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

\[ C_u = C_{\text{plasma}} \times f_u \]

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

Whole Blood (unbound) concentration is sensitive to
• Hematocrit \( H \)
• Unbound fraction \( f_u \) 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.

**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)
Conclusion: Fingerstick plasma overestimates venous plasma for compound O
Conclusion: Fingerstick plasma overestimates venous plasma for compound O
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

Sampling site ratio

Nominal Sampling Time, h

Concentration Capillary Blood DBS/venous Whole Blood DBS, %
## 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
  - $f = 1 - (0.693R/(t_{1/2}Q))$ 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
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Q&A