Drug Transporter Induction: Can We Leverage P450 Data to Streamline Our Clinical Pharmacology Programs?

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Transporter Induction: Uncertainty Negatively Affects Development/Labeling

-Assumed parity between transporters and CYP3A induction, but what if this isn’t true?
  - If DDI study performed: Possibly unnecessary study
  - If DDI study not performed: Conservative labeling
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Clinically relevant, known or potential strong CYP3A inducers assumed to be strong P-gp inducers

- Rifampin
- Rifabutin
- Phenytoin
- St. John’s Wort
- Rifapentine
- Phenobarbital
- Carbamazepine
- Tipranavir/Ritonavir
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  – phenytoin
  – Phenobarbital
  – Ritonavir

- Co-regulation of many transporters and P450s
  – Can one P450 induction study tell us anything about transporters?
Overview of Presentation:
3 Questions

1. Can P-gp induction be predicted from CYP3A?
2. Can induction of other transporters/P450s be predicted from CYP3A?
3. What are the implications for clinical development?
Rifampin: Dose Level Titration to Elicit Weak, Moderate, and Strong Induction

Study Design, Part 1

<table>
<thead>
<tr>
<th>Days 1–8</th>
<th>9–18</th>
<th>19–26</th>
<th>27–36</th>
<th>37–44</th>
</tr>
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<tbody>
<tr>
<td>Cassette</td>
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Cohort 1, n=20

- RIF 10 mg qd
- RIF 75 mg qd

♦ Rifampin (RIF) is a prototypical PXR agonist

Rifampin: Dose Level Titration to Elicit Weak, Moderate, and Strong Induction

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- Rifampin (RIF) is a prototypical PXR agonist
- Adaptive design attempting to target weak, moderate and strong CYP3A induction

Focused on P-gp vs. CYP3A, But What Else Can We Learn From This Study?

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<tr>
<th>Probe Drug Cassette</th>
<th>Dose</th>
<th>Abbreviation</th>
<th>Transporter/P450</th>
<th>Dosing Day</th>
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<tr>
<td>Dabigatran etexilate*</td>
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<td>P-gp</td>
<td>1</td>
</tr>
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<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>
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*CDE was analyzed as total dabigatran (TDAB), the sum of conjugated and unconjugated active species.*
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*DE was analyzed as total dabigatran (TDAB), the sum of conjugated and unconjugated active species.

- Are transporters as inducible as P450s?
- Is there a relationship between transporter and P450 induction?
Verification Step 1: Carbamazepine (CBZ) and Rifabutin (RBT)

Study Design, Part 2

<table>
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<tr>
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<tr>
<td>Escalated to CBZ 300 mg bid</td>
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<tr>
<td>Cassette</td>
<td></td>
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</tr>
<tr>
<td>RBT 300 mg qd</td>
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→ Do RIF relationships predict other inducers?
 Verification Step 2: Sofosbuvir (SOF), a P-gp Substrate

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|                | Escalated to CBZ 300 mg bid |       | RBT 300 mg qd |

- Do RIF relationships predict other inducers?
- Do RIF relationships predict other drug transporter substrates?
Overview of Presentation: 3 Questions

1. Can P-gp induction be predicted from CYP3A?
   - Establish: Relative RIF induction between probes
   - Verify (Step 1): P-gp induction by RBT and CBZ
   - Verify (Step 2): Decreased SOF exposure

2. Can induction of other transporters/P450s be predicted from CYP3A?

3. What are the implications for clinical development?
Probe Induction As a Function of RIF Dose

- Individual observed
- Mean observed

DDI (AUCR)
- Weak (0.5-0.8)
- Moderate (0.2-0.5)
- Strong (<0.2)
$E_{\text{max}}$ and $ED_{50}$ values were estimated for each probe

- $ED_{50} = 68$ mg
- $E_{\text{max}} = 15$

Max DDI $= 1/(1+E_{\text{max}})$

- RIF Dose, mg
- MDZ AUCR

- DDI (AUCR)
  - Weak
  - Moderate
  - Strong

♦ $ED_{50}$ and $E_{\text{max}}$: Induction affinity versus capacity
Midazolam Exposure is Decreased More Than Dabigatran

\[ ED_{50} = 68 \text{ mg} \]
\[ E_{\text{max}} = 15 \]

\[ ED_{50} = 54 \text{ mg} \]
\[ E_{\text{max}} = 2.2 \]

Are differences due to probe sensitivity?

- Weak
- Moderate
- Strong
P-gp is Less Inducible than CYP3A

ED_{50} = 68 mg  
E_{max} = 15  
E_{max,c}^* = 16

ED_{50} = 54 mg  
E_{max} = 2.2  
E_{max,c}^* = 3.7

\*E_{max,c} = E_{max} corrected for differences in probe sensitivity (f_{m/t})

Strong P-gp induction (>5-fold CL increase) is unlikely to be observed

How Do We Characterize and Interpret Relationships Between Probes?

- Can we predict Probe Y induction based on Probe X?
Example 1: Induction Parity Only Occurs When $E_{\text{max}}/ED_{50}$ Are Similar

- Combining $E_{\text{max}}/ED_{50}$ curves allows for evaluation of relative induction, independent of inducer

Green areas represent similar induction between probes
Example 2: Line Falls Outside of Area of Parity When Induction Affinity is Different

\[ \begin{align*} &E_{\text{max},x} = E_{\text{max},y} \\ &E_{50,x} > E_{50,y} \end{align*} \]

Green areas represent similar induction between probes

- Combining \( E_{\text{max}}/ED_{50} \) curves allows for evaluation of relative induction, independent of inducer.
Example 3: Line Falls Outside of Area of Parity 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 relative induction, independent of inducer

Green areas represent similar induction between probes
MDZ AUCR is Decreased More Than TDAB AUCR Across DDI Categories

Green areas represent similar induction between probes
Induction of P-gp is One DDI Category Weaker Than CYP3A

This relationship holds true when correcting for probe fraction metabolized/transported (f_{m/t})
How Do We Predict P-gp Induction by CBZ and RBT? Back to Basics

Black line is RIF
MDZ – TDAB relationship
RIF Induction Relationship: Directly Applied for CBZ and RBT Prediction

Black line is RIF MDZ – TDAB relationship

Blue area is predicted TDAB DDI category based on observed MDZ DDI
P-gp Induction by CBZ and RBT is Predicted by the RIF CYP3A – P-gp Relationship

Black line is RIF MDZ – TDAB relationship

Blue area is predicted TDAB DDI category based on observed MDZ DDI
How Do We Predict SOF Exposure Decrease?
Back to Basics

- Estimated

Black line is RIF
MDZ – TDAB relationship
SOF AUCR Can Be Predicted From TDAB AUCR

Black line is RIF
MDZ – TDAB relationship

Orange line is predicted
MDZ – SOF Relationship
“New SOF Relationship” Determines the SOF DDI Category at any MDZ AUCR

Orange line is predicted MDZ – SOF relationship

Orange area is predicted SOF DDI category based on observed MDZ DDI
Effect of RIF, CBZ and RBT on SOF is Predicted by MDZ – TDAB Relationship

CBZ and RBT considered moderate CYP3A inducers based on MDZ
Elicit weak induction of SOF CL/F (AUC ≥0.50)

Overview of Presentation: 3 Questions

1. Can P-gp induction be predicted from CYP3A?
   – Defined induction relationship between CYP3A and P-gp
   – Accurate prediction of RBT and CBZ induction
   – Accurate prediction of SOF exposure decrease

2. Can induction of other transporters/P450s be predicted from CYP3A?

3. What are the implications for clinical development?
Overview of Presentation: 3 Questions

1. Can P-gp induction be predicted from CYP3A?

2. Can induction of other transporters/P450s be predicted from CYP3A?
   – **Establish:** Relative RIF induction between probes
   – **Verify:** Transporter/P450 induction by RBT and CBZ

3. What are the implications for clinical development?
Like P-gp, Only Moderate Induction of OATP After High Dose RIF

- PRA and ROS results suggest that OATP, but not BCRP, is induced
- OATP induction is a working hypothesis
  - No change in PRA/ROS renal CL
  - More data is needed to substantiate
Like P-gp and OATP, Only Moderate Induction of CYP2C9 After High Dose RIF

- Weak induction of CYP1A2 was expected
OATP and CYP2C9 Induction Is Less than CYP3A

Both observed and corrected relationships fall above the area of parity.
P-gp, OATP and CYP2C9 Demonstrate Induction DDI Classification Parity

- The relationships between P-gp, OATP and CYP2C9 approximate the line of unity
- Suggests that induction is similar for all three

![Graphs showing the relationships between P-gp, OATP, and CYP2C9](image)

- Mean observed ± 90% CI
- Estimated
- Corrected
CBZ-Mediated OATP Induction is Under-Predicted

- **CBZ: CYP3A – OATP parity**
  - Both moderate
  - Is CBZ inducing via a non-PXR pathway?
    OATP is regulated by several non-PXR pathways

CBZ-Mediated OATP Induction is Under-Predicted, Unlike RBT

♦ RBT: Induction follows RIF CYP3A – OATP relationship
  Over-prediction is of less concern than under-prediction
RBT Induces OATP and CYP2C9 As Expected From the RIF Induction Relationships

diamond P-gp, CYP2C9 and CYP3A are all primarily PXR regulated
Simple co-regulatory system allows for accurate predictions
Overview of Presentation:
3 Questions

1. Can P-gp induction be predicted from CYP3A?

2. Can induction of other transporters/P450s be predicted from CYP3A?
   - Defined relationships between transporters and P450s
   - Accurate prediction of RBT induction
   - Presence and prediction of OATP induction is uncertain

3. What are the implications for clinical development?
Hypothesis and Mechanistic Interpretation

- Nuclear receptor involvement is important for predictability
  - Primarily PXR involvement:
    Strong CYP3A = Moderate P-gp, OATP, CYP2C9

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Nuclear receptor involvement is important for predictability

- Primarily PXR involvement:
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- Additional non-PXR agonism:
  - CYP3A may mispredict OATP induction magnitude

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    - Strong CYP3A = Moderate P-gp, OATP, CYP2C9
  - Additional non-PXR agonism:
    - CYP3A may mispredict OATP induction magnitude
  - Little to no PXR involvement:
    - More study is warranted

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<td>Primarily Non-PXR</td>
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<tr>
<td></td>
<td>Unknown if true or false; not tested but not recommended</td>
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Overview of Presentation: 3 Questions

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2. Can induction of other transporters/P450s be predicted from CYP3A?
3. What are the implications for clinical development?
Clinical Development Implications: Increased Utility of DDI Data

- RIF dose can be titrated to elicit weak, moderate and strong PXR-dependent induction as desired for DDI assessment

  Standardized DDIs and better facilitate transporter/P450 induction extrapolation
Clinical Development Implications: Strong Transport Induction Unlikely

- Doses of <600 mg RIF can be tailored to represent weak, moderate and strong PXR-dependent induction
  - Standardized DDIs facilitate transporter induction database development
- In contrast to P-gp, OATP and CYP2C9, only strong induction was observed with CYP3A after potent PXR agonism
Clinical Development Implications: Increased CBZ and RBT DDI Categorization

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

  Standardized DDIs facilitate transporter induction database development

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♦ Carbamazepine and rifabutin induction categorization:

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*Strong CYP3A inducer as per FDA DDI Guidance

Acknowledgments

I would like to thank the DDI-2019 conference organizers for inviting me to present today

This work was previously published:
