Can finger-prick sampling replace venous sampling? A pharmacokinetic perspective.

Bart Remmerie, Chem. Eng.
Clinical Pharmacology

Outline

- Pharmacokinetic aspects related to blood PK
- Cases
- Pharmacokinetic aspects related to fingerstick sampling
- Conclusions

Pharmacokinetic considerations as to when to use dried blood spot sampling

M. Rowland & G. Emmons, Bioanalysis 2 (11), 1791-1796, 2010

The unbound concentration as driving force for pharmacokinetics and pharmacodynamics

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

$$C_u = C_{blood} \; / \left[\frac{1 - H}{f_u} + H \; x \; R \right]$$

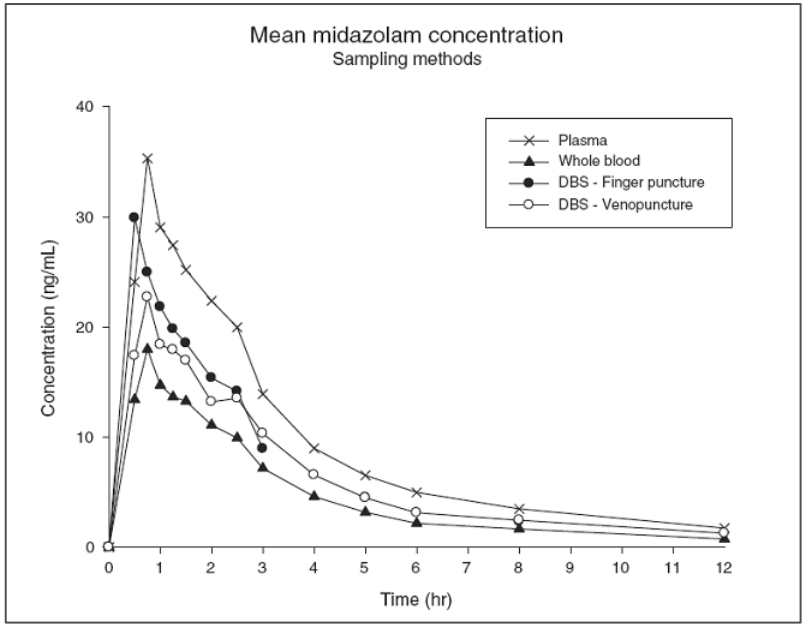
Whole Blood (unbound) concentration is sensitive to

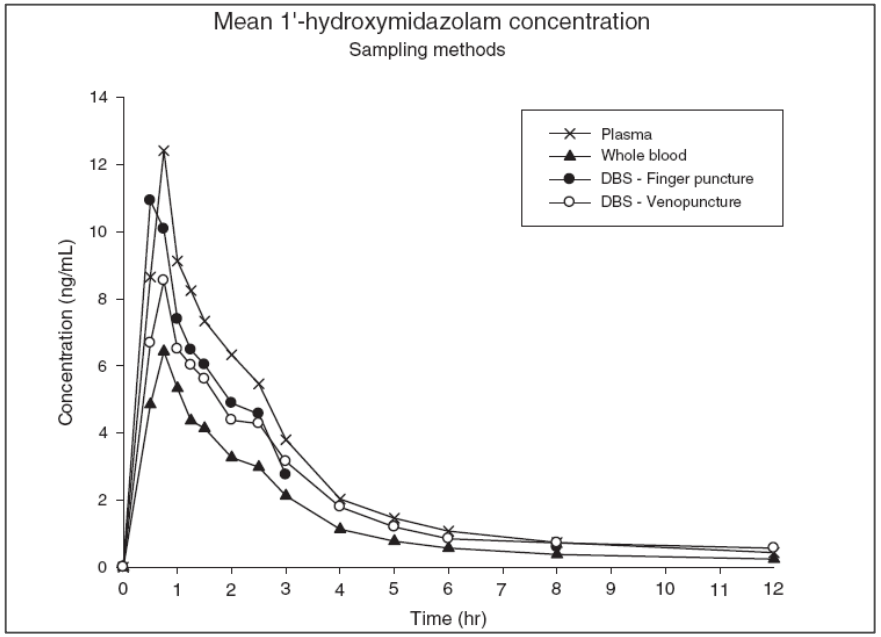
- Hematocrit H
- Unbound fraction fu in plasma
  - Ratio R of blood cell concentration-to-unbound concentration in plasma water, which can change, e.g. due to saturation of binding affinity in red blood cells, binding to platelets, …

Application of DBS-LC-MS/MS to Geno- and Phenotyping of P450 enzymes.

De Boer T, Wieling J, et al. Biomed. Chromatogr. 25 (10): 1112-1123, 2011

Single Dose, Healthy Volunteers (N=12)
Venous blood (DBS, blood, plasma)
Finger puncture (DBS)



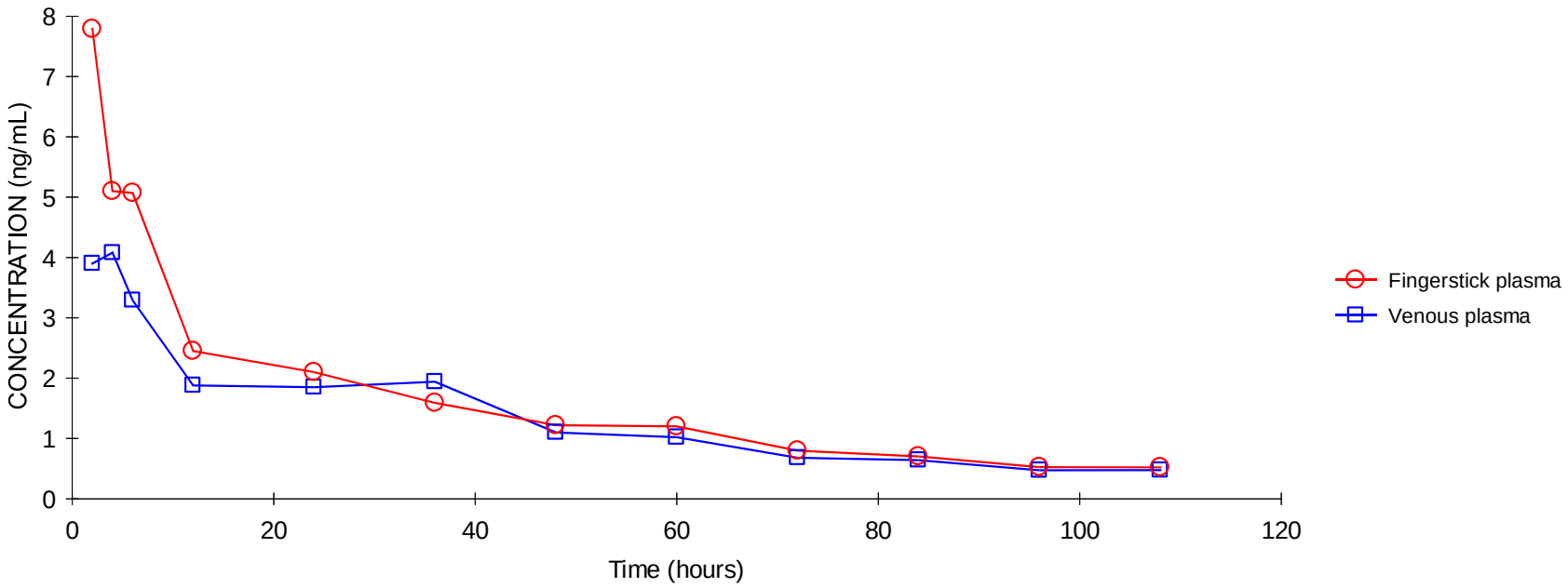


Conclusion DB: DBS suitable for PK analysis and Genotyping
Conclusion BR: DBS overestimates reference procedure; Finger puncture blood concentration > venous blood concentration, may be adequate for TDM.

Internal case 1: study design

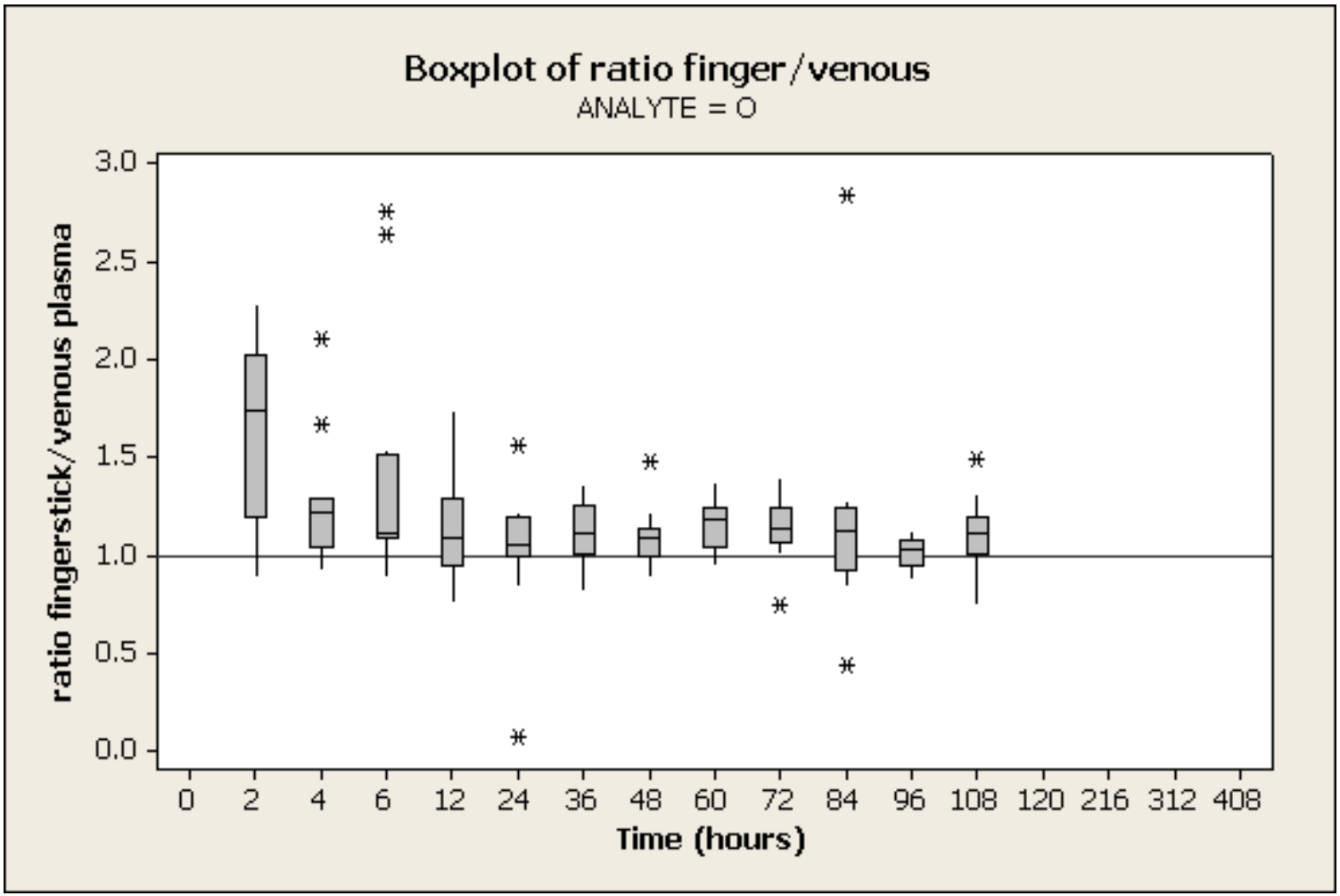
- Objective: evaluate feasibility finger-prick derived blood for TDM
- Parallel-group (N= 5)
- Single dose, N= 12 healthy volunteers per treatment group
- Extensive PK sampling (total < 122 mL):
  - Venous blood and plasma (total: 3 mL/sample)
  - Fingerstick blood and plasma (total: 0.5 mL/sample)

Compound O



Conclusion: Fingerstick plasma overestimates venous plasma for compound O

Ratio fingerstick/venous plasma versus time



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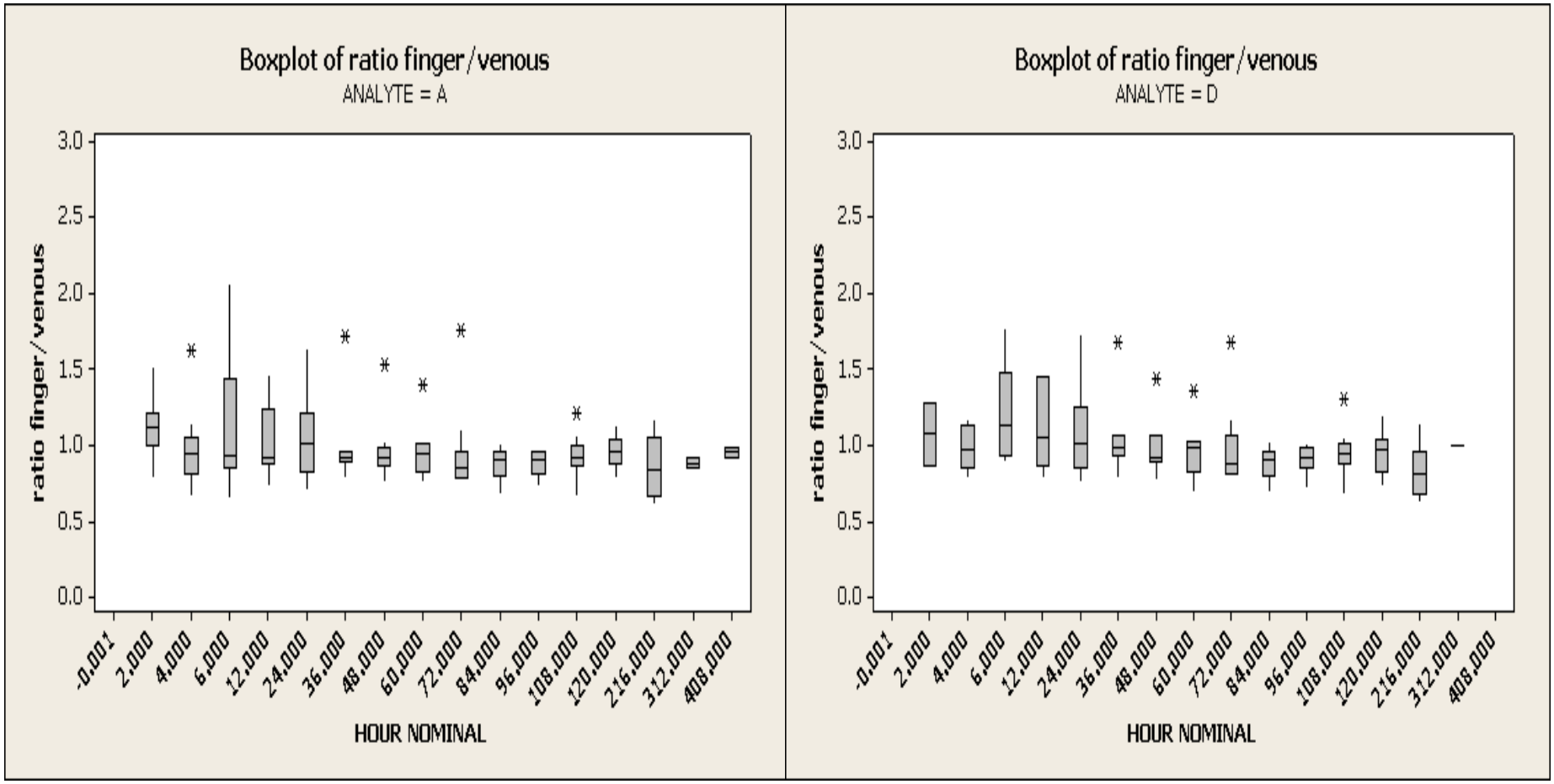
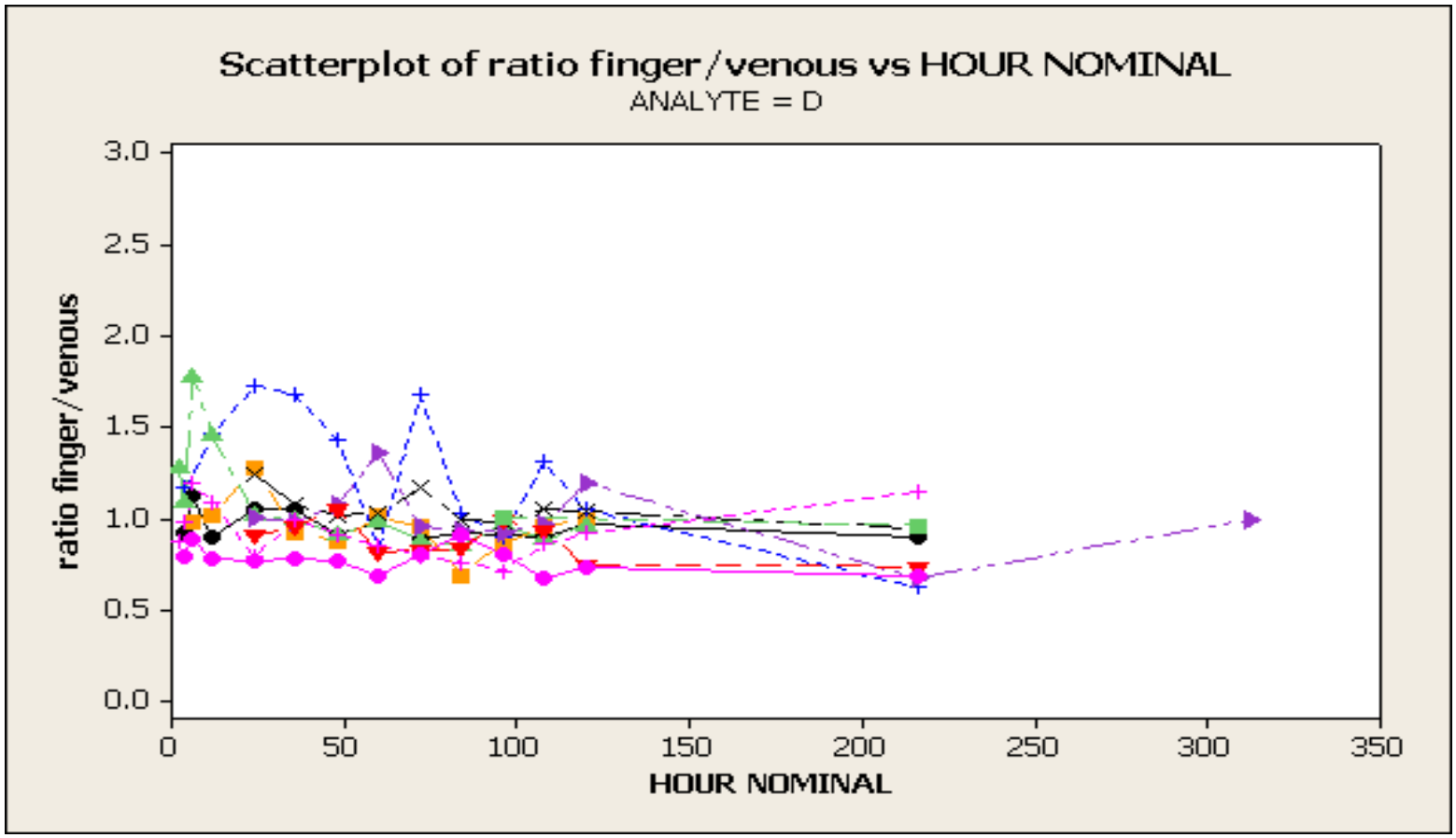


Conclusion: Fingerstick plasma = venous plasma for compounds A and D (except for first hours?)….

Ratio fingerstick/venous plasma versus time



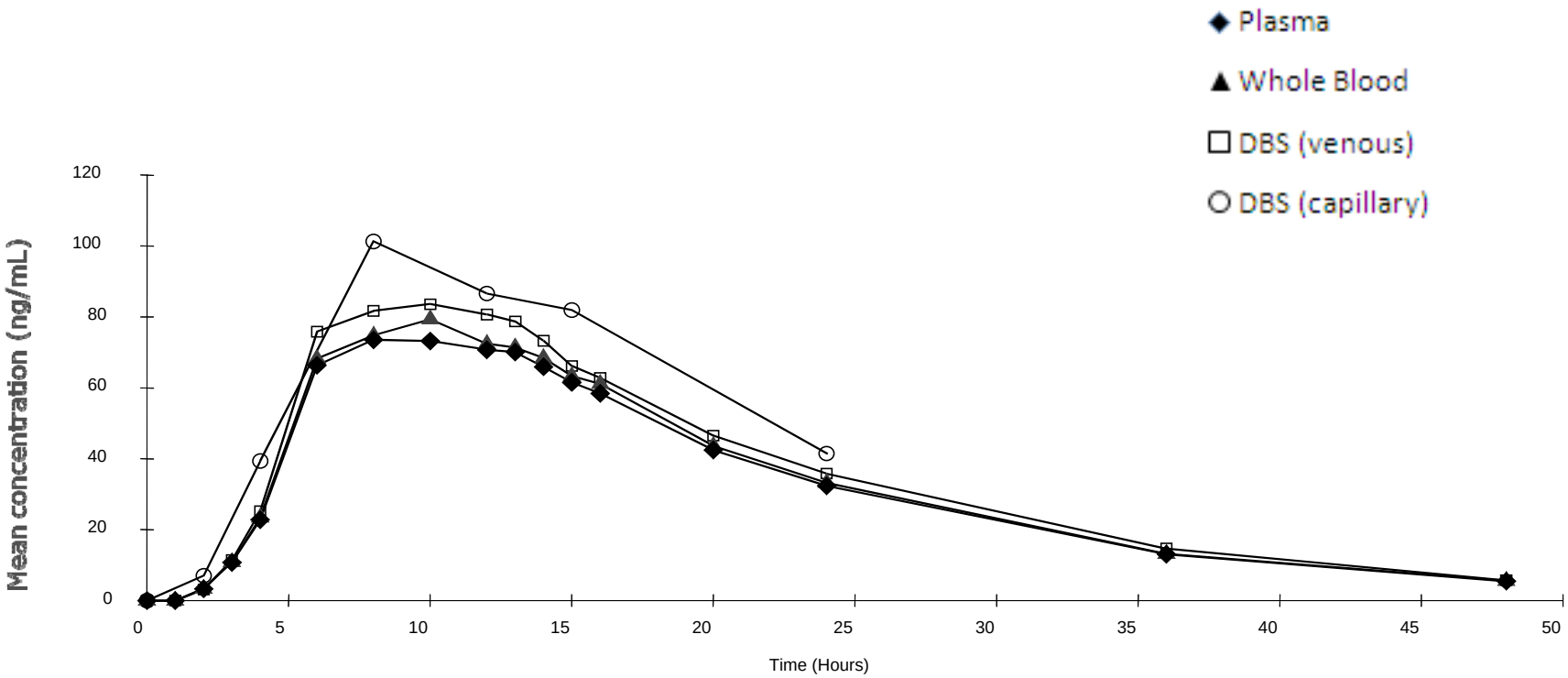
… however, fingerstick plasma may overestimate venous plasma in some individuals

Case 2

- Single Dose, cross-over study (25, 50, 100 mg dose), fasted
- Matrices collected:
  - Venous plasma (LCMS)
  - Venous blood (LCMS/DBS)
  - Fingerprick blood (DBS)

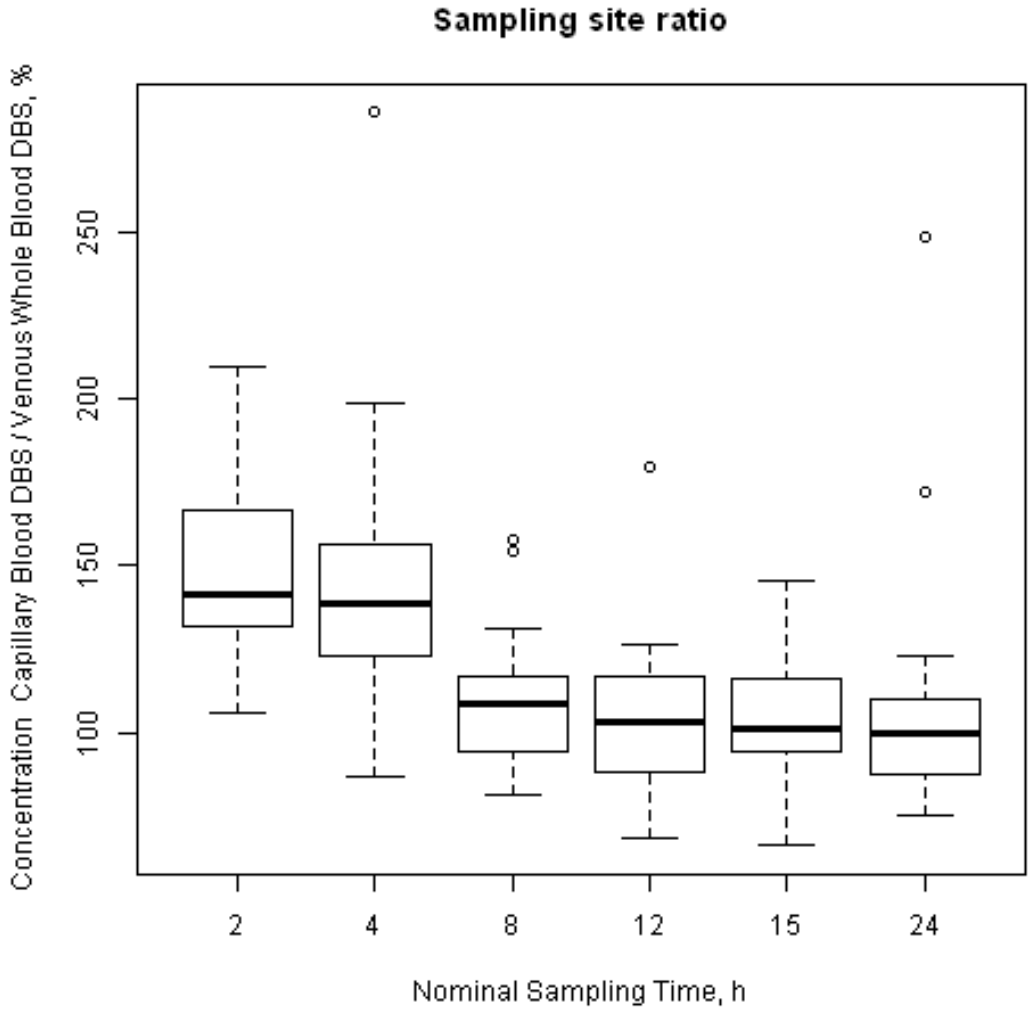
- F_{abs}: 75%
- V_d: 2.6 and 2.9 L/kg
- PPB: 20%
- T_{max}: 12h ; $T_{1/2}$: 9h

Case 2 (highest dose)



Conclusion 1: DBS overestimates reference method
Conclusion 2: Fingerstick blood > venous blood concentrations

Case 2: ratio fingerstick/venous versus time

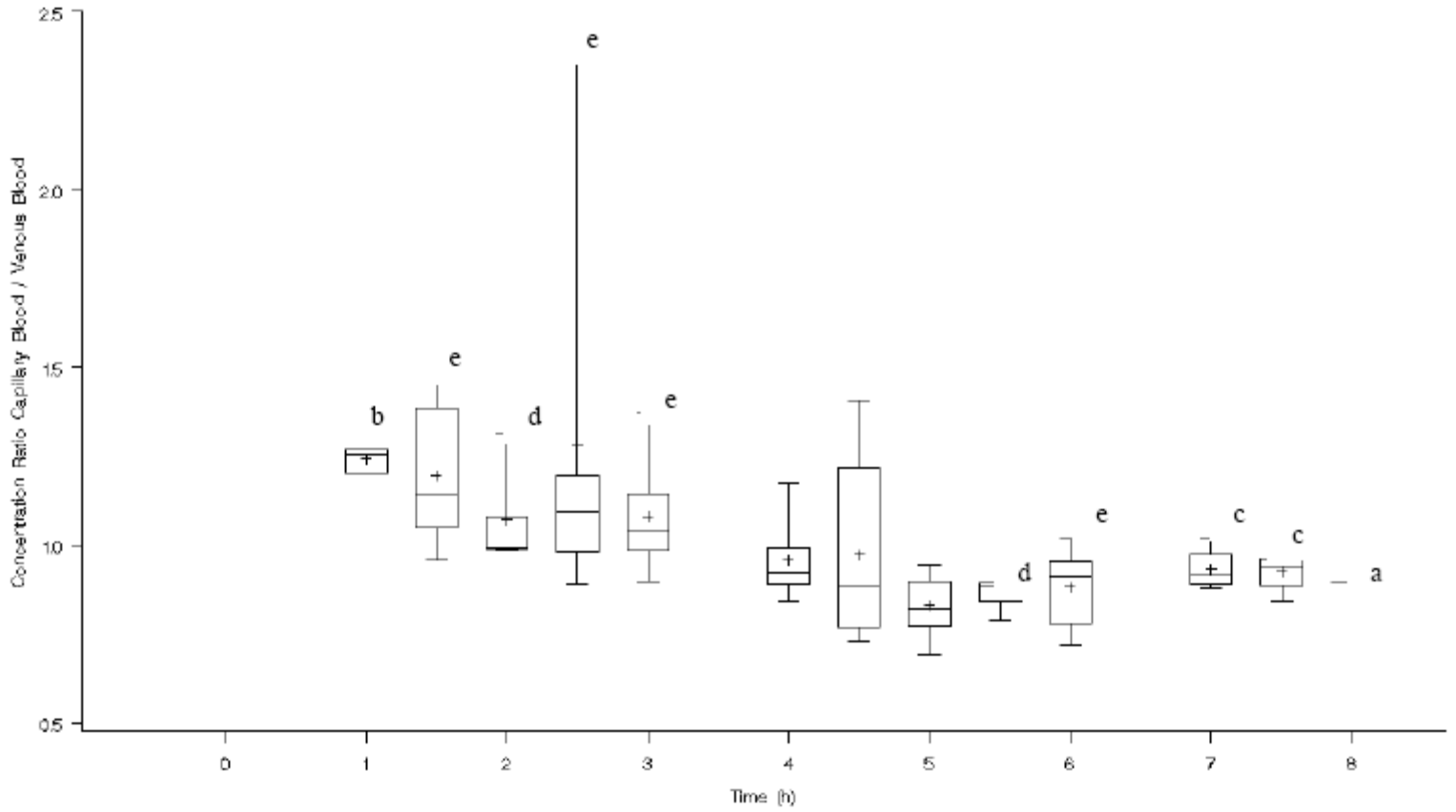


Case 3

- Single Dose, parent drug and metabolite measured
- Matrices collected:
  - Venous plasma
  - Fingerstick plasma
  - DBS (fingerstick)

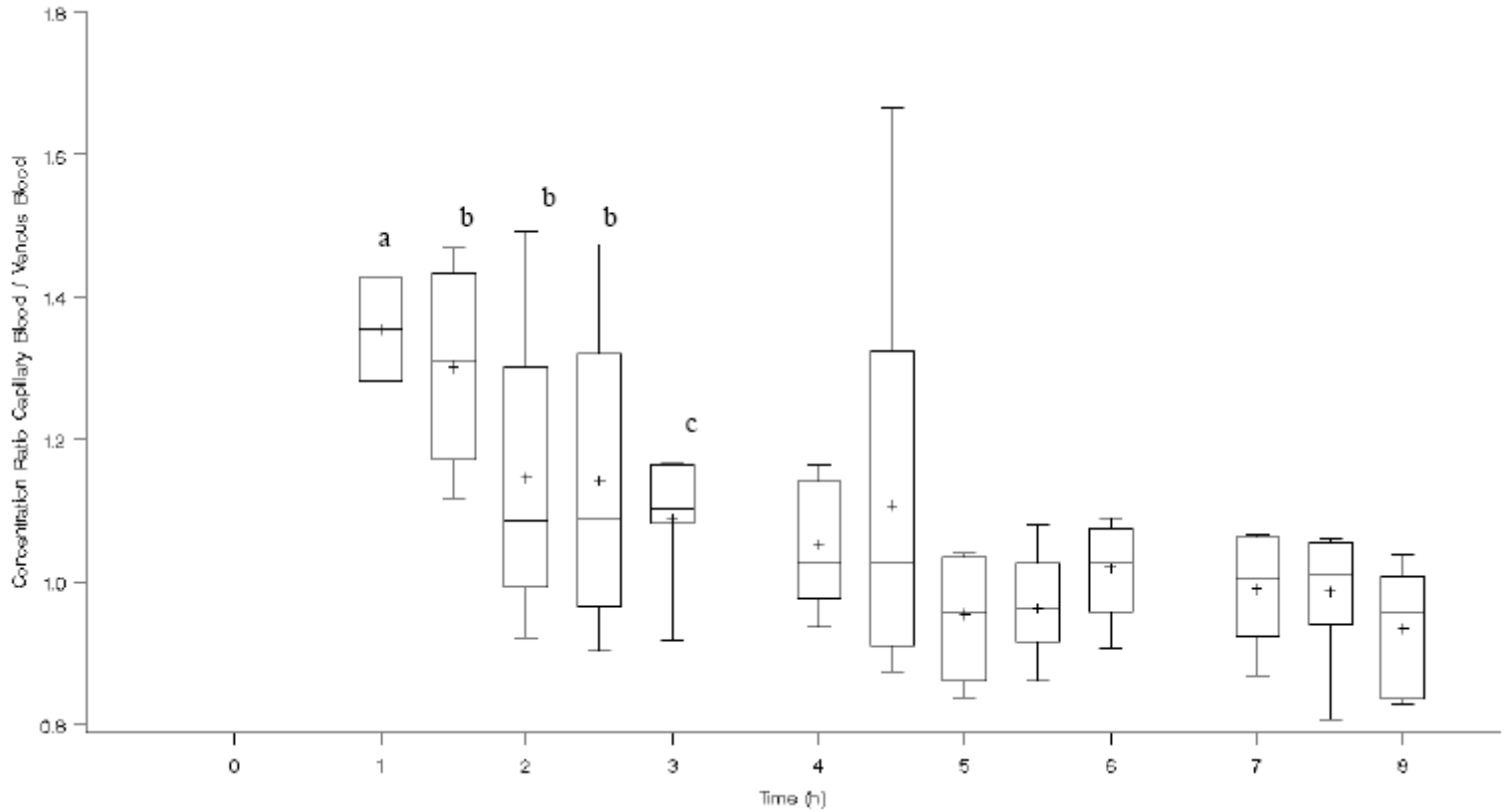
- Fabs: 52%
- Vd: 0.34 L/kg
- PPB: 96.3%
- Tmax: 2-5h ; T1/2: 1.3h

Case 3 (parent drug)



Conclusion: Fingerstick plasma > venous plasma concentrations

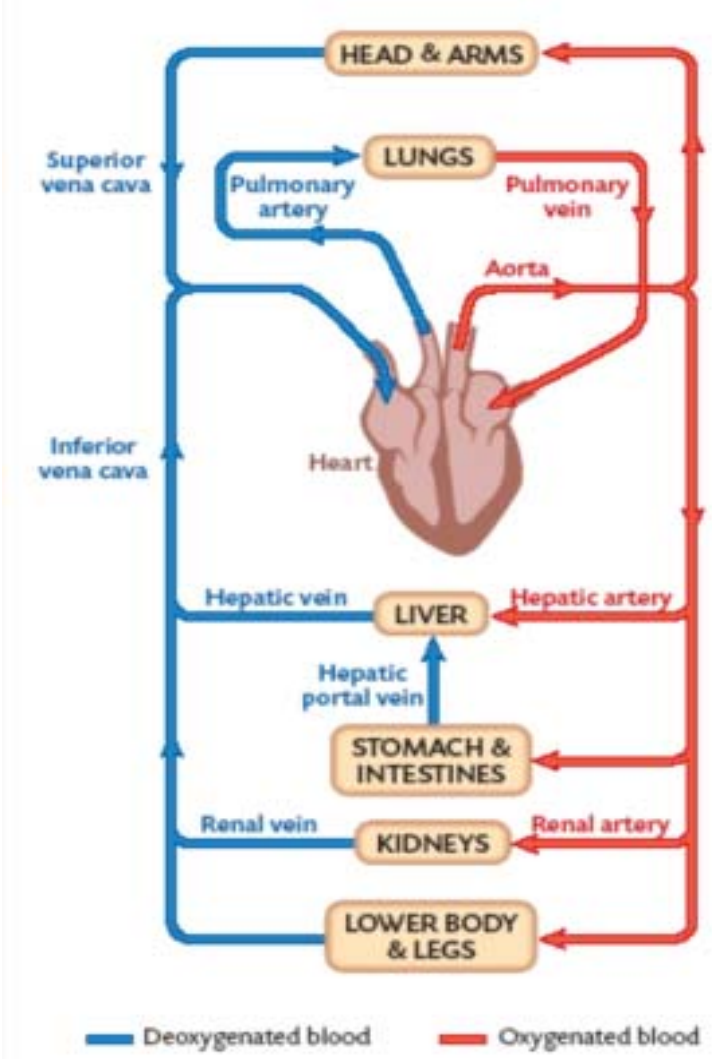
Case 3: metabolite



Conclusion: Fingerstick plasma > venous plasma concentrations

W. L. Chiou. The phenomenon and rationale of Marked Dependence of Drug Concentration on Blood sampling Site. Clin Pharm. 17 (3) 1989

- 40+ examples
- Mechanistic hypothesis
  - $f=1-(0.693*R/(t_{1/2}*Q))$ with,
  - f= arterial/venous concentration ratio
  - R= apparent partition coefficient tissue/venous blood
  - Q: blood flow
- "… virtually all compounds of clinical interest…will be more or less affected by the sampling site chosen."
- "… marked arteriovenous differences can exist for hrs or days…"
- Initial distribution vs. elimination phase



Potential reasons for dissociation

- Physiological
  - Initial contamination with interstitial fluid?
  - Effect of stimulation?
  - Location distinct from arm?
  - Capillary blood more reflective of arterial blood?
  - Extraction (Cl/V) of drug by surrounding sampling tissue?
  - Effect of blood flow?

- Drug-related
  - High (first-pass) extraction?
  - High V_d/R?
  - Small, lipophilic molecules, neutral at pH=7.4?
  - Related to duration of absorption?
  - Multi-factorial?

Final comments & conclusions

- Plasma-based PK may be more directly related to PD
- Fingerstick based drug levels can overestimate venous plasma levels
- Bias especially observed after SD (less at SS?)
- Adequacy depends on objective (S.D., M.D., TDM)
- What about PD parameters, biomarkers?
- Consistent data across/between studies requires consistent methodology
- Evaluate consequences of methodological change for project

Acknowledgements

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Q&A