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Complications in Assessing the Hepatic First-Pass Component of Bioavailability

Determinants of Bioavailability

Data Analysis Following PK Studies:

$$AUC_{po} = \frac{F.Dose_{po}}{CL}$$

$$AUC_{iv} = \frac{Dose_{iv}}{CL}$$

$$F = \frac{AUC_{po}}{AUC_{iv}} \times \frac{Dose_{iv}}{Dose_{po}}$$

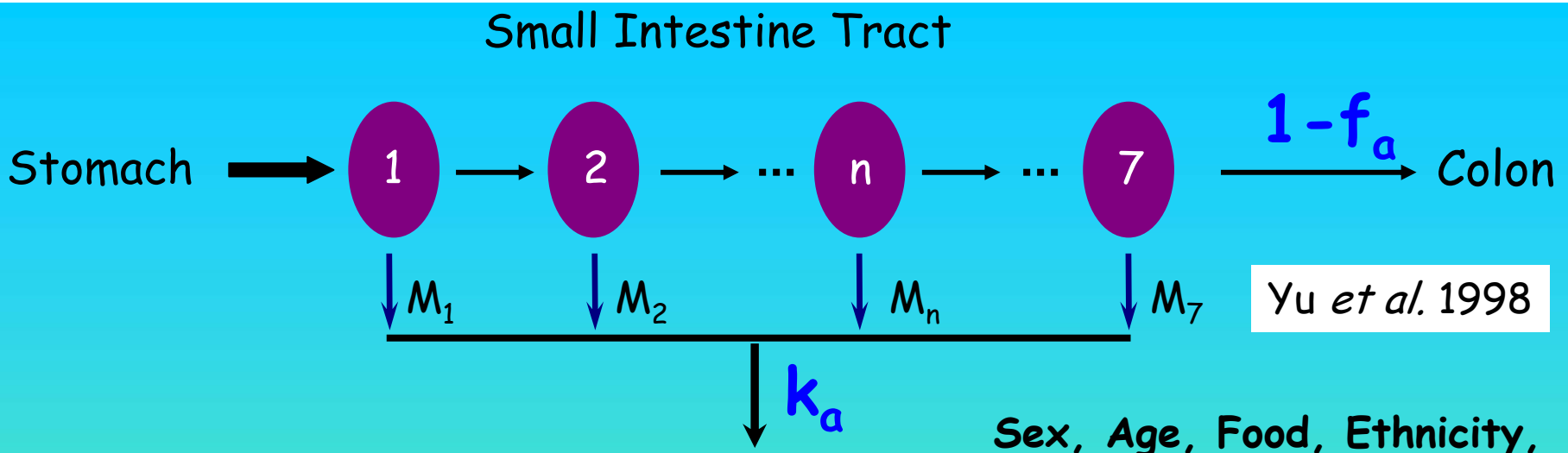
However, Simulations Using *In Vitro* Data:

$$AUC_{po} = \frac{F.Dose}{\sum (Q_i.E_i)}$$

$$F = fa \times F_G \times F_H$$

- fa: Release from Formulation & Ability to Get Across GIT Membrane
- F_G: Gut Wall First-Pass Metabolism
- F_H: Hepatic First-Pass Metabolism

fa - Compartmental Absorption and Transit (CAT)



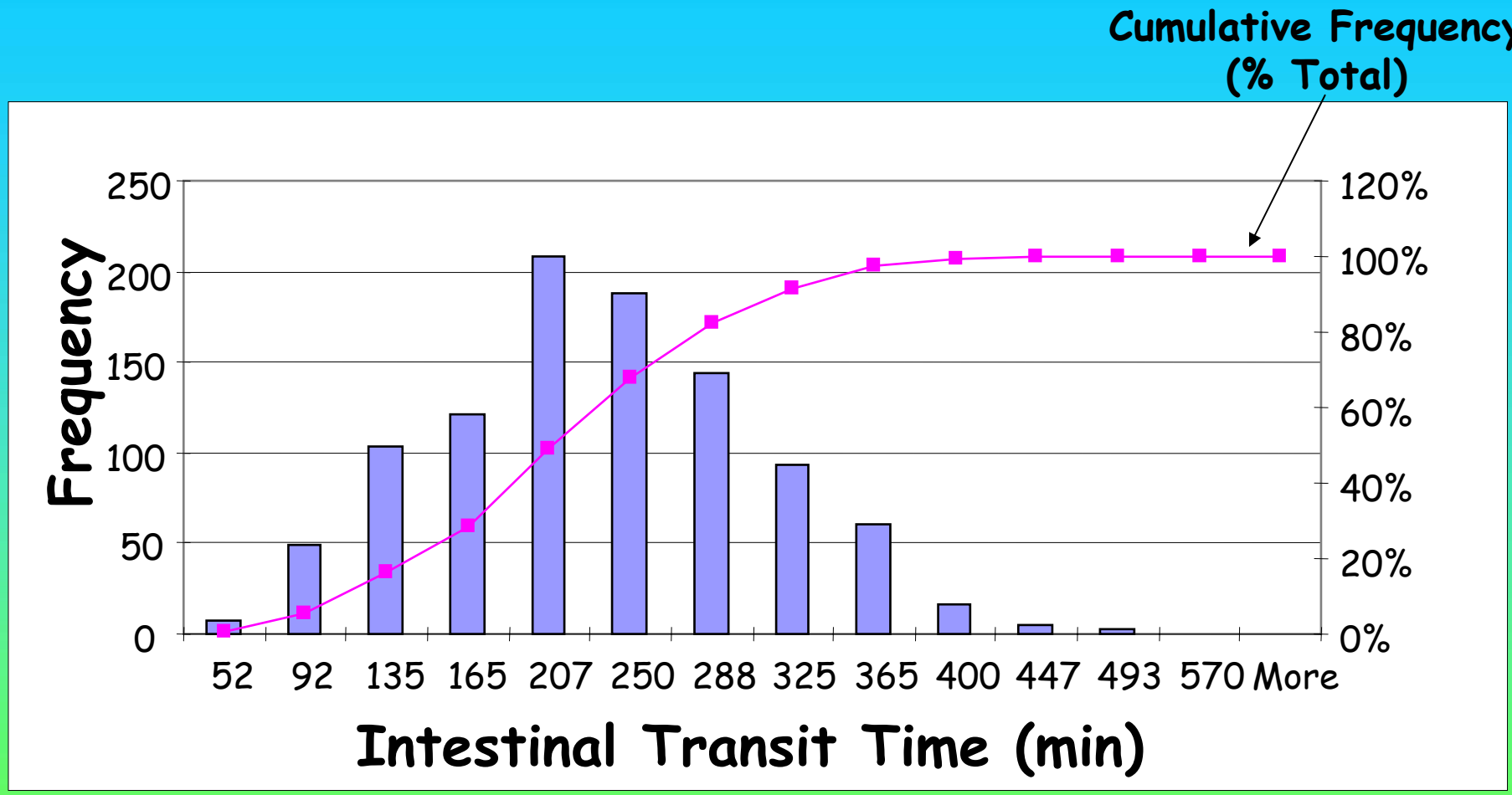
Yu *et al.* 1998

Sex, Age, Food, Ethnicity, Disease, …

Model Parameters:

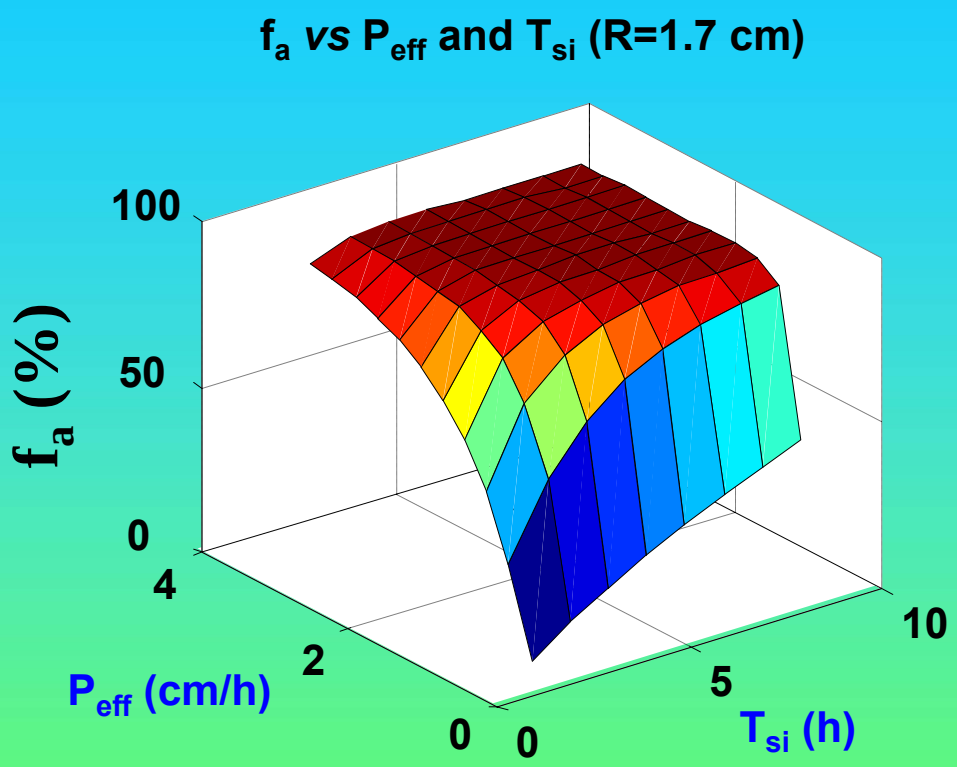
- Gastric Residence Time,
- Small Intestine Transit Time,
- Small Intestine Radius,
- Effective Permeability.

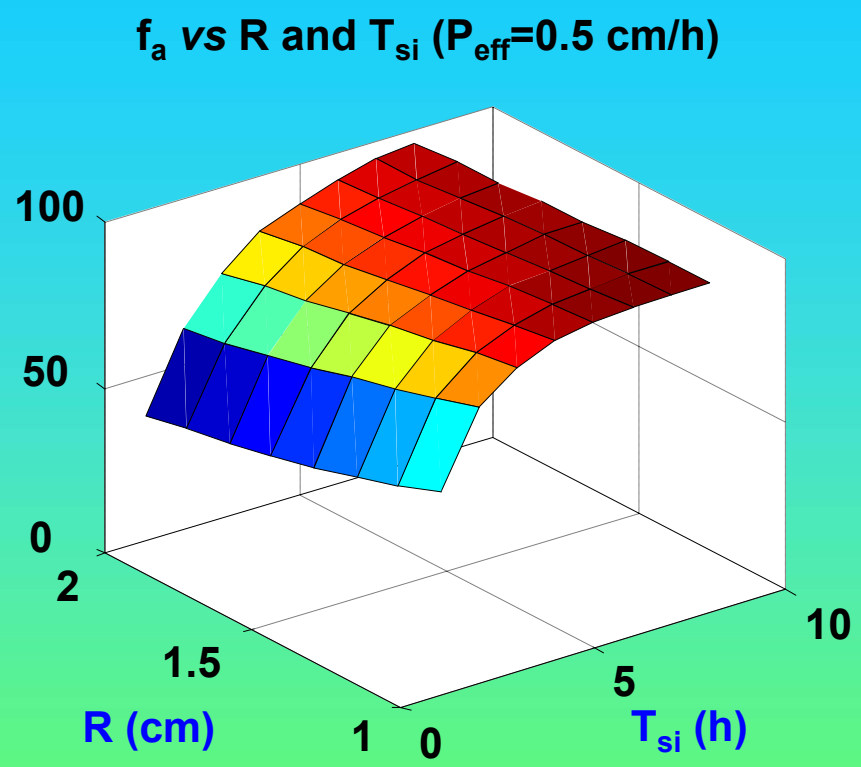
Inter-individual Variability in Intestinal Transit Time



Yu et al. (1998)

Influence of Inter-individual Variability on fa

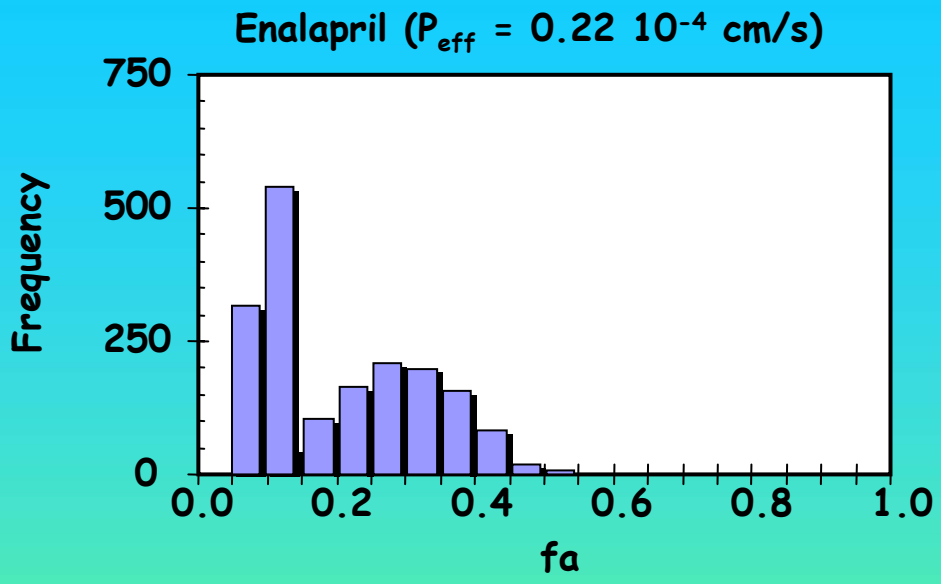


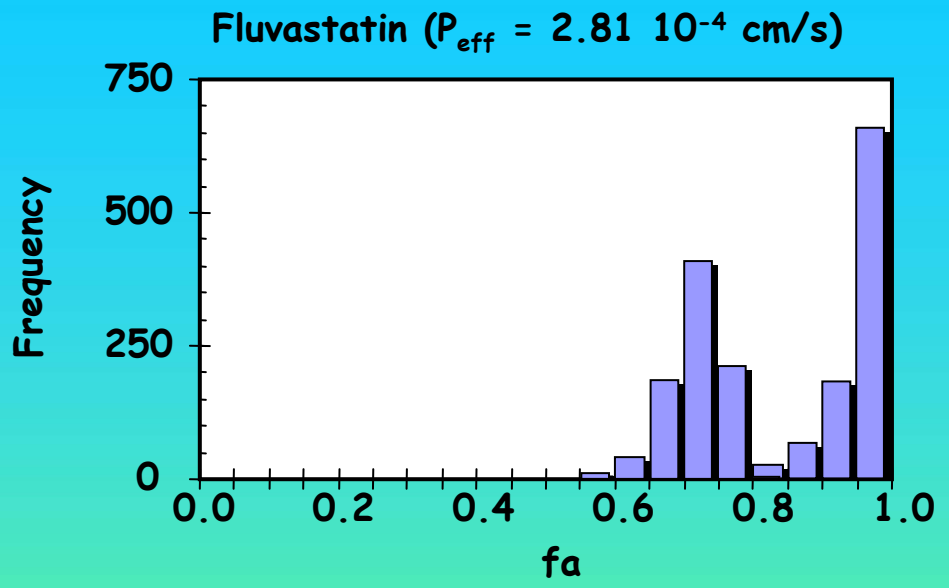


M Jamei *et al*, LogP 2004, Switzerland

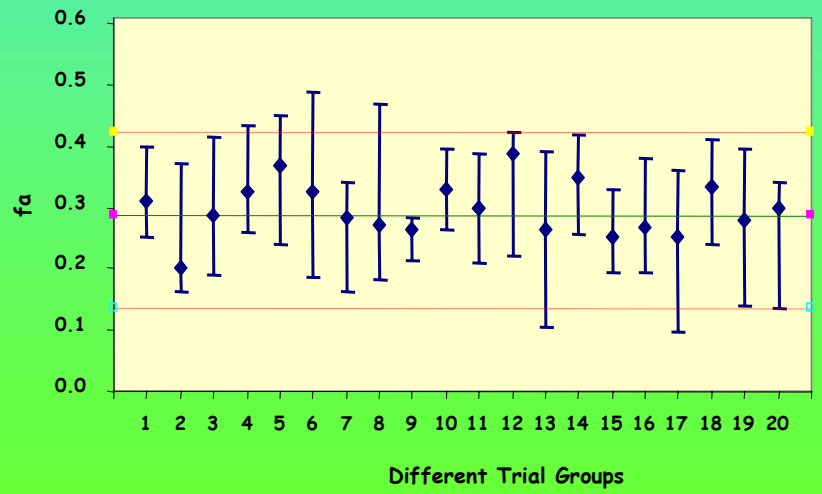
Predefined Population Libraries: Faster Transit

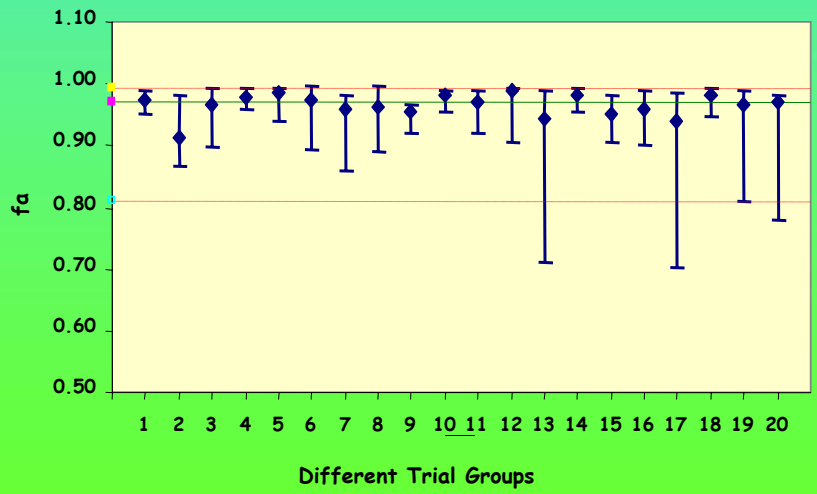
Coeliac Patients: Reduced Transit Time Compared to Healthy Population





Enalapril and Fluvastatin: 20 Virtual Trials
(6 Individuals Randomly Selected for Each Trial from a Population of 1000)





Various Sources of In Vitro Permeability Data

Cell-based Systems **Caco-2; MDCK ; etc.**

Non-cell-based Systems **PAMPA ; etc.**

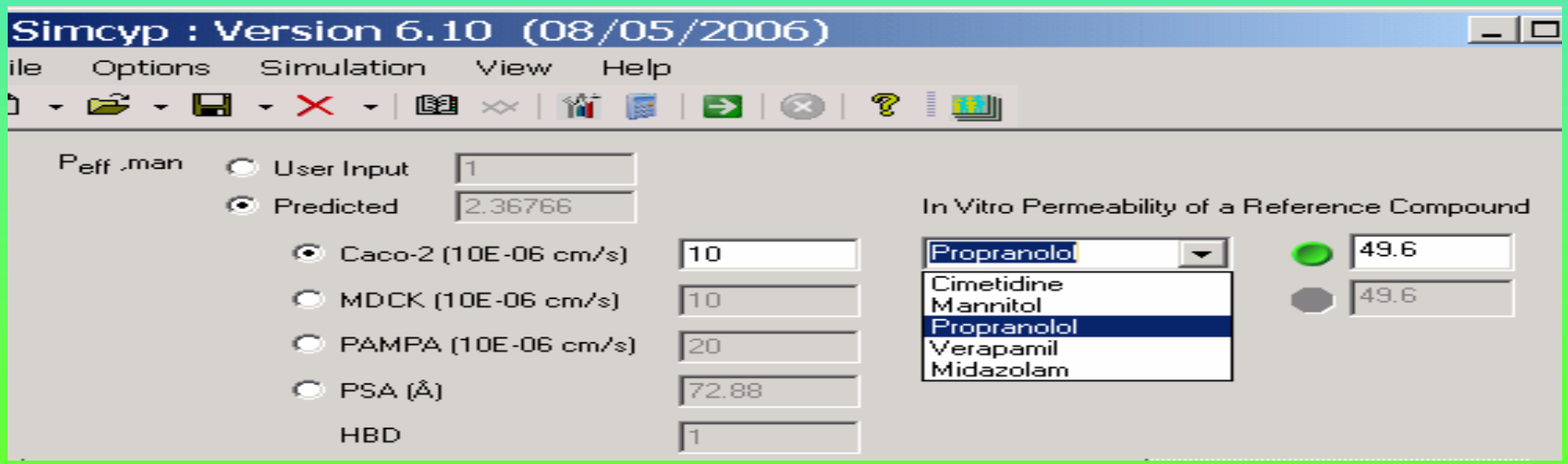
To account for lab to lab variation of Caco-2 and MDCK:

$$P_{app\ (calibrated\ to\ Sun\ 2002)} = P_{app,Measured} \cdot \frac{P_{Calibrator\ in\ Sun2002}}{P_{Calibrator,Measured}}$$

where

$[P_{Measured}]$ = permeability values of the test and the calibrator compounds from the user's Caco-2/MDCK system

$[P_{Calibrator\ (Sun\ 2002)}]$ = permeability reported for the calibrator compound in the reference system (i.e. Sun *et al* 2002).



F_G - Combining metabolism and permeability

$$F_G = \frac{Q_{Gut}}{Q_{Gut} + fu_{Gut}.CLu_{int\ Gut}}$$

Yang *et al. Br J Clin Pharmacol* 2001, 52: 472-473
Rostami-Hodjegan A and Tucker GT. *Hepatology* 2002 35: 1549-50

Q_{Gut}: Exposure to gut enzymes determined by enterocytic permeability and enterocytic blood flow

fu_{Gut}: Fraction of drug unbound within the enterocyte (= fu_B; fu; >fu; 1)

$CLu_{int\ Gut}$: CLu_{int}(3A) x 3A gut abundance (70,000 pmol) J. Yang et al. (2004), CPT 76:391

High CLu_{int}: $F_{Gut} \rightarrow 0$

Low CLu_{int}: $F_{Gut} \rightarrow 1$

$$Q_{Gut} = \frac{CL_{perm} \cdot Q_{villi}}{CL_{perm} + Q_{villi}}$$

Inter-individual Variability in Metabolism

Genetics & Ethnicity

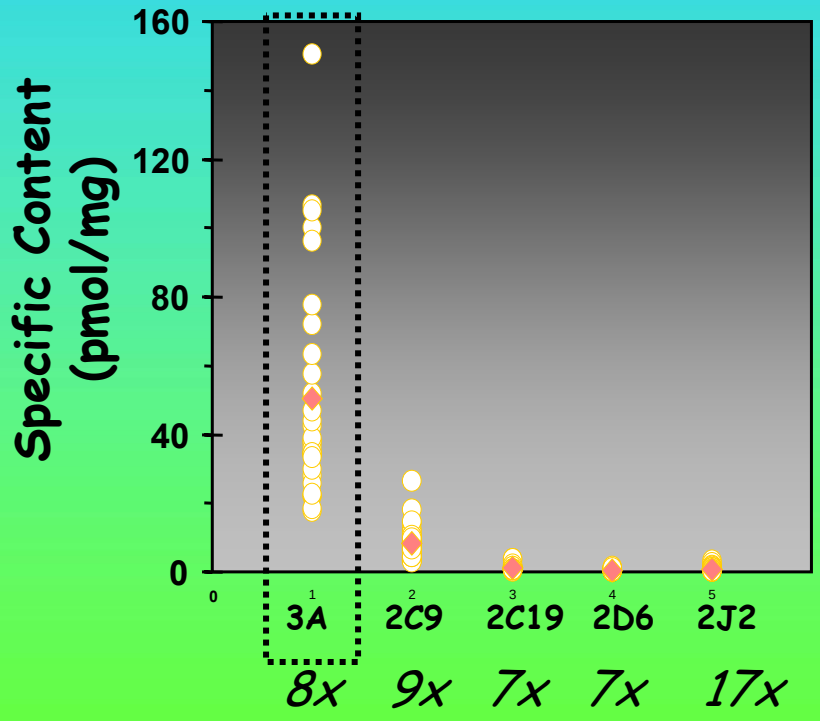
(3A5*1 vs 3A5*3 population frequency in Black vs Caucasians)

Environment & Food

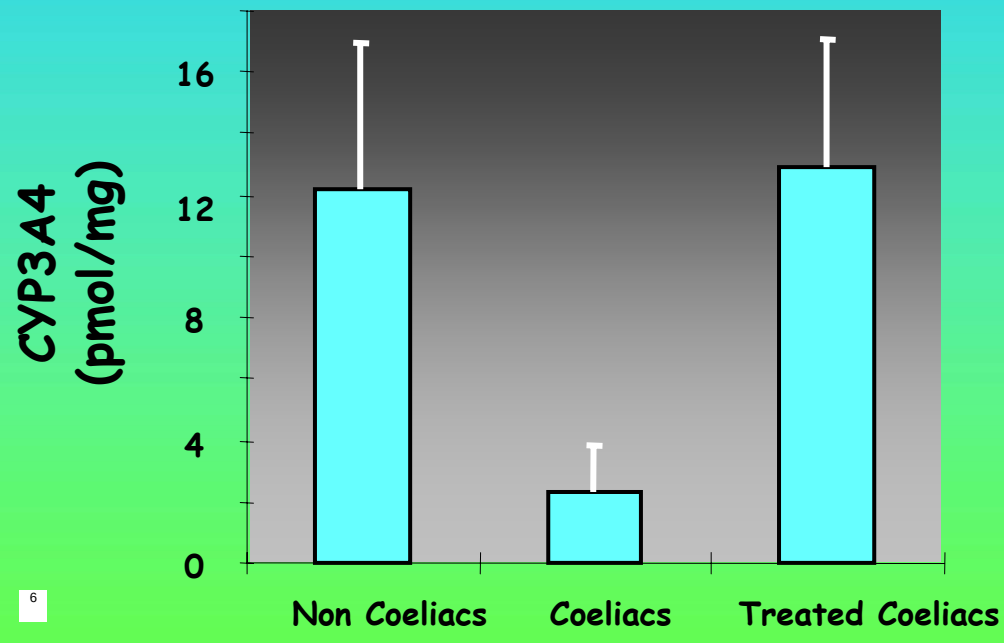
(Grapefruit juice, cruciferous vegetables, St. John's wort …)

Disease and Concomitant Drug Intake

(Coeliac, ketoconazole, rifampicine, …)



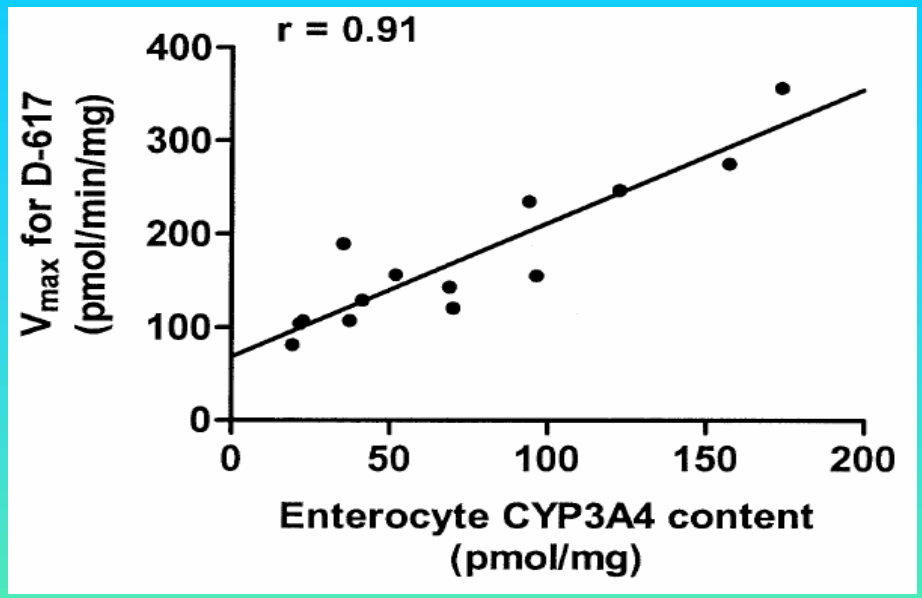
Paine et al. (2006) DMD 34:880-6

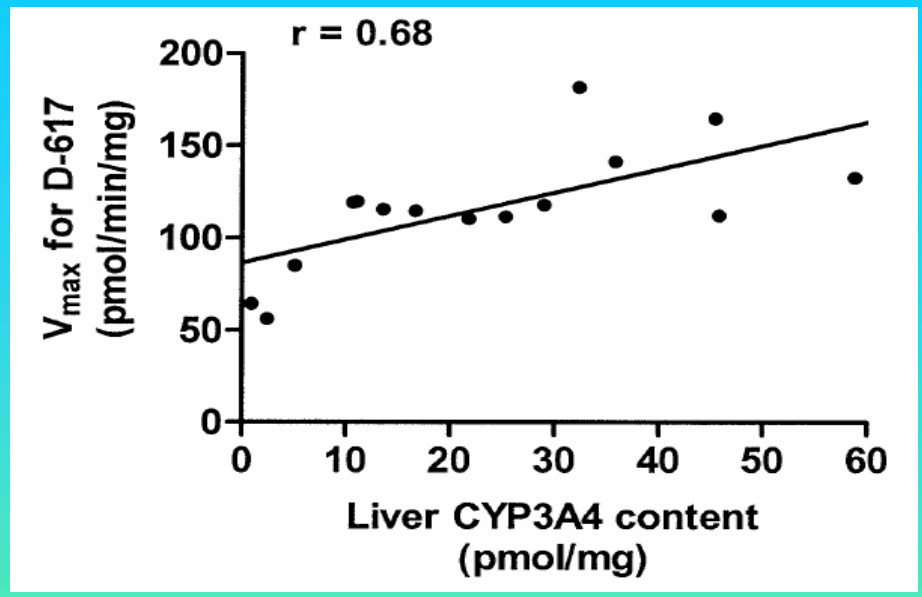


Johnson et al. (2001) BJCP 51: 451-60

Activity per Unit of CYP3A: Small Intestine vs Liver

J. Yang et al. (2004), CPT 76:391 [using data from von Richter et al. 2004]





k_{cat}=1.4 ± 0.7 pmol/min/pmol CYP

k_{cat}=1.2 ± 0.9 pmol/min/pmol CYP

(p=0.20)

$$k_{cat}\ (\text{pmol/min/pmol CYP}) = \frac{V_{max}\ (\text{pmol/min/mg protein})}{\text{CYP content (pmol CYP/mg protein)}}$$

Also see Galetin et al. (2006) DMD (in press, Fast Forward)

F_H: Unresolved Issues of Time-Dependent Binding

First pass vs subsequent passes through the liver

$$AUC_{po} = \frac{\frac{f_a \cdot F_G \cdot Dose \cdot Q_H}{Q_H + fu_B \cdot CLu_{int}}}{\frac{Q_H \cdot fu_B \cdot CLu_{int}}{Q_H + fu_B \cdot CLu_{int}}} \rightarrow = \frac{f_a \cdot F_G \cdot Dose}{fu_B \cdot CLu_{int}}$$

F_H

CL

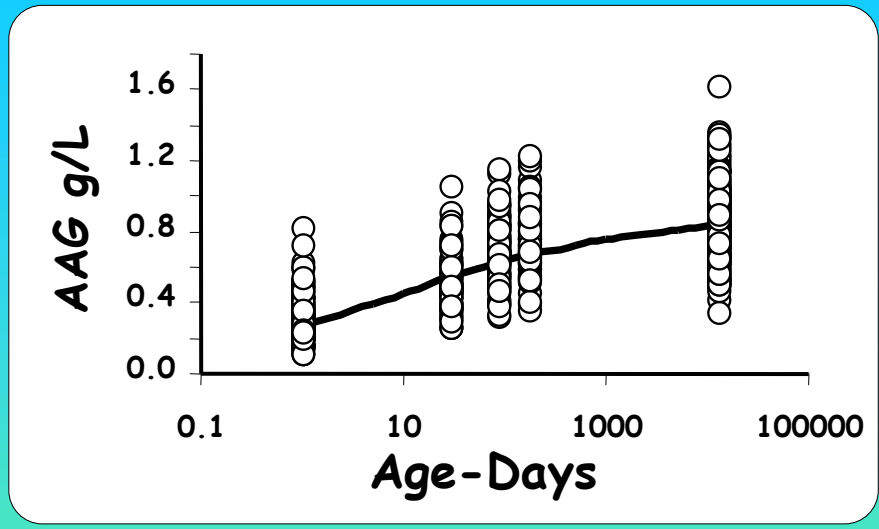
$$F_H = \frac{Q_H}{Q_H + fu_{B"1st-pass"} \cdot CLu_{int"1st-pass}}$$

$$fu_{B"1st-pass"} \neq fu_{B"systemic"}$$

$$CLu_{int"1st-pass} \neq CLu_{int"systemic"}$$

Variation in Protein Binding (fu)

fu	AAG	Albumin
↓	stress, cancer, M.I., arthritis	myalgia
↑	neonate, OCT, nephrosis	H. failure, burns



$$fu = \frac{1}{1 + \frac{[P]}{K_D}}$$

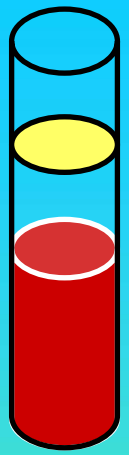
K_D = Dissociation Constant
[P] = Serum Protein Concentration

$$K_D = \frac{[P]}{\frac{1}{fu} - 1}$$

In the absence of changes in dynamics of binding:

$$fu = \frac{1}{1 + \frac{(1 - fu_{av}) \times [P]}{[P]_{av} \times fu_{av}}}$$

Haematocrit & fu_B



Min (C_B/C_p) = 1- Hematocrit

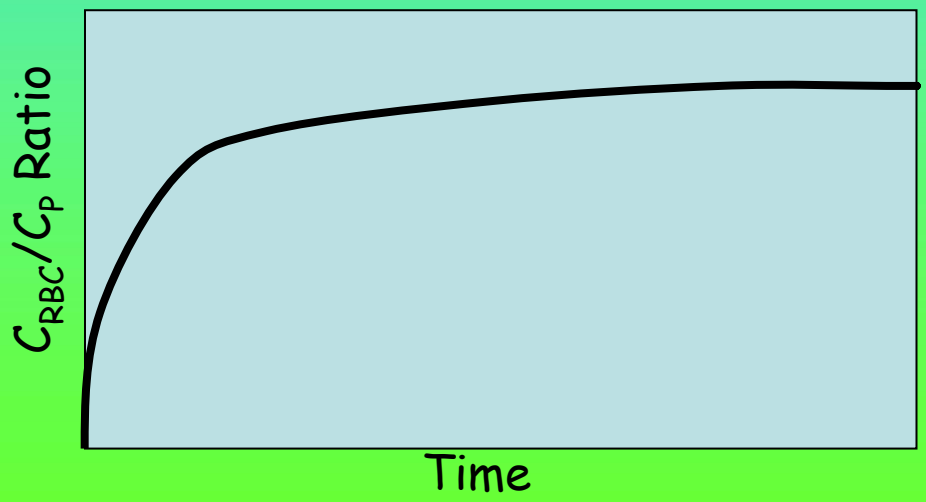
Max (C_B/C_p) = ∞

$$fu_B = \frac{fu}{C_B/C_p}$$

Covariation of Hc:

Sex: - Female ↓

Individual characteristics: - Athletes ↑



Environment: - High Altitude ↑

Age: - Children ↓

Implications of time-dependent displacement:

First pass vs subsequent passes through the liver

$$AUC_{po} = \frac{\frac{f_a \cdot F_G \cdot Dose \cdot Q_H}{Q_H + fu_B \cdot CLu_{int}}}{\frac{Q_H \cdot fu_B \cdot CLu_{int}}{Q_H + fu_B \cdot CLu_{int}}}$$

F_H

CL

$$\frac{AUC_{po"disturbed"}}{AUC_{po}} = \frac{CLu_{int}}{CLu_{int"disturbed"}}$$

$$\frac{AUC_{\text{po with inhibitor}}}{AUC_{\text{po control}}} = \frac{\frac{fu_B \cdot CLu_{int}}{Q_H + fu_{B"disturbed-1st"} \cdot CLu_{int"disturbed-1st"}}}{\frac{fu_{B"disturbed-sys"} \cdot CLu_{int"disturbed-sys"}}{Q_H + fu_{B"disturbed-sys"} \cdot CLu_{int"disturbed-sys"}}}$$

No effects on fa or F_G assumed

Theoretical solution:

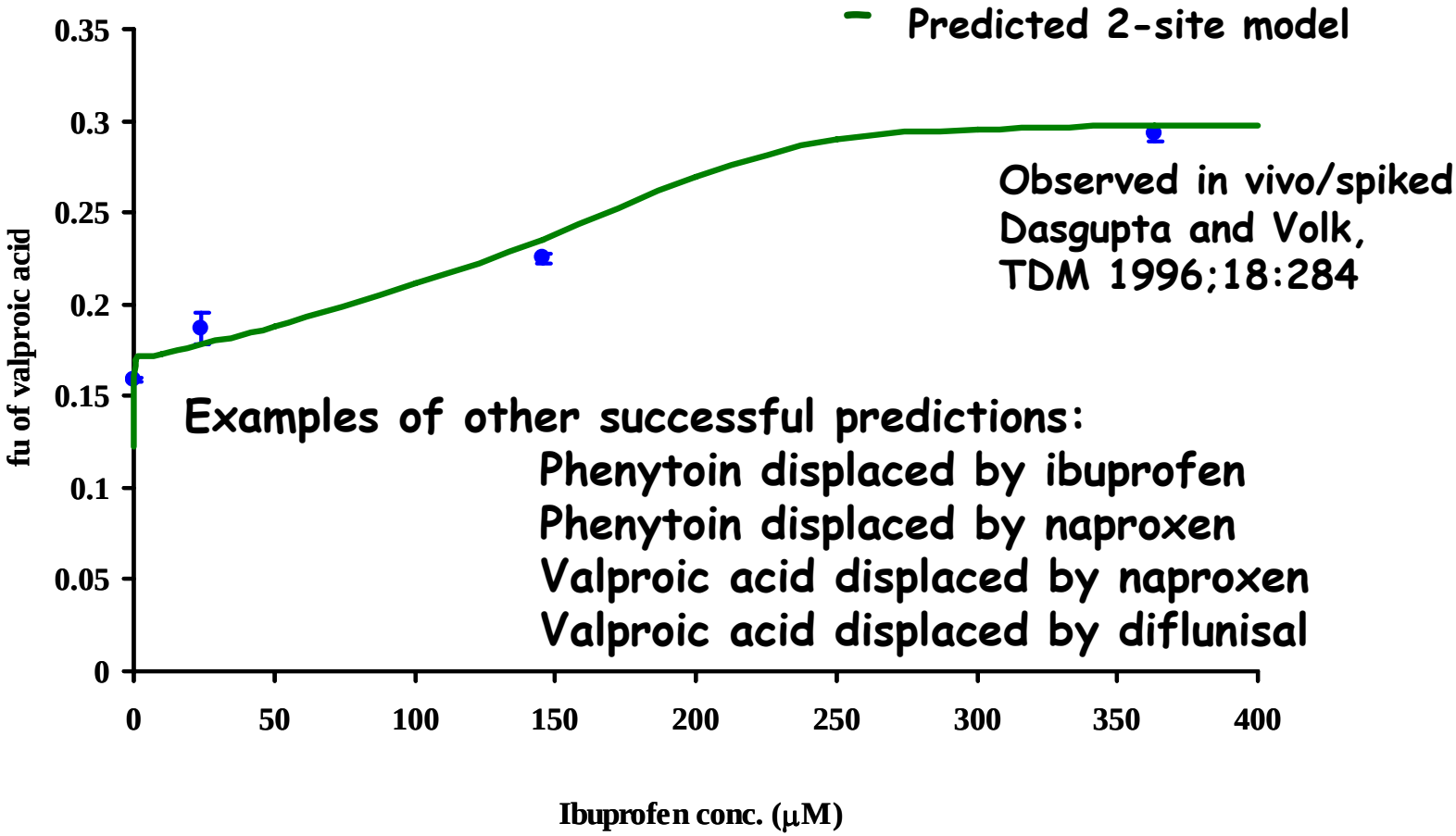
$$f_{u,A} - 1 + \frac{K_{A1} \cdot f_{u,A} \cdot [P_t]^{n_1}}{1 + K_{A1} \cdot f_{u,A} \cdot C_A + K_{B1} \cdot f_{u,B} \cdot C_B} + \frac{K_{A2} \cdot f_{u,A} \cdot [P_t]^{n_2}}{1 + K_{A2} \cdot f_{u,A} \cdot C_A} = 0$$

$$[P_t]^{n_1} = [P_1]' + (1 - f_{u,A}) \cdot C_A + (1 - f_{u,B}) C_B$$

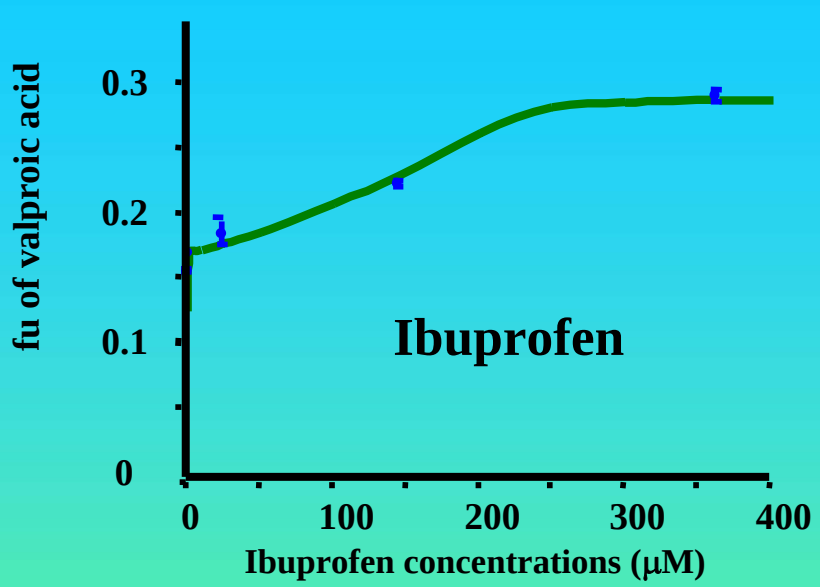
$$[P_1]' = \frac{[P_t]^{n_1}}{1 + K_{A1} \cdot f_{u,A} \cdot C_A + K_{B1} \cdot f_{u,B} \cdot C_B}$$

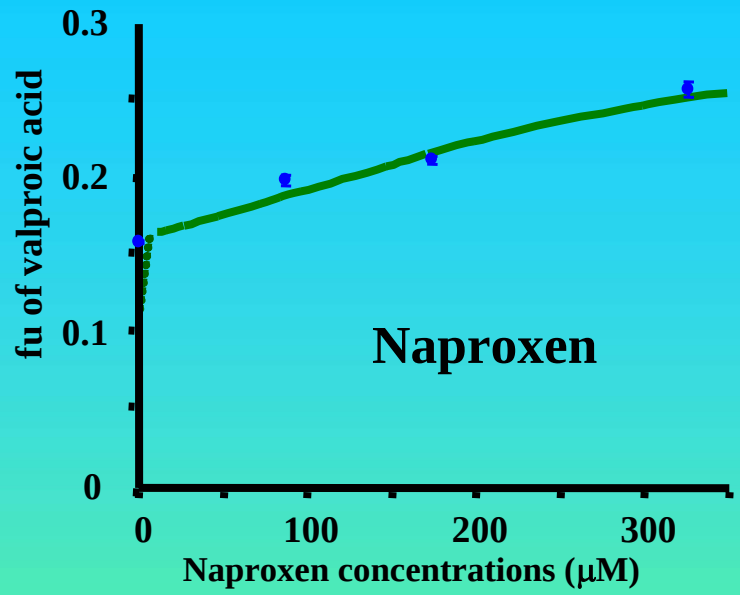
Example:

Valproic acid displaced by ibuprofen



Other Examples for Valproate:

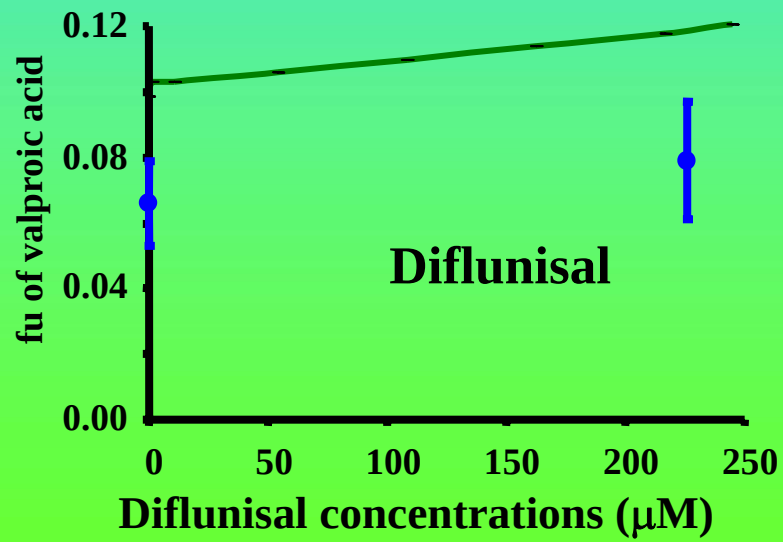




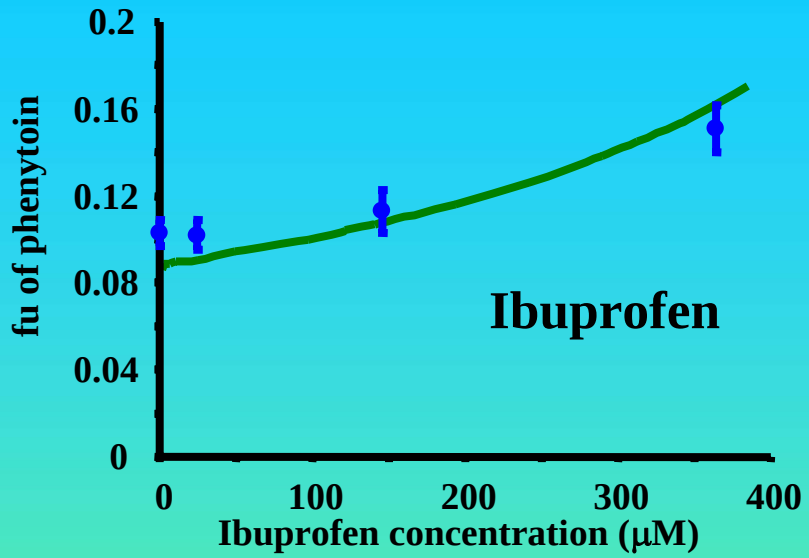
Dasgupta and Volk, Ther Drug Monit 1996; 18: 284 In vivo/spiked

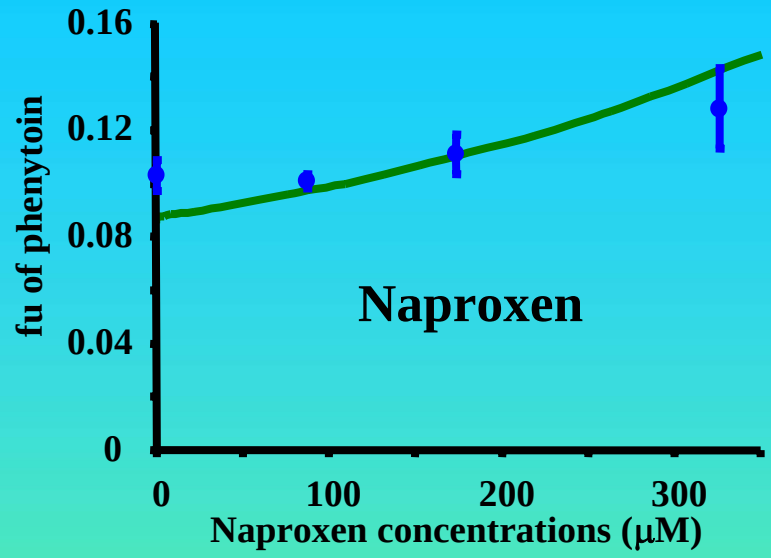
Addison et al. Eur J Clin Pharmacol 2000; 56:715

Low dose sodium valproate (200 mg x 2); 169 μM
&
Moderate dose diflunisal (250 mg x 2); 226 μM



Other Drugs: Displacement of Phenytoin

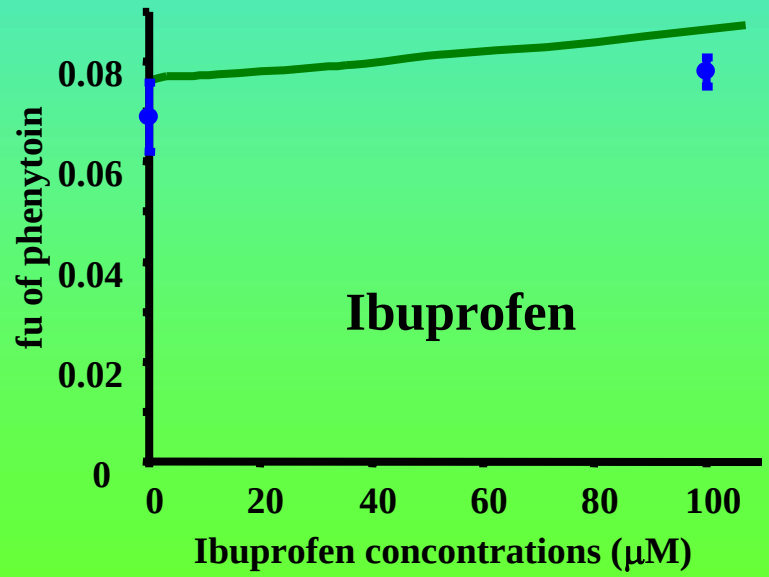




Dasgupta and Volk, Ther Drug Monit 1996;18:97 In vivo/spiked

Bachmann et al. Br J Clin Pharmac 1986; 21: 165

Low dose phenytoin (300 mg ; C_{av} 11 µM)
&
Moderate dose ibuprofen (400 mg x 4 ; C_{ss} 100 µM)

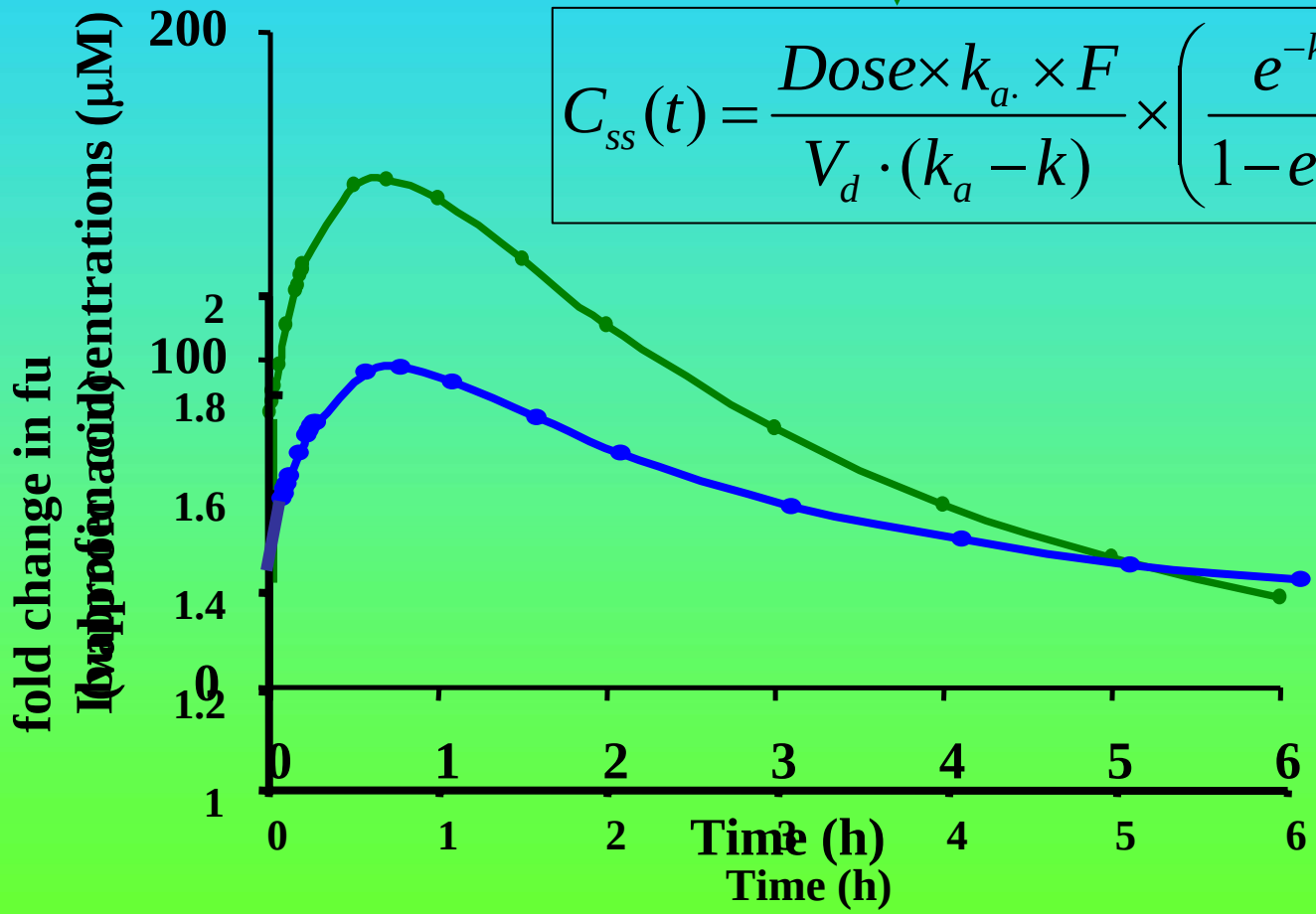


Incorporating into PK:

ibuprofen concentrations in the portal vein

$$C_{p.v.} = C_{ss} + \frac{f_a \cdot k_a \cdot (Dose_{(0)} . e^{-k_a . t})}{Q_H}$$

$$C_{ss}(t) = \frac{Dose \times k_{a\cdot} \times F}{V_d \cdot (k_a - k)} \times \left(\frac{e^{-k \cdot t}}{1 - e^{-k \cdot \tau}} - \frac{e^{-k_a \cdot t}}{1 - e^{-k_a \cdot \tau}} \right)$$



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