Induction: Drug Transporters versus Enzymes

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Transporter Induction: How Do We Inform Our Labels?

- Difficult to predict in vivo transporter induction liability from in vitro data
- P450 induction parity is assumed
Transporter Induction: Conservative/Minimal Guidance Due to Lack of Data

- Difficult to predict in vivo transporter induction liability from in vitro data
- P450 induction parity is assumed
- **Ultimately, overly conservative recommendations are adopted**
  - May restrict patient access to still efficacious therapy
- How do we fill in the gaps?
  - We generate data!

**FDA**

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Inducer</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp</td>
<td>Avasimibe, carbamazepine, phenytoin, rifampin, St. John’s wort, tipranavir/ritonavir</td>
</tr>
<tr>
<td>BCRP</td>
<td>Not known</td>
</tr>
<tr>
<td>OATP1B1</td>
<td>Not known</td>
</tr>
<tr>
<td>OATP1B3</td>
<td>Not known</td>
</tr>
</tbody>
</table>

**EMA**

If there are inducers of the transporter marketed within the EU, an interaction study with such an inducer is recommended.

_FDA. Guidance for industry: drug interaction studies 2012; EMA. Guideline on the investigation of drug interactions 2013._
Rifampin: a Prototypical In Vivo PXR Agonist

<table>
<thead>
<tr>
<th>Probe Drug Cassette</th>
<th>Dose</th>
<th>Abbreviation</th>
<th>P450/Transporter</th>
<th>Cassette Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran etexilate*</td>
<td>75 mg</td>
<td>DE</td>
<td>P-gp</td>
<td>1</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>20 mg</td>
<td>PRA</td>
<td>OATP</td>
<td>3</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10 mg</td>
<td>ROS</td>
<td>OATP/BCRP</td>
<td>5</td>
</tr>
<tr>
<td>Midazolam</td>
<td>2 mg</td>
<td>MDZ</td>
<td>CYP3A</td>
<td></td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>500 mg</td>
<td>TOL</td>
<td>CYP2C9</td>
<td>7</td>
</tr>
<tr>
<td>Caffeine</td>
<td>200 mg</td>
<td>CAF</td>
<td>CYP1A2</td>
<td></td>
</tr>
</tbody>
</table>

*DE was analyzed as total dabigatran (TDAB), the sum of conjugated and unconjugated active species.

- Are transporters as inducible as P450s?
- Can transport induction be predicted from P450s?
Rifampin: Multiple Dose Levels to Elicit Weak, Moderate, and Strong Induction

Are transporters as inducible as P450s?
Can transport induction be predicted from P450s?
Probe Induction As a Function of RIF Dose

- $\text{ED}_{50} = 66 \text{ mg}$
- $E_{\text{max}} = 13$

- $E_{\text{max}}$ and $\text{ED}_{50}$ values were estimated for each probe
- AUC Ratio: Weak (0.5–0.8), moderate (0.2–0.5) and strong (<0.2) induction
Dabigatran Is Less Inducible Than Midazolam

- **ED$_{50}$** = 66 mg
- **$E_{\text{max}}$** = 13

- **ED$_{50}$** = 31 mg
- **$E_{\text{max}}$** = 2.0

Are differences due to probe sensitivity?
After Accounting for Probe Sensitivity: P-gp is Less Inducible than CYP3A

- $E_{\text{max,c}} = E_{\text{max}}$ corrected for (divided by) differences in probe sensitivity ($f_{\text{m/t}}$)

- Strong P-gp induction (>$5\text{-}\text{fold CL increase}$) is unlikely to be observed

### CYP3A

- $ED_{50} = 66\text{ mg}$
- $E_{\text{max}} = 13$
- $E_{\text{max,c}} = 14$

### P-gp

- $ED_{50} = 31\text{ mg}$
- $E_{\text{max}} = 2.0$
- $E_{\text{max,c}} = 3.6$
Similar to P-gp, Only Moderate Induction of OATP and CYP2C9 Is Observed

- PRA and ROS results suggest that OATP, but not BCRP, is induced
- RIF may elicit weak induction of CYP1A2 via PXR crosstalk or weak AHR agonism
How Do We Characterize and Interpret Relationships Between Probes?

Can we predict Probe Y induction based on Probe X?
Linear Relationships Only Occur When $E_{max}/ED_{50}$ Are Similar

- Combining $E_{max}/ED_{50}$ curves allows for evaluation of PXR agonism, independent of RIF
- Gray areas represent similar induction between probes
Nonlinear Relationships Occur When Induction Capacity is Different

\[ E_{\text{max},x} > E_{\text{max},y} \]
\[ E_{50,x} = E_{50,y} \]

Combining \( E_{\text{max}}/ED_{50} \) curves allows for evaluation of PXR agonism, independent of RIF.

Gray areas represent similar induction between probes.
Induction of P-gp is One DDI Category Weaker Than CYP3A
Similarly, OATP and CYP2C9 Induction Is Always Less than CYP3A

This relationship holds true even after accounting for probe sensitivity.

- Mean observed ± 90% CI
- Corrected

Weak
- Moderate
- Strong
P-gp, OATP and CYP2C9 Demonstrate Induction DDI Classification Equivalence

- The relationships between PRA, ROS and TOL approximate the line of unity
- Parity suggests simplicity in clinical interpretation and prediction
What are the Clinical Implications?

- Doses of <600 mg RIF can be tailored to represent weak, moderate and strong PXR-dependent induction

  Standardize DDIs and facilitates extrapolation
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  - Standardize DDIs and facilitates extrapolation
- Compared to CYP3A, strong induction of P-gp, OATP or CYP2C9 is unlikely to be elicited by potent PXR agonists
- Observed relationships should apply to other inducers
  - This hypothesis is currently being tested with rifabutin and carbamazepine
What are the Clinical Implications?

- Doses of <600 mg RIF can be tailored to represent weak, moderate and strong PXR-dependent induction. Standardize DDIs and facilitates extrapolation.

- Compared to CYP3A, strong induction of P-gp, OATP or CYP2C9 is unlikely to be elicited by potent PXR agonists.

- Observed relationships should apply to other inducers. This hypothesis is currently being tested with rifabutin and carbamazepine.

- Application of these results could provide for
  - More informed labeling recommendations
  - Decreased # of DDI studies via better leveraging of available data
Acknowledgments

We extend our thanks to the study subjects.

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