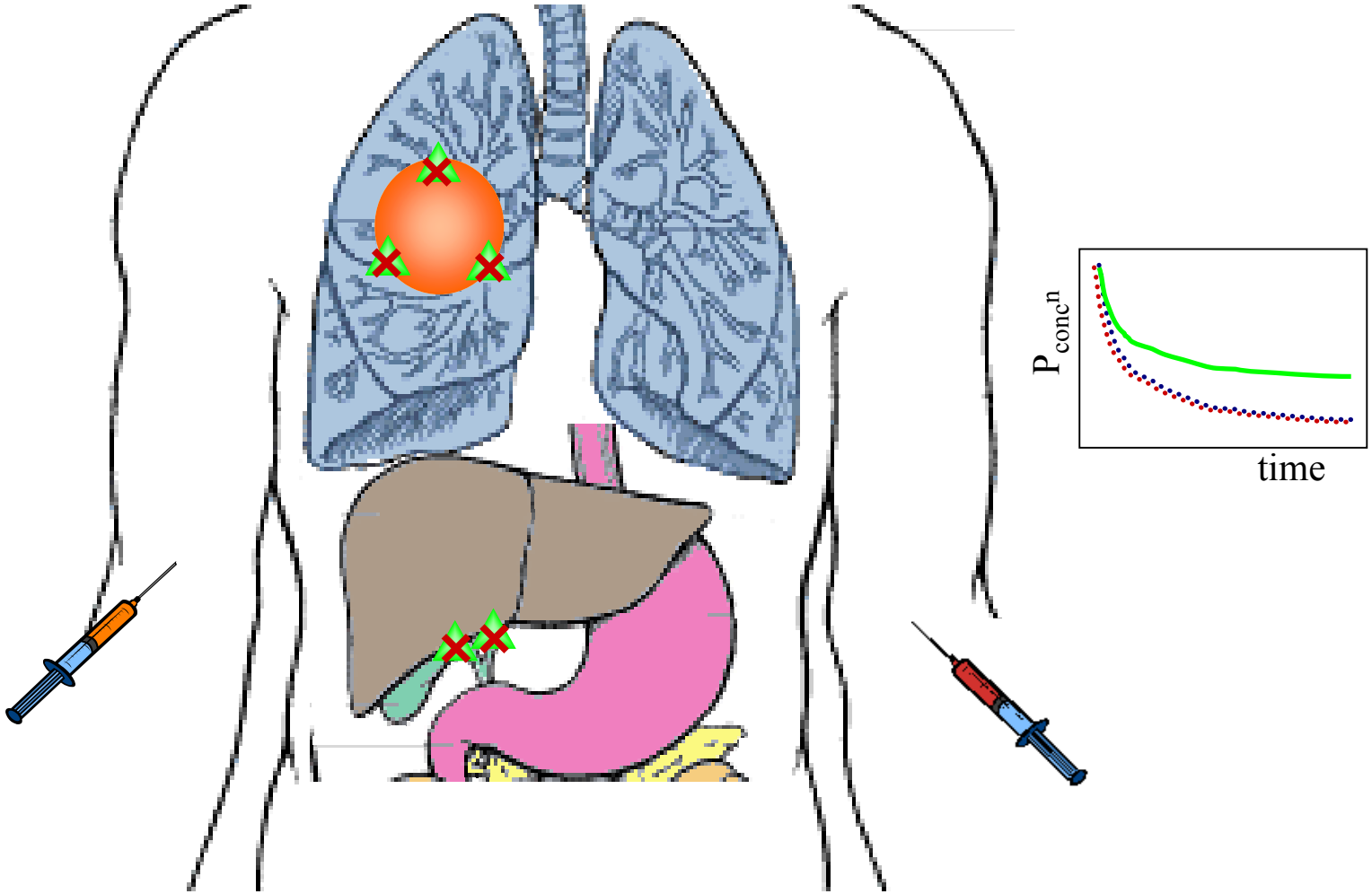
P-gp



P-gp



P-gp



Agents Targeting P-gp Mediated Drug Resistance - The Early Generations

The drugs:	Reasons for failing:
Verapamil	Did not inhibit P-gp
Quinidine	
Quinine	Toxicity in its own right
Tamoxifen	
Cyclosporin A	
PSC-833	PK interaction
GF-120918	

PK Interactions with P-gp inhibitors & co-administered chemotherapy

In theory this depends on:

- Relative contribution of each transporter to drug efflux.
- The distribution of the transporter in normal tissue vs tumour
- Specificity of the inhibitor/drug

Modulator	Pgp	MRP1	MRP2	BCRP
PSC 833	+	–	+	–
VX-710	+	+	–	–
GF120918	+	–	–	+
Zosuquidar	+	–	–	–

Duration of inhibition ??

The Pharmacokinetic Effect of PSC833 on Doxorubicin (50 mg/m^2) & Doxorubicinol

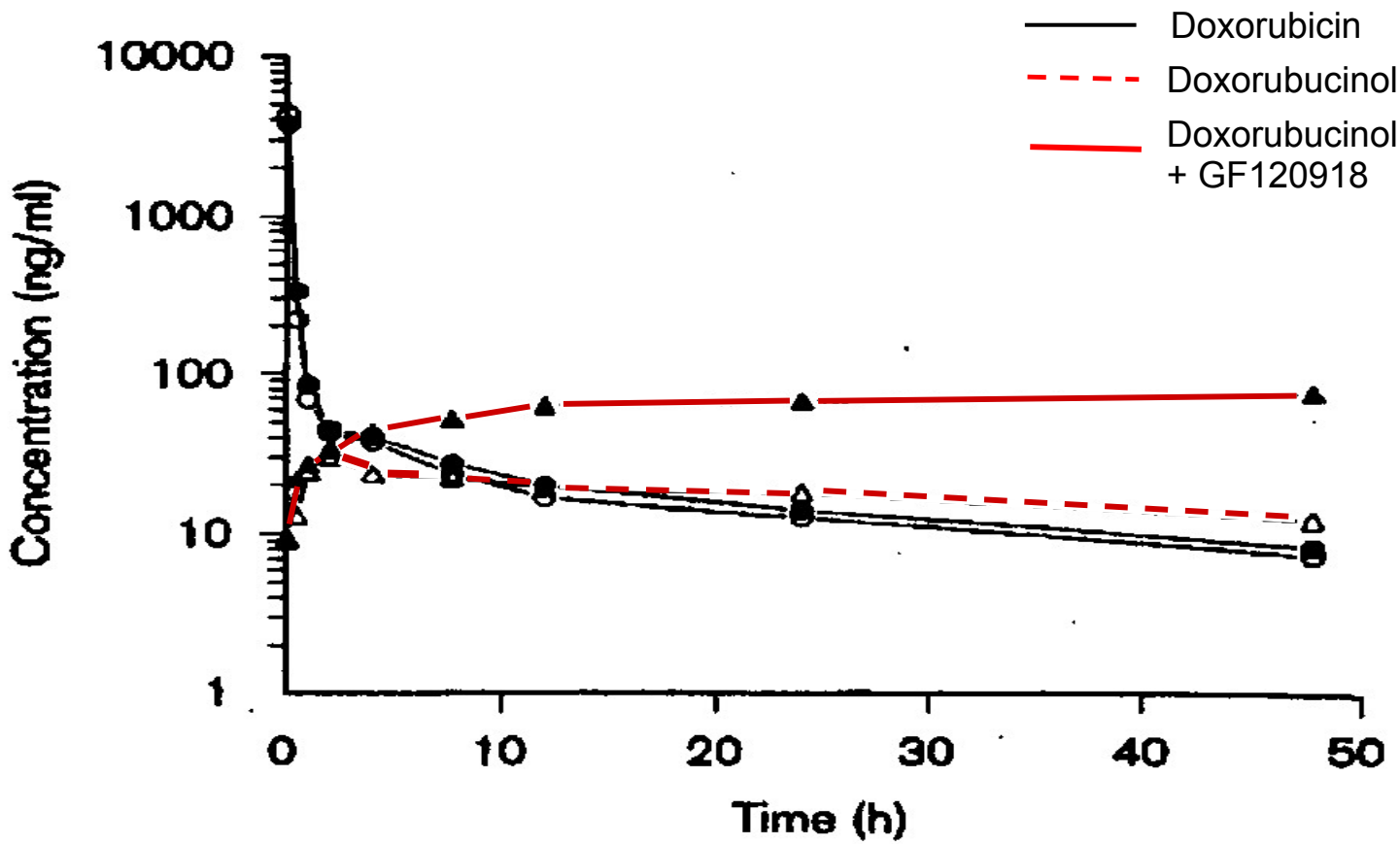
	% Change (based on arithmetic mean)
Doxorubucin PK	
CL	- 30
Doxorubicinol PK	
$AUC_{(0-\infty)}$	+1063
C_{max}	+101

(Giaccone et al., Clinical Cancer Research. 3, 2005-2015, 1997)

PSC 833 administered orally 2.5 to 25 mg/kg/d x 5 d

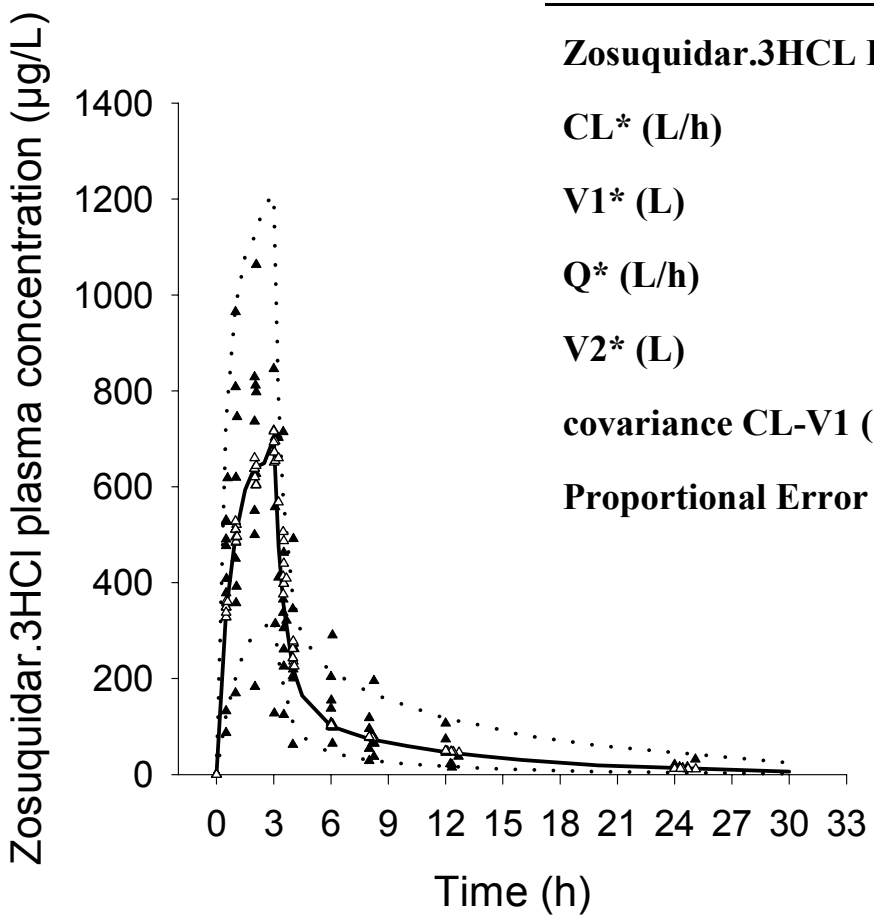
Impact on Doxorubicin- Doxorubicinol PK by GF120918

50mg/m^2 of Dox with or without
400mg BID of GF120918



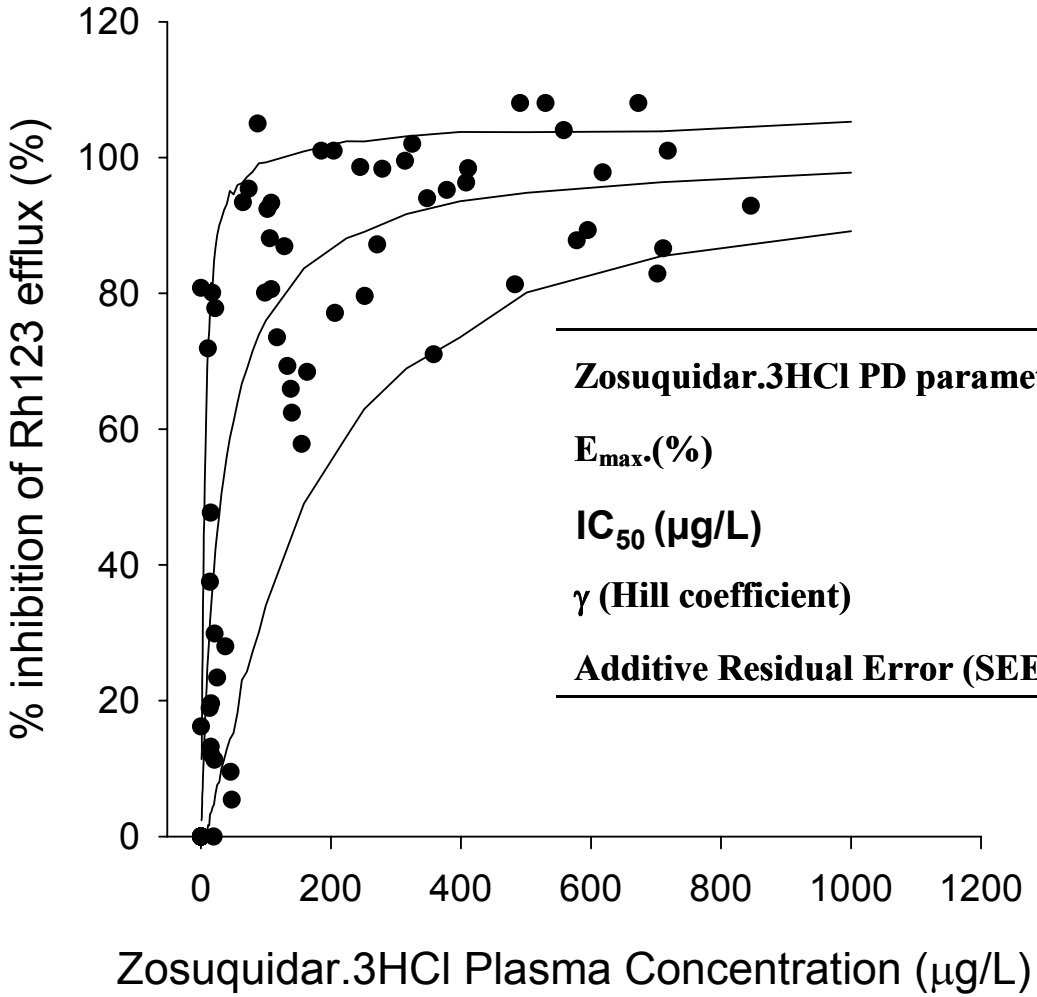
(Sparreboom et al., Anti-Cancer Drugs. 10, 719-728, 1999)

Zosuquidar.3HCL PK Model



Zosuquidar.3HCL PK parameters	Mean (SEE%)	IIV (SEE %)
CL* (L/h)	127 (9.45)	35.1 (56.0)
V1* (L)	127 (16.5)	62.0 (51.4)
Q* (L/h)	79.9 (11.9)	NE
V2* (L)	412 (7.0)	11.3 (49.4)
covariance CL-V1 (%)		43.5 (62.4)
Proportional Error (SE %)	27.0 % (9.3)	

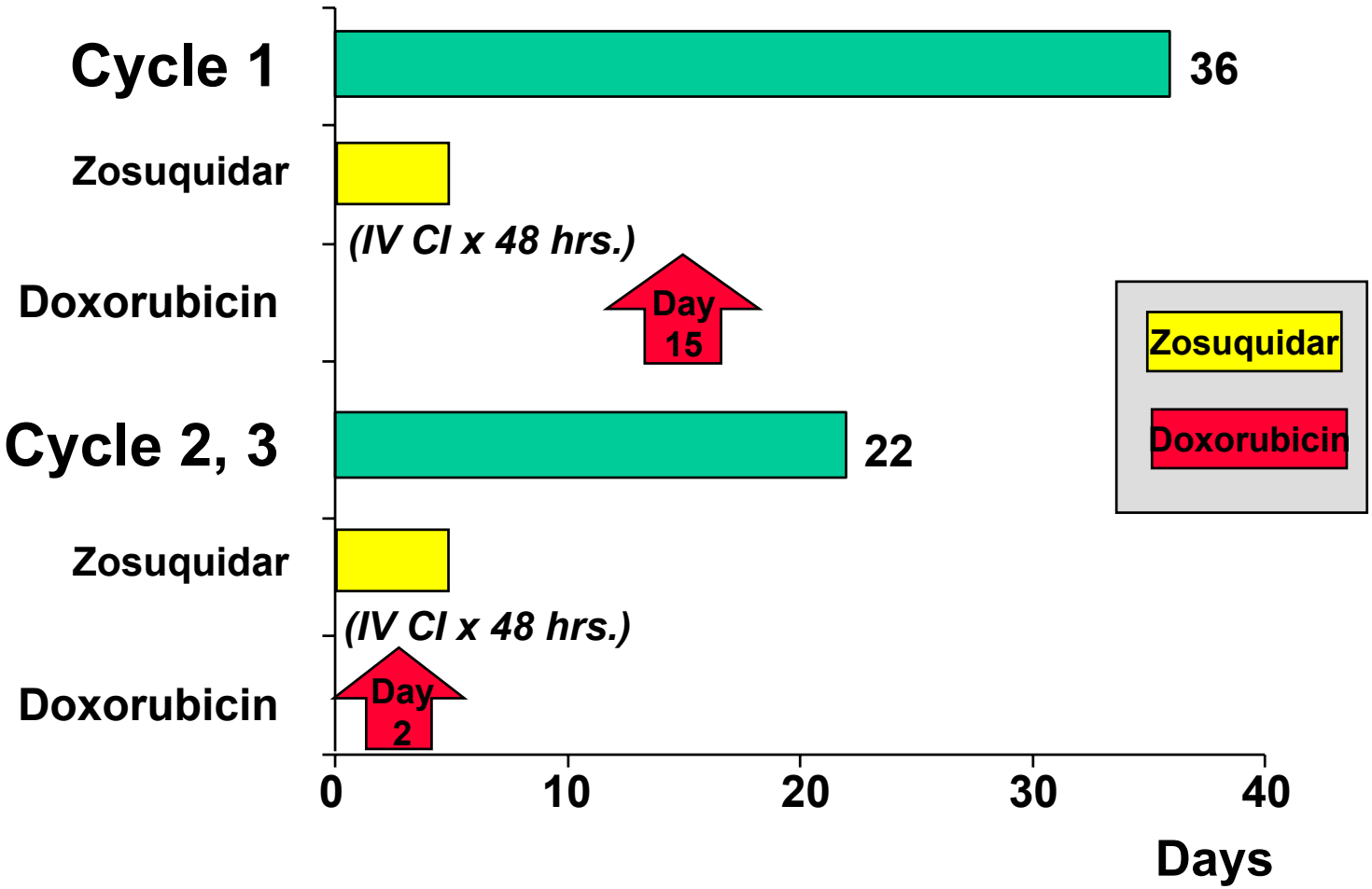
Zosuquidar.3HCL PK/PD Model



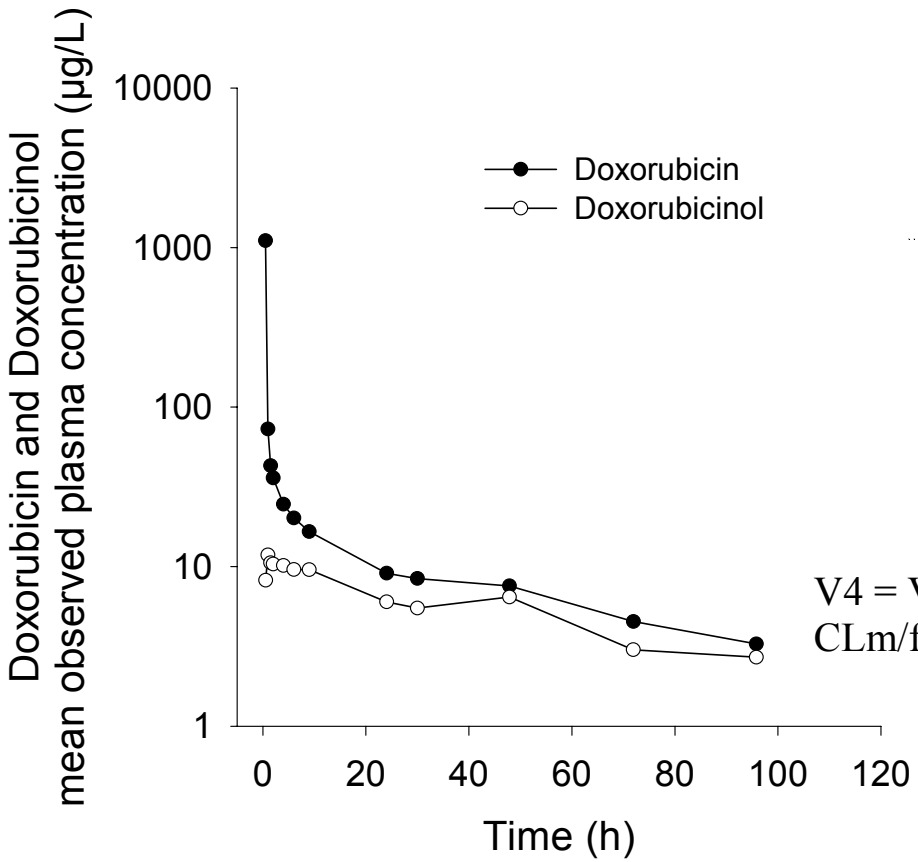
Zosuquidar.3HCl PD parameters	Mean (SEE%)	IIV (SEE %)
E_{max}.(%)	100 Fixed	
IC_{50} (µg/L)	31.7 (32.2)	103 (30.0)
γ (Hill coefficient)	1.31 (11.7)	
Additive Residual Error (SEE%)**	13.5 % (57.9)	

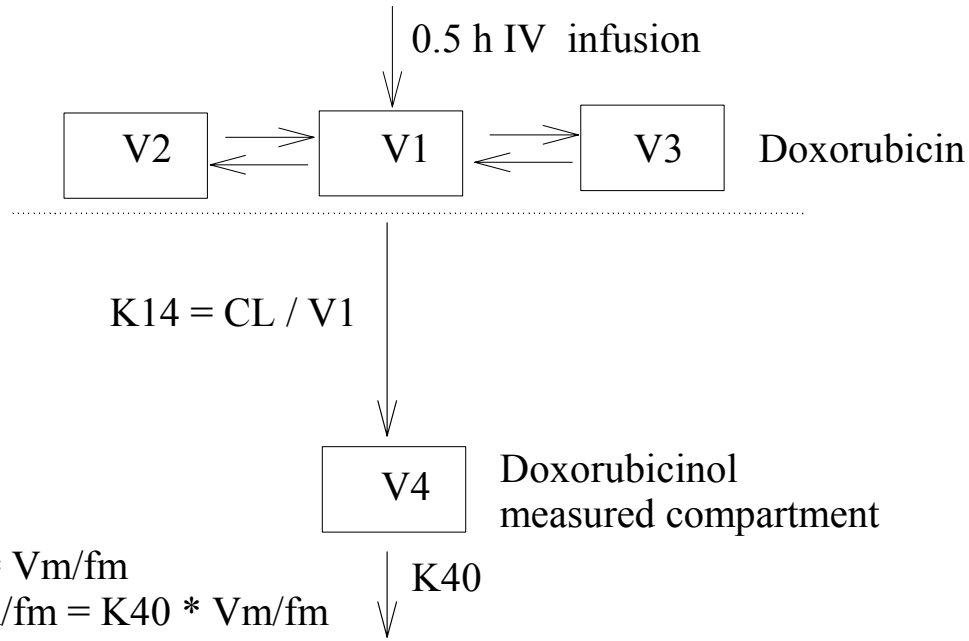
Estimated IC_{90} = 169 µg/L

Clinical Study of Intravenous Zosuquidar in Combination with Doxorubicin



Dox-Doxol PK Model in Absence of Zosuquidar

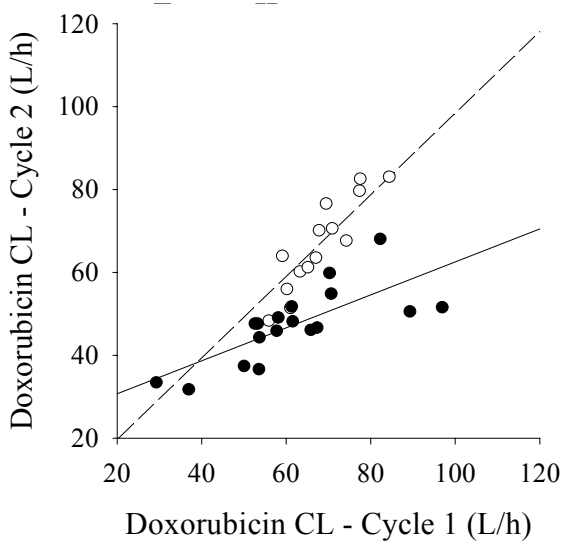


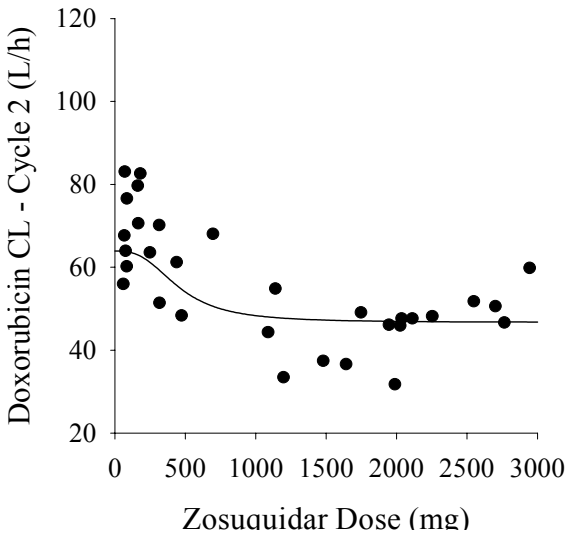


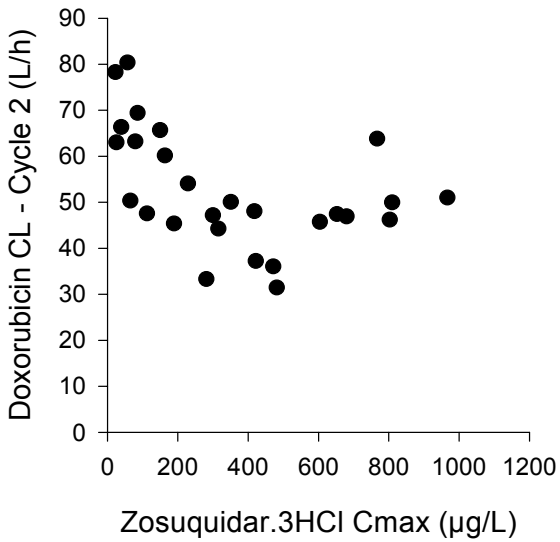
V4 = Vm/fm
CLm/fm = K40 * Vm/fm

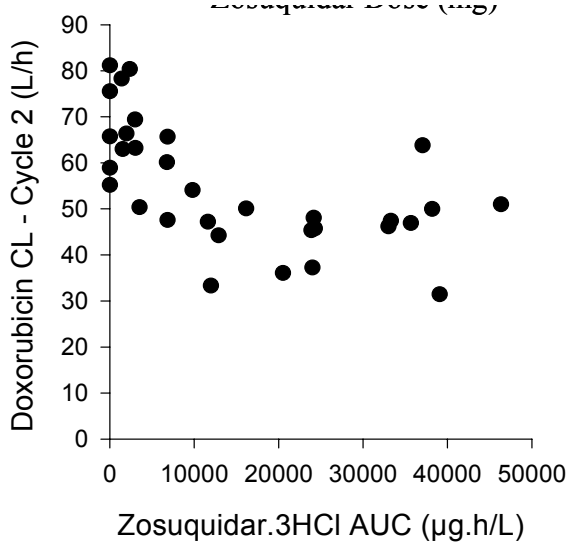
CLm/fm= Apparent CL, fm is fraction of doxorubicin converted to doxorubicinol

Relationship between Dox PK and Zosuquidar Dose & Exposure

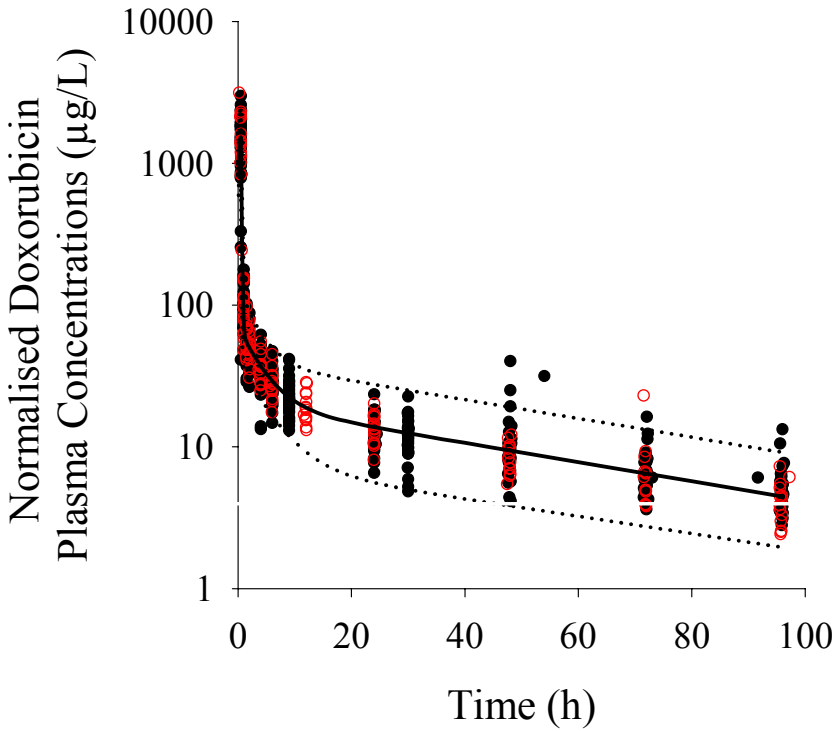




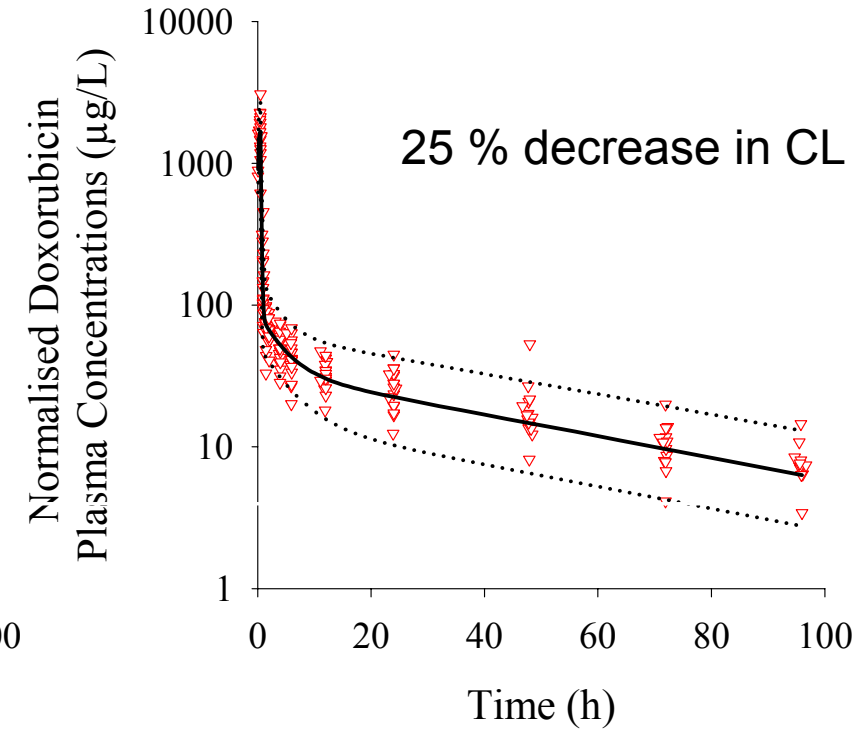




Observed & Predicted Dox PK in the presence & absence of Zosuquidar

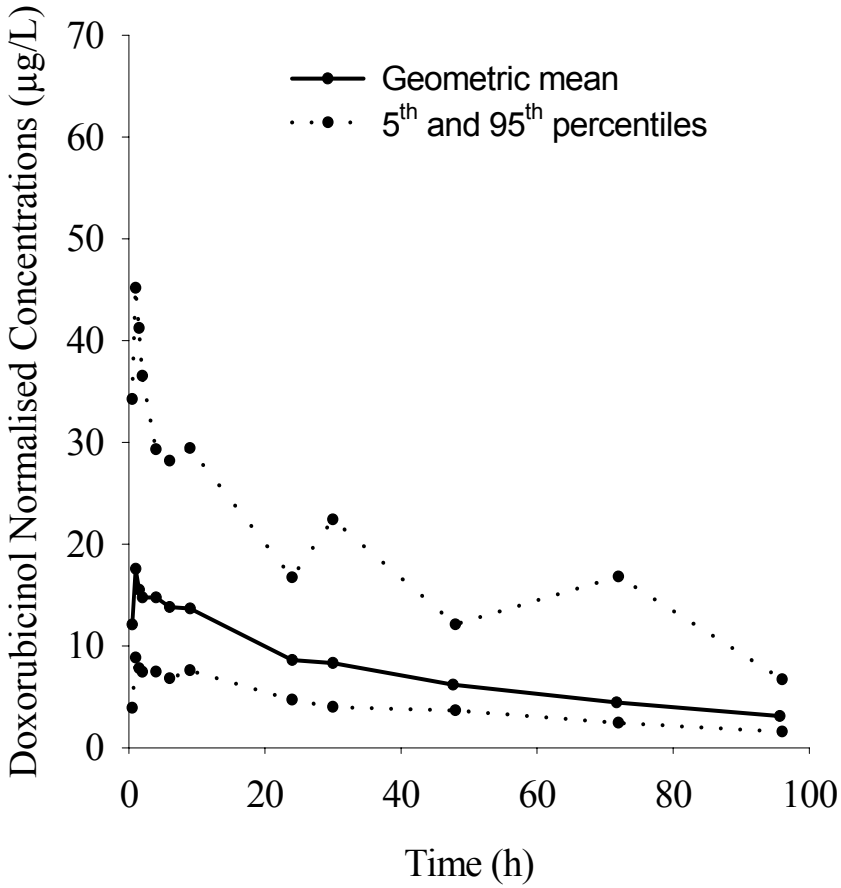


Zosuquidar Dose either 0 or <500mg

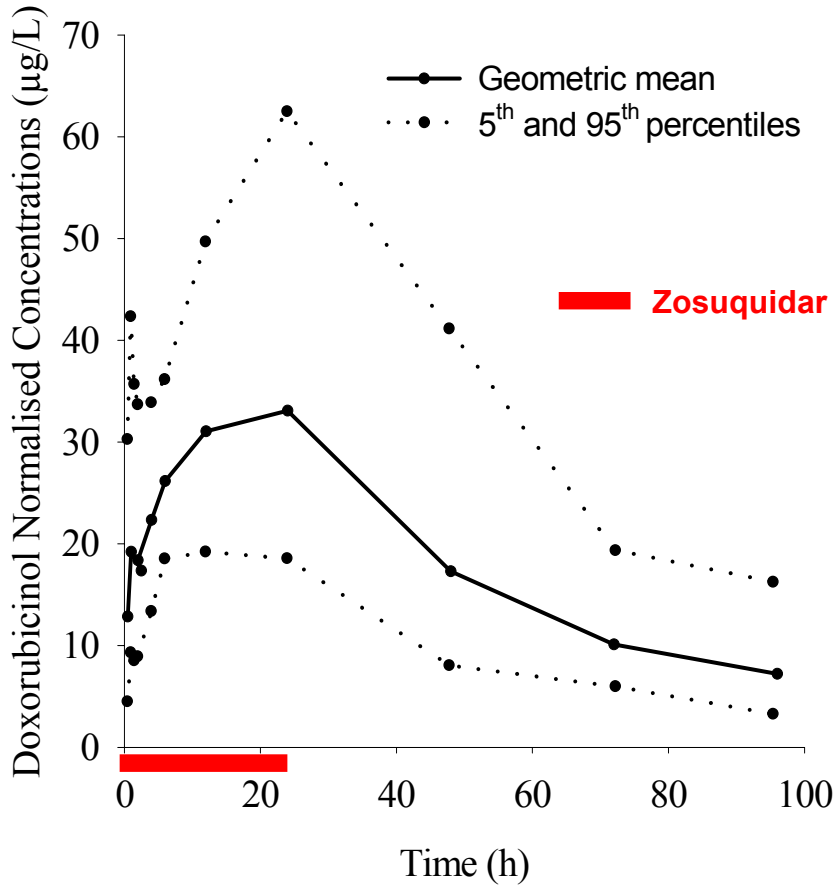


Zosuquidar Dose ≥500 mg

The Observed Doxorubicinol Concentration-Time Curves in the Presence and Absence of Zosuquidar



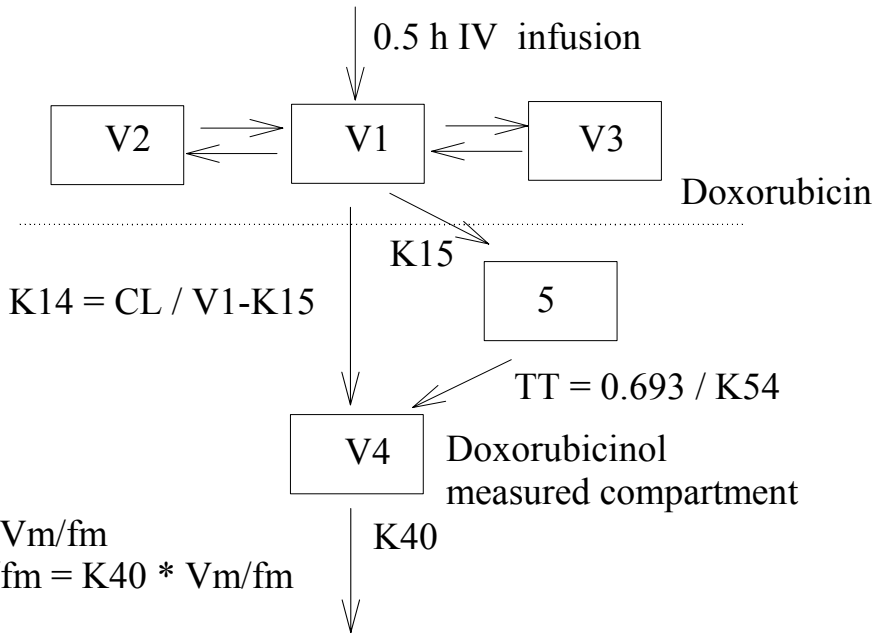
Dose either 0 or <500mg



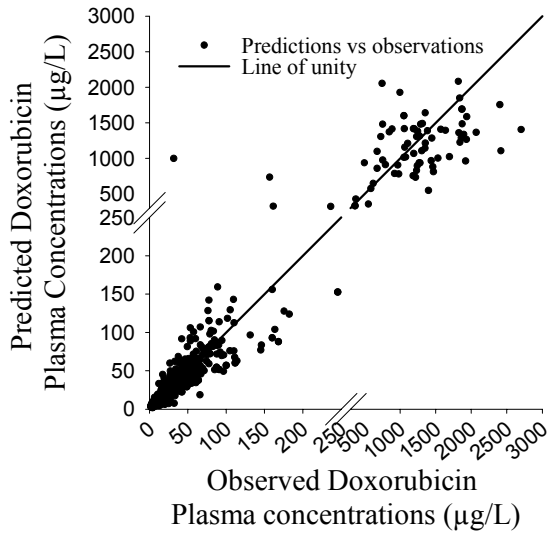
Dose ≥500 mg

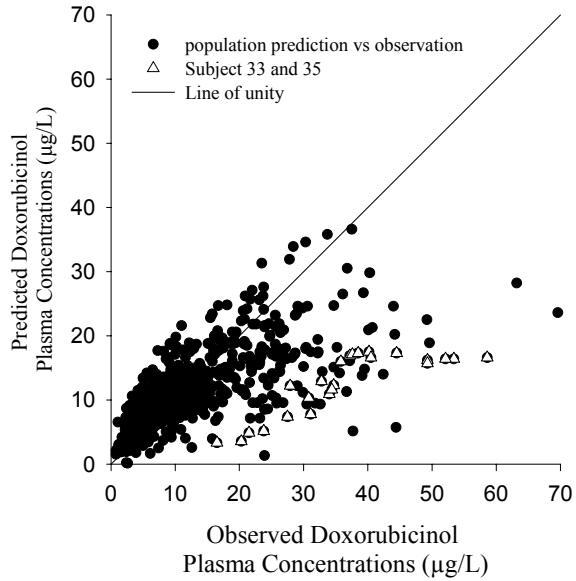
Dox-Doxol PK model in the presence of Zosuquidar (dose ≥ 500mg)

Model Regimen Dependent

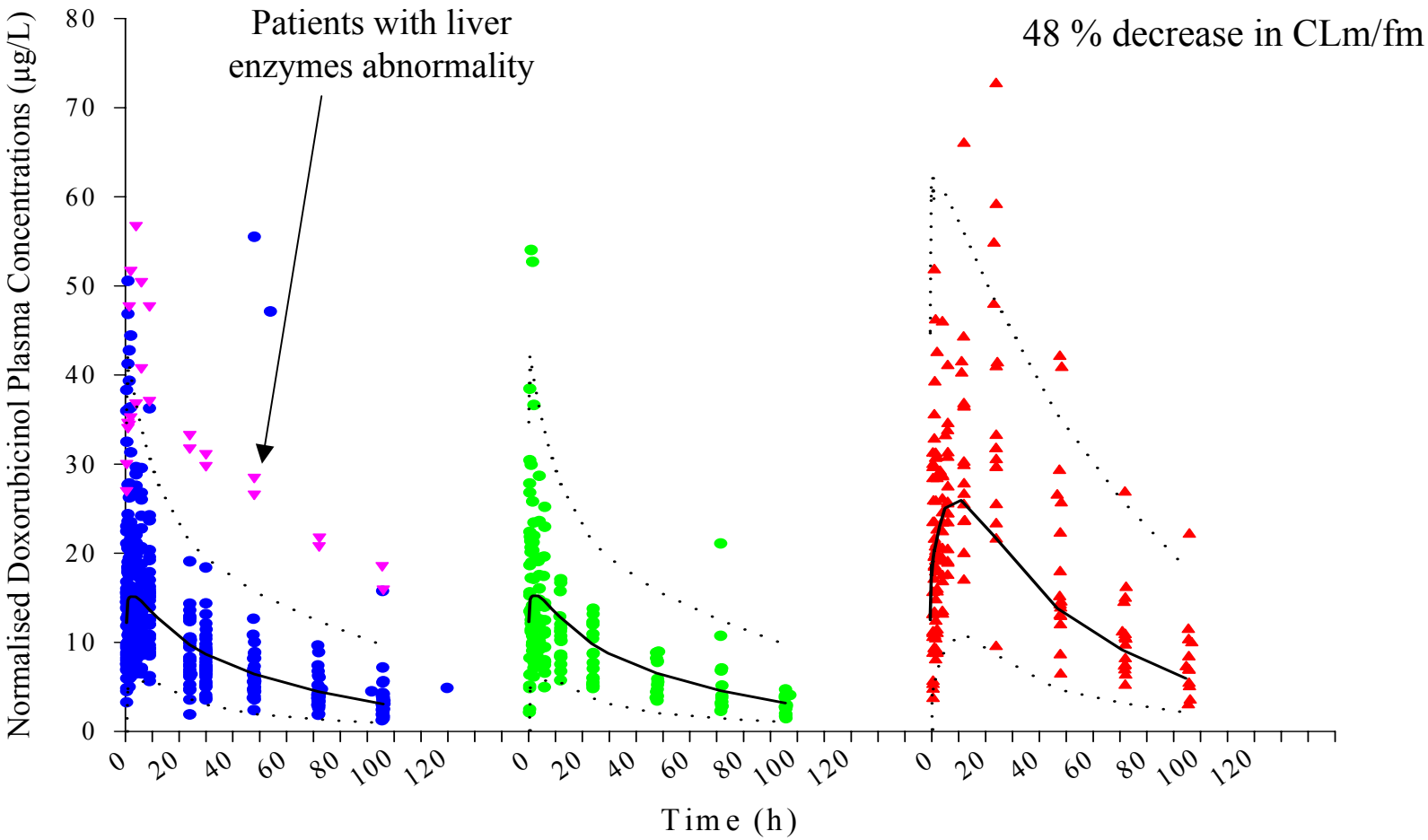


CLm/fm= Apparent CL, fm is fraction of doxorubicin converted to doxorubicinol





Posterior Predictive Check of Dox-Doxol Model

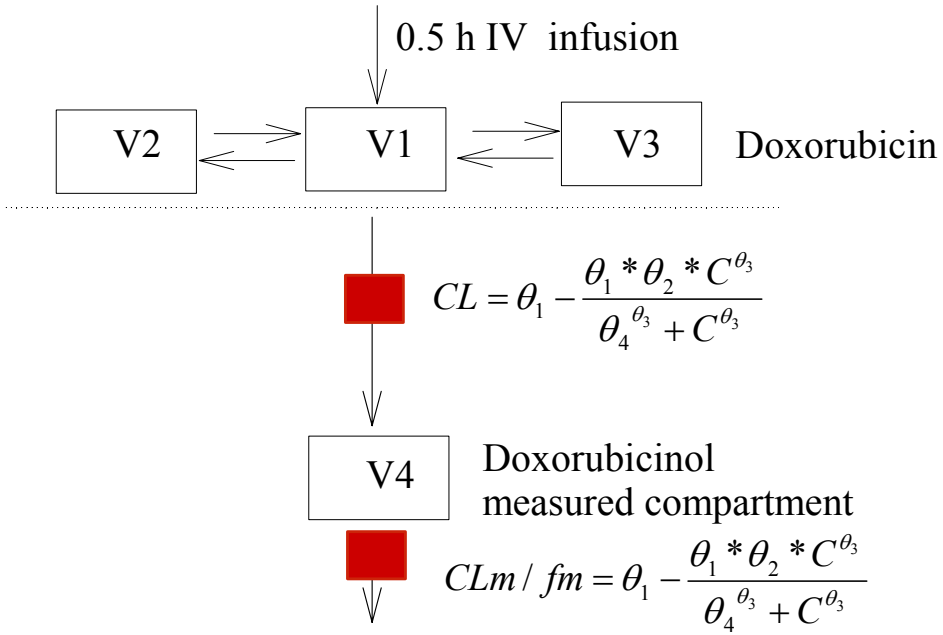


Absence of LY

Presence of LY < 500 mg/48h

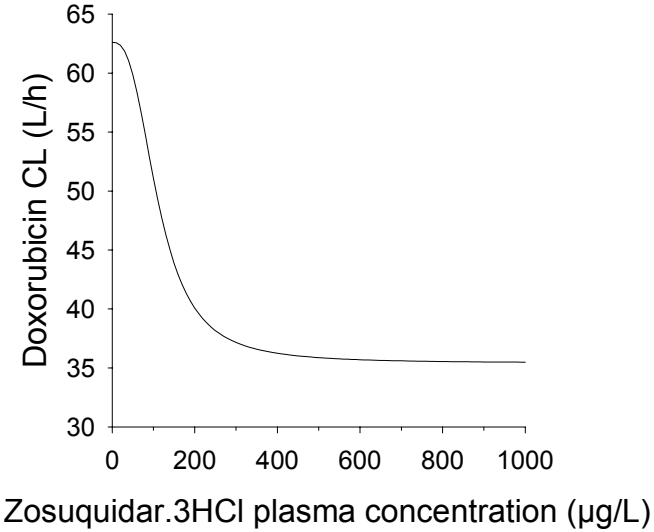
Presence of LY≥ 500 mg/48h

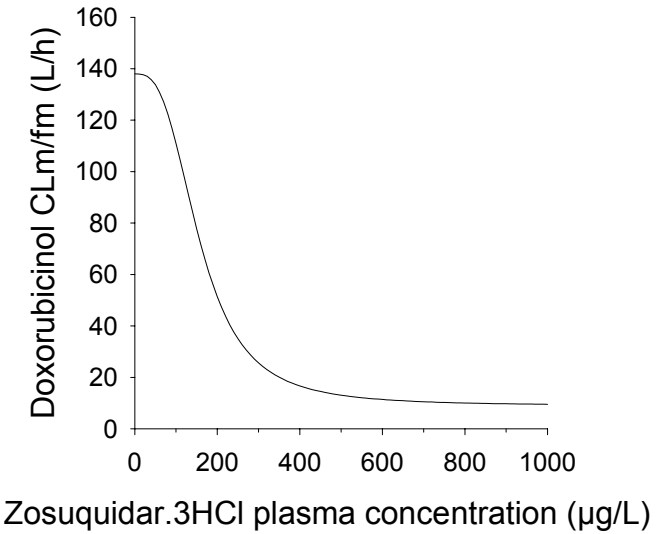
Dox-Doxol Regimen Independent PK model in the presence of Zosuquidar



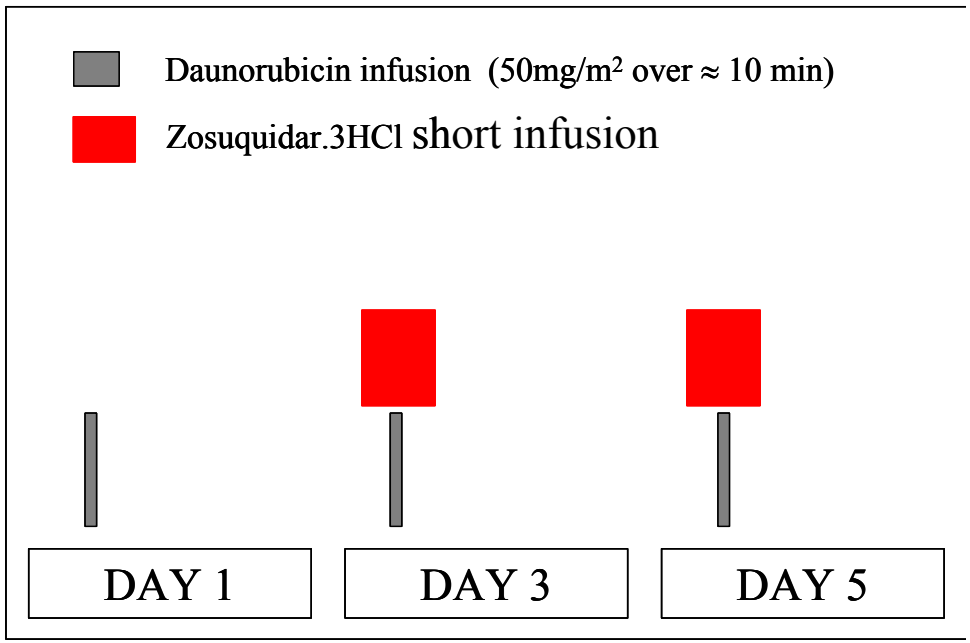
Pgp inhibition effect on PK
C = Zosuquidar.3HCl predicted concentration

CLm/fm= Apparent CL, fm is fraction of doxorubicin converted to doxorubicinol

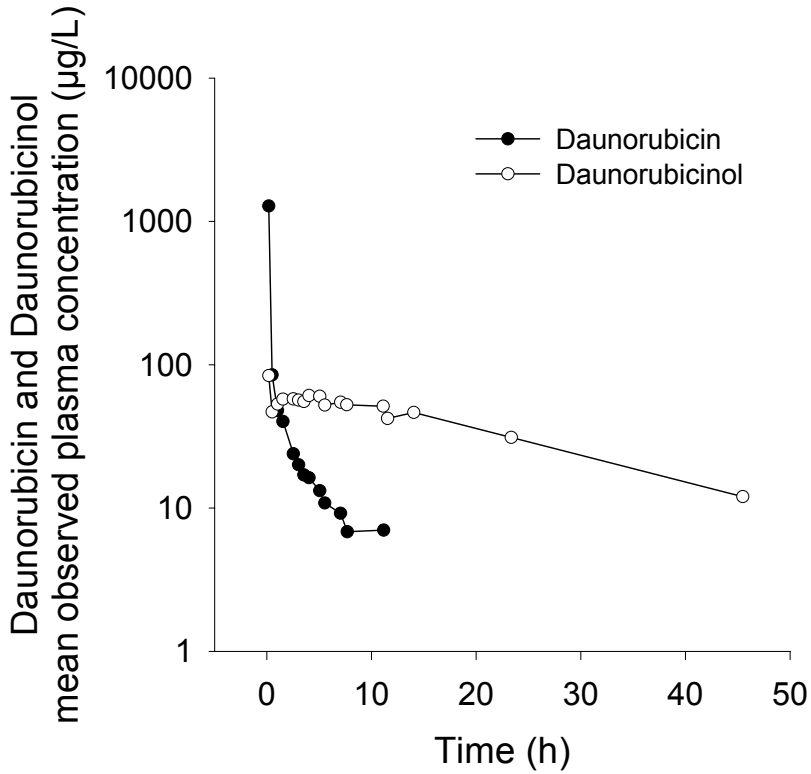




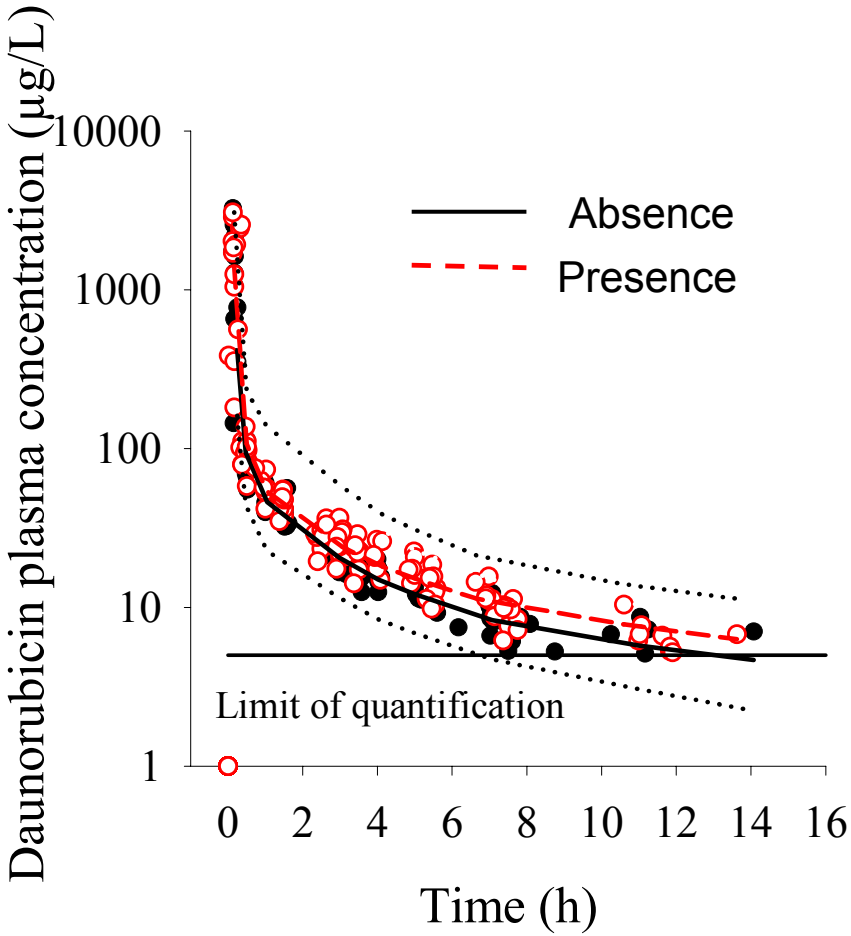
Design of Phase 1 Study with Daunorubicin + Zosuquidar short infusion

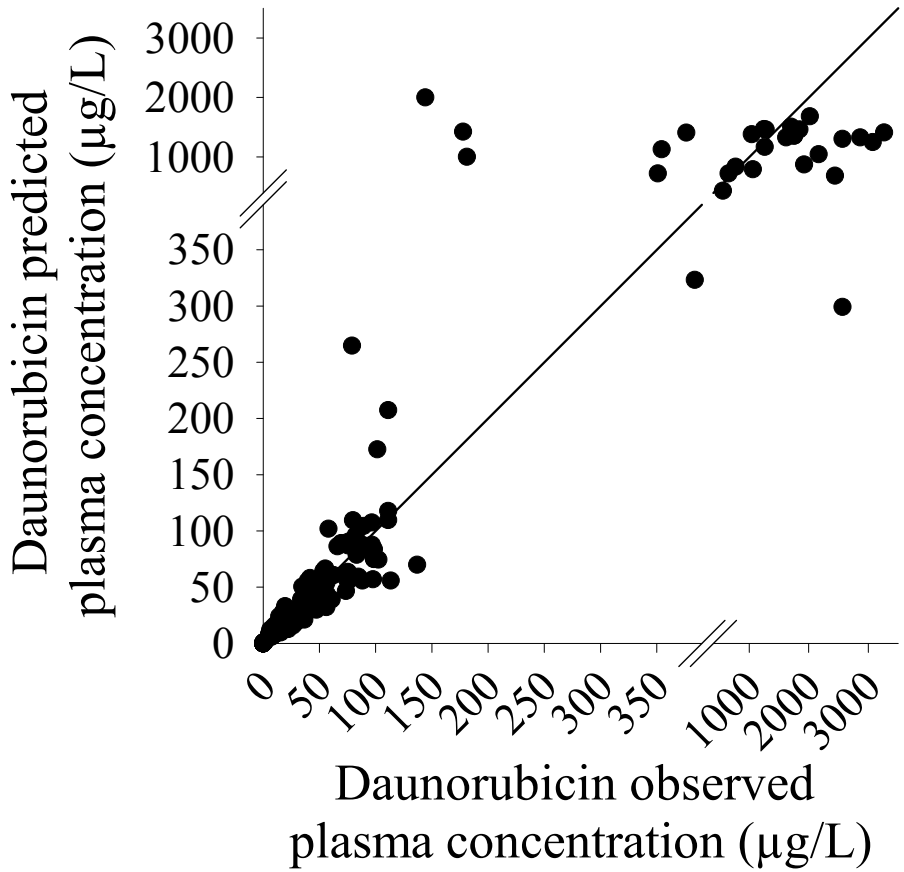


Mean Daunorubicin-Daunorubicinol Profile in the absence of Zosuquidar



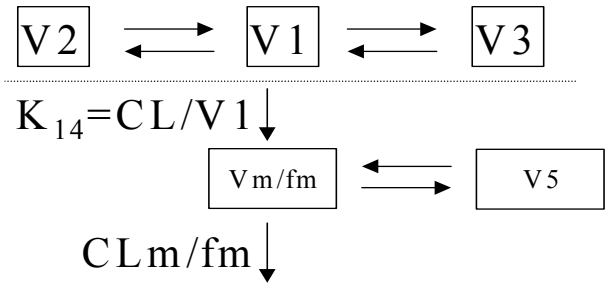
Impact on Daun PK (6 h or less Zosuquidar infusion) - Daun CL decreased by 10 %



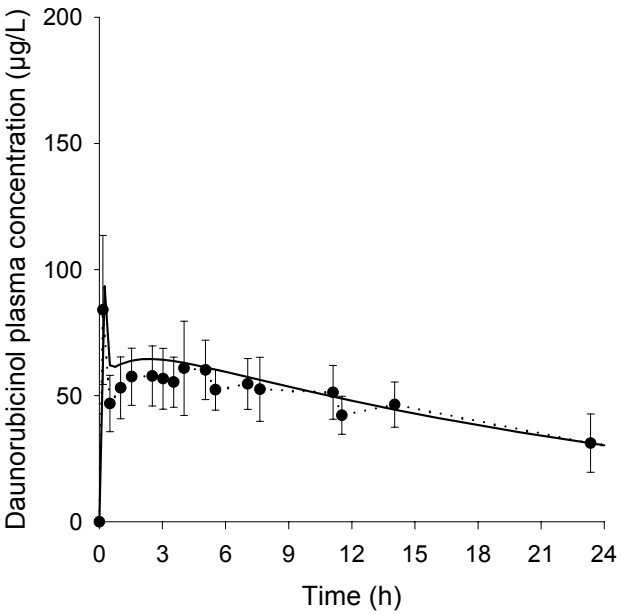


Impact on Daunol PK (55 % decrease in CLm/fm) in the Presence of Zosuquidar

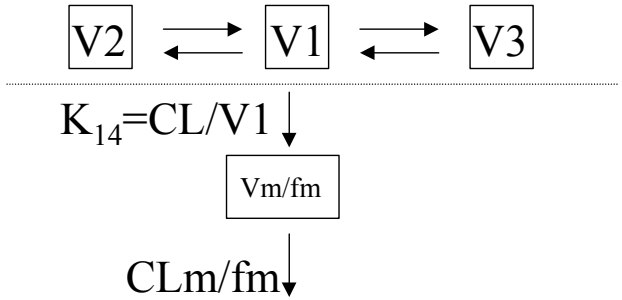
Daunorubicin



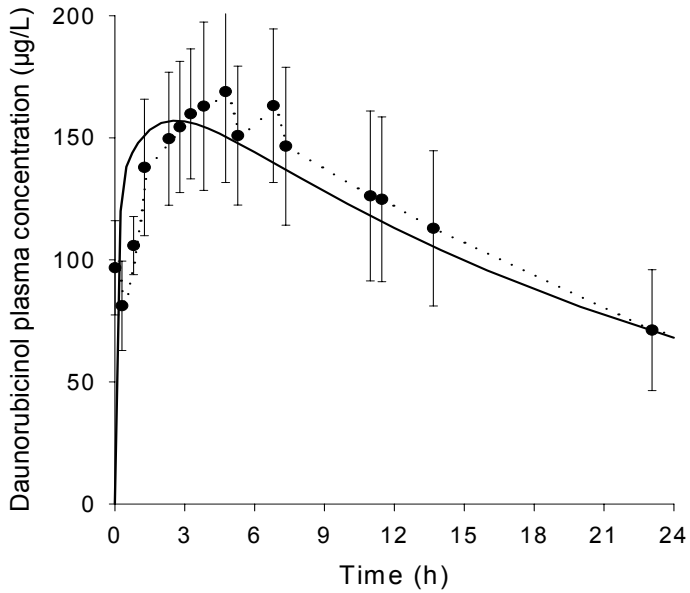
Daunorubicinol



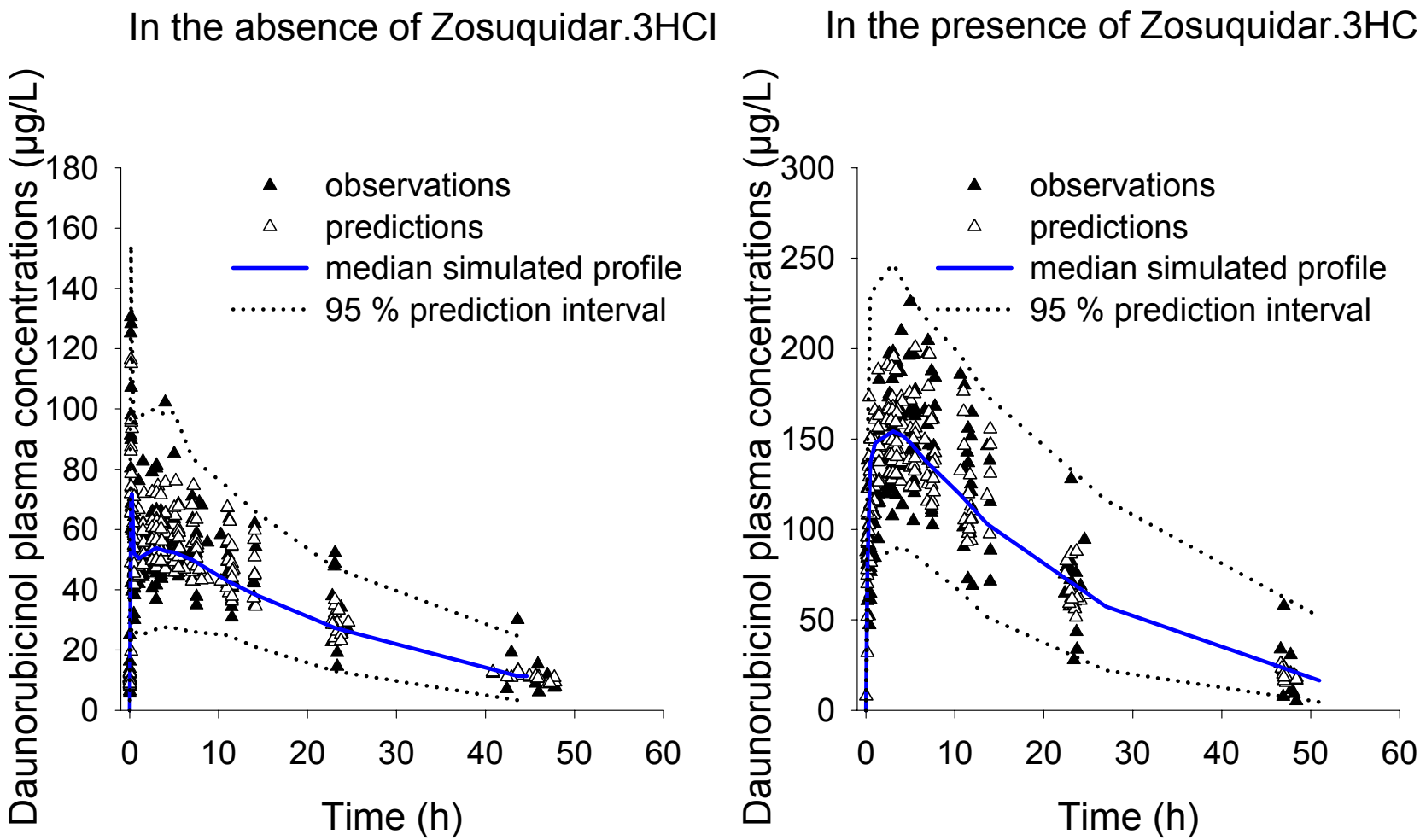
Daunorubicin



Daunorubicinol



Observed vs Simulated PK Profiles for Daunol (Median & 95 % Prediction Intervals)



Conclusions

•Lack of modelling of this type has precluded the efficient testing of P-gp inhibition in the clinic

•We developed a population PK model which allowed us to explore the balance between effect and toxicity. The model highlights the duration of inhibition as an important determinant of toxicity.

•Based on our understanding we developed a short IV infusion of Zosuquidar which is feasible and produces maximal P-gp inhibition, but reduced PK interactions.

•A randomized Phase 3 study with full dose chemotherapy in each arm is required to validate these hypothesises and the models from this work.

•This study is already on-going in 450 AML patients, application of the model has already allowed 390 patients enrolled without any obvious imbalance of toxicity, which hitherto has not been possible.

•We await the efficacy results from this trial with interest.