Blood and Plasma: a Magic Twin or Single in Human Pharmacokinetics ?

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Relevance of Blood in physiologically (mechanistically) based PK

Hepatic Clearance is expressed in blood flow, unbound drug in blood, and unbound intrinsic metabolic clearance

$$Cl_{H,blood} = \frac{Q_{H,blood} \times fu_{blood} \times Clu_{\text{int},H}}{Q_{H,blood} + fu_{blood} \times Clu_{\text{int},H}}$$

Hepatic Clearance	First Pass Extraction	Absolute Oral Bioavailability
Close to $Q_{H,blood}$	High	Low (e.g . < 10%)
Low compared to $Q_{H,blood}$ $Cl_{H,blood} \simeq fu_{blood} \times Clu_{int,H}$	Low	High (e.g. > 85%)

Pharmacokinetic considerations as to when to use dried blood spot sampling

Gary Emmons and Malcolm Rowland, Bioanalysis 2 (11), 1791-1796, 2010

The unbound concentration as driving force for pharmacokinetics and pharmacodynamics

$$C_u = C_{plasma} * f_u$$

$$C_u = C_{blood} / [\frac{1 - H}{f_u} + H \times R]$$

Whole Blood (unbound) concentration is sensitive to

- Hematocrit H
- Unbound fraction fu in plasma
- Ratio R of blood cell concentration-to-unbound concentration in plasma water,
  which can change, e.g. due to saturation of binding affinity in red blood cells, binding to platelets, …

Plasma and whole blood pharmacokinetics of topiramate: the role of carbonic anhydrase

Shank RP et al. Epilepsy Research 63: 103-112, 2005

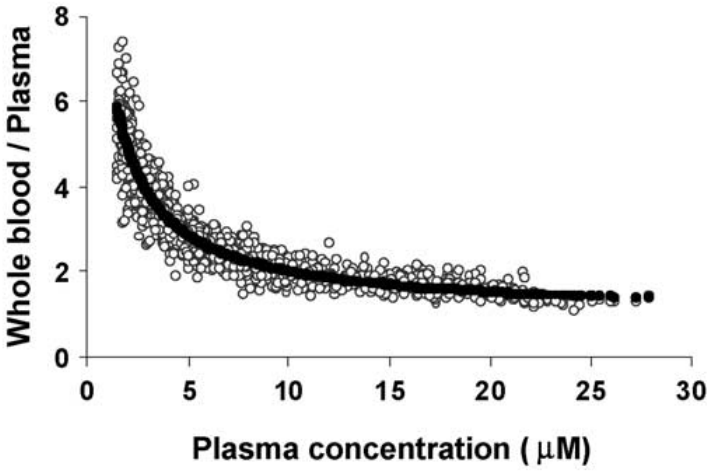


Fig. 2. Plot of the whole blood/plasma concentration ratio for TPM as a function of the plasma concentration. The open circles represent individual results of 1278 blood samples obtained from 27 male subjects. The curvilinear line formed by the filled circles represents values predicted by a curve-fit analysis of the data assuming two saturable binding sites as defined in Eq. (1).

2.4. Analysis of the binding of TPM to erythrocytes

TPM dissociation binding constant (K_d) and maximum binding rate (B_{max}) values for its saturable binding to erythrocytes were obtained by a curve-fit analysis of the data applied to forms of Eq. (1) that contained one or two saturable sites.

$$C_b = \frac{B_{max}1 \times C_{pu}}{C_{pu} + K_d1} + \frac{B_{max}2 \times C_{pu}}{C_{pu} + K_d2} + CF \times C_p \quad (1)$$

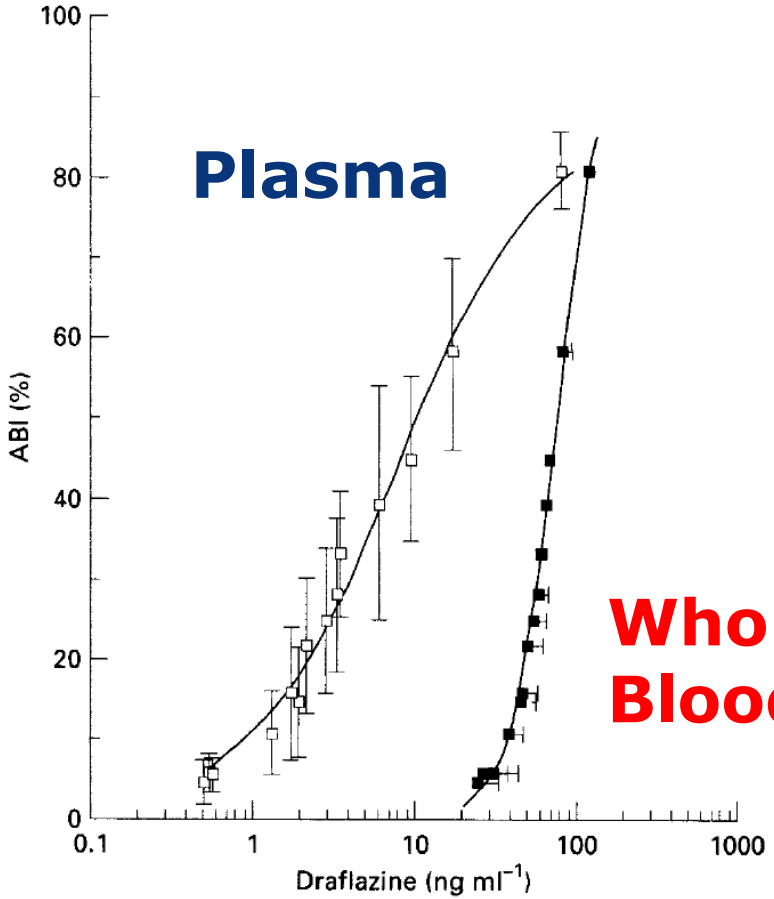
Plasma and whole blood pharmacokinetics of topiramate: the role of carbonic anhydrase

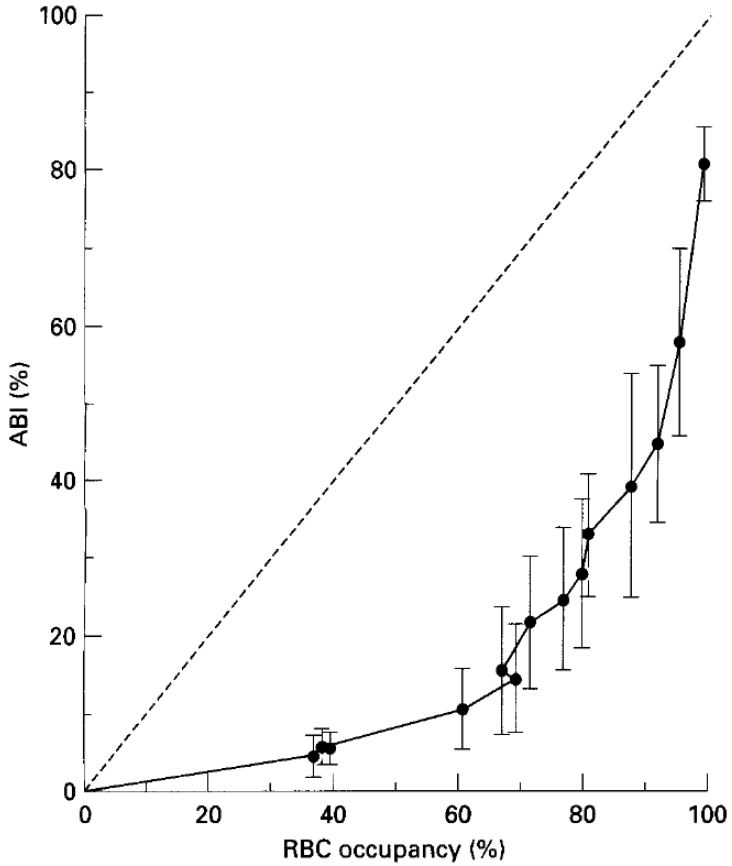
Shank RP, et al. Epilepsy Research 63: 103-112, 2005

	Plasma			Whole Blood		
	100 mg	200 mg	400 mg	100 mg	200 mg	400 mg
CL/F (L/h)	1.5	1.5	1.5	0.2	0.3	0.5
Vss/F (L)	80	69	65	22	33	43
$t_{1/2}$ (h)	47	33	30	71	78	58
C_{max} (mg/L)	1.6	3.5	7.3	4.9	7.1	11.5

A different mindset !

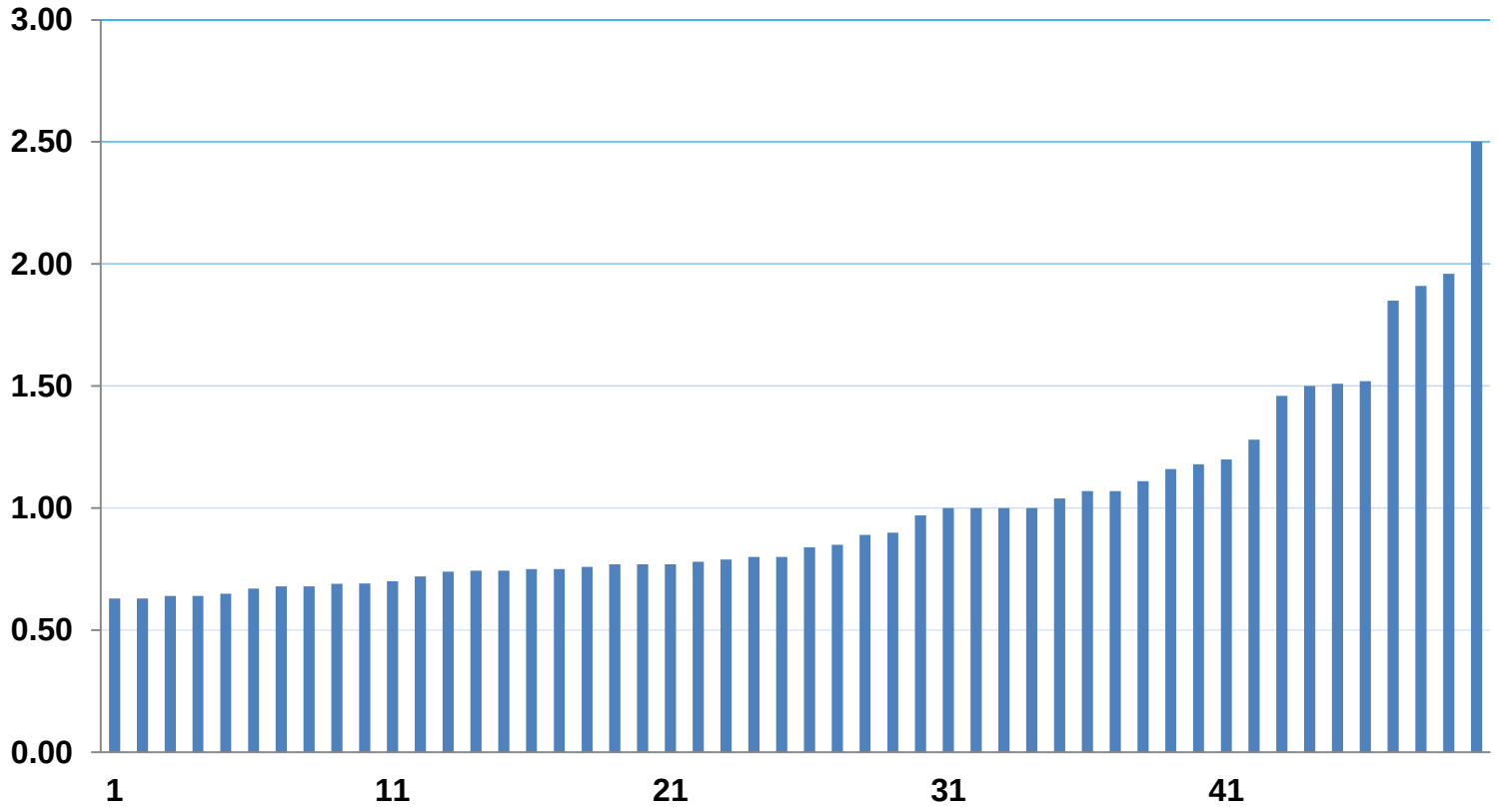
Concentration-response relationship between inhibition of nucleoside transport and draflazine concentrations in plasma, whole blood and RBC





Snoeck E, Piotrovskij V, et al. Br J Clin Pharmacol 43: 603-612, 1997

Blood : Plasma Drug Concentration Ratios of 50 structurally diverse compounds



De Buck S, Sinha VK, et al. DMD 35: 649-659, 2007

Decision tree for choosing plasma or dried blood spot matrix

Emmons G and Rowland M, Bioanalysis 2(1): 1791-1796, 2010

Table 1. Decision tree for choosing plasma or dried blood spot matrix.

Blood:plasma ratio	Hematocrit constant†	fu constant	ρ constant	Plasma and/or DBS
0.55 < 2.0	Y	Y	Y	Plasma or DBS can equally be used
0.55 < 2.0	Y	N	Y	Plasma or DBS can be used, but the reasons for variability in plasma protein binding need to be understood and accommodated
≥2.0	Y	Y	Y	DBS is preferred due to hemolysis concerns
≥2.0	Y	N	Y	DBS is preferred due to hemolysis concerns
≥2.0	Y	Y	N	Depending on the situation and the objectives of the study either plasma or DBS can be used, but if DBS is used the reasons for the lack of constancy in the blood cell partitioning need to be understood and accommodated
Any	N	Y/N	Y/N	Decision depends on value of R as in above scenarios with the additional need to correct for hematocrit when using DBS if R approaches 0.55 or ≥2.0

†By constant it is meant that the parameter value varies to a sufficiently small extent not to materially affect the relationship between unbound plasma and total concentrations.
DBS: Dried blood spot; fu: Unbound fraction in plasma; N: No; R: Blood-to-plasma concentration ratio; Y: Yes.

Conclusions

Blood is physiologically and mechanistically the better biological fluid,

However, attention for

- **Specific and saturable drug binding to erythrocytes** as source of non-linear pharmacokinetics and deviations in concentration-time profiles between blood and plasma. Think of the relevance for the drug action.
- **Verify constancy**
  - in unbound fractions in plasma and blood,
  - in biochemistry (haematocrit, proteins, … , associated with diseases)
- **Perform early in vitro assessments of**
  - Blood to plasma concentration ratios
    - over broad range of drug concentrations
    - animal species may miss the binding target in blood
  - Concentration dependency of protein binding
  - Metabolites may compete for binding sites in blood