The Role of protein binding and stereochemistry in drug-drug interactions

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The Role of protein binding and stereochemistry in drug-drug interactions: What you don’t know can hurt you!

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Difficult-to-explain drug-drug interactions
Effect of Telaprevir on HIV PI’s

van Heeswijk et al., CROI 2011
Effect of HIV PI’s on Telaprevir

van Heeswijk et al., CROI 2011
Effect of Boceprevir on HIV PI’s

Hulskotte EGJ et al., CROI 2012
Any unexpected drug interaction can be understood if you ask the right question(s).
Unusual mechanisms for clinically significant drug-drug interactions

- Drug transport proteins
- Chelation
- Altered gastrointestinal pH
- Enzyme inhibition that looks like induction
- Enzyme induction that looks like inhibition
- Protein binding displacement
- Stereochemistry
Unusual mechanisms for clinically significant drug-drug interactions

- Drug transport proteins
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Plasma protein binding of drugs

Two main proteins:

- **Albumin**
  - High capacity
  - Low affinity
  - Constitutive

- **Alpha$_1$-acid glycoprotein (AAG)**
  - Low capacity
  - High affinity
  - Inducible
What effect does plasma protein binding have on PK and PD?
Effect of telaprevir on methadone PK

van Heeswijk et al., IWCPHepT, 2011, Abstract PK_18
Effect of telaprevir on methadone PK

van Heeswijk et al., IWCPHepT, 2011, Abstract PK_18
The effect of RTV/SQV on methadone AUC on day 0 (before RTV/SQV) and day 15 (after two weeks of RTV/SQV). Data are mean ± SEM. From Gerber et al., JAIDS 2001; 27: 153
Effect of SQV/RTV on methadone PK

Figure 3: The effect of RTV/SQV on the stereospecific methadone AUC. From Gerber et al., JAIDS 2001; 27: 153
Can free drug concentrations be accurately predicted without direct measurement?
Applying the law of mass action to predict EFV unbound concentrations

- Efavirenz is highly protein bound.
  - 99.8%, mainly to albumin (HSA)

- CSF concentrations of EFV are substantially (>130-fold) lower than plasma concentrations.

- HSA concentrations are ~200-fold lower in CSF than in plasma.

- Are unbound EFV concentrations in plasma and CSF different, and can the EFV unbound fraction be predicted by a simple mathematical model?

- Avery et al., *Antimicrob Agents Chemother* 2013;57:1409
Correlating efavirenz total and unbound drug in plasma and CSF

Avery et al., *Antimicrob Agents Chemother* 2013;57:1409
Predicting Efavirenz Free Fraction

\[
P = \text{Protein (HSA) concentration} \\
CT = \text{Total (Bound + Unbound) drug concentration} \\
Cu = \text{Unbound drug concentration} \\
K_d = \text{Dissociation Rate Constant} \\
f_u = \text{Fraction of drug unbound}
\]

\[
P - (CT - Cu) \quad \text{Protein} + \text{Drug} \quad K_d \quad \text{Protein} \cdot \text{Drug} \\
CT - Cu \quad C_u \quad C_T - C_u
\]

\[
K_d = \frac{(P - C_T + C_u) \cdot C_u}{C_T - C_u} \\
K_d = \frac{f_u^n}{1 - f_u} \cdot (nP - C_T + C_T f_u) \cdot C_T^{n-1}
\]

\[
f_u = \frac{(C_T - K_d - P) + \sqrt{(C_T - K_d - P)^2 + 4K_d C_T}}{2C_T}
\]

Where:

\[
P = \text{Protein (HSA) concentration} \\
C_T = \text{Total (Bound + Unbound) drug concentration} \\
C_u = \text{Unbound drug concentration} \\
K_d = \text{Dissociation Rate Constant} \\
f_u = \text{Fraction of drug unbound}
\]

Avery et al., *Antimicrob Agents Chemother* 2013;57:1409
How to measure EFV unbound concentrations?

- Separation of free from total EFV by ultracentrifugation.
- Efavirenz binds to plastic and filters used for ultracentrifugation.
- Filters blocked first by 10% polyethylene glycol prior to ultracentrifugation.
- 100% recovery of EFV in validation experiments.

- Avery et al., *Antimicrob Agents Chemother* 2013;57:1409
Model validation: predicted versus measured efavirenz unbound fraction

Avery et al., Antimicrob Agents Chemother 2013;57:1409
Can in vitro models also predict extent of binding to AAG?
AAG binding affinity (fluorescence quenching) of HIV protease inhibitors

- Bakker et al., 1997
HIV PROTEASE INHIBITORS: AAG BINDING AFFINITY

- Indinavir $K_a = <1 \times 10^1 \text{ M}^{-1}$
- Ritonavir $K_a = 1 \times 10^4 \text{ M}^{-1}$
- Nelfinavir $K_a = 2 \times 10^5 \text{ M}^{-1}$
- Saquinavir $K_a = 8 \times 10^5 \text{ M}^{-1}$
- SC-52151 $K_a = 2 \times 10^6 \text{ M}^{-1}$

- Bakker et al., 1997
Protein binding and disease states

Extent of drug binding to plasma proteins can be affected by:

- **HSA concentration**
  - Lower in advanced liver disease
- **AAG concentration**
  - Higher with acute inflammation, menses, etc.
- **Plasma or body fluid pH**
Are plasma protein concentrations affected by acute or chronic HIV infection?
Impact of HIV Treatment on AAG

Are plasma protein concentrations affected by acute or chronic HCV infection?
Cross-Study Comparison of Boceprevir PK
(AUC and $C_{8\text{hr}}$ values estimated from population PK model)

- Wenning et al., AASLD 2012, Abstract 770
Relationship between free drug concentrations in plasma and intracellular drug concentrations?
Effect of Boceprevir on HIV PI’s?

Hulskotte EGJ et al., CROI 2012
Does protein binding explain TPV and BOC DDI’s with boosted HIV PI’s?

**FOR:**
- TPV-Methadone example

**AGAINST:**
- TPV and BOC are not “highly” protein bound (60-75% in human plasma)

**Other possible explanations:**
- Saturation of AAG
- Stereo-specific interactions (for BOC)
- Something other than protein binding
Unusual mechanisms for clinically significant drug-drug interactions

- Displacement from plasma protein binding sites may explain decreases in total concentrations for some combinations of highly protein bound drugs.
- Protein binding may be different for stereoisomers in a mixture of enantiomers.
- Mass action can accurately predict free drug fraction if the total drug concentration, $k_d$ (or $k_a$), and concentration of plasma drug binding proteins are known.
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Boceprevir PK/PD
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