PEARLS OF
LABORATORY MEDICINE

Pharmacogenomics in Pain Management
DOI: 10.15428/CCTC.2013.212456

Gwen McMillin, PhD, DABCC(CC,TC)
University of Utah, ARUP Laboratories

www.traineeecouncil.org
© Clinical Chemistry
AACC
Pharmacogenomics of Drug Response

- Genes of pharmacodynamics
- Genes of pharmacokinetics
- Endogenous and Exogenous Factors

Drug Response Phenotype
Examples Pharmacogenomic Targets

➢ Pharmacokinetics genes
  ▪ Drug metabolizing enzymes
    - CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5
    - TPMT, NAT1/2, DPYD, G6PD, UGT1A1, UGT2B7

➢ Pharmacodynamics genes
  ▪ Receptors, ion channels, enzymes
    - VKORC1, IL28B, OPRM1, COMT, KRAS, EGFR, ABL1, ALK, BCR, KIT, DRD2, SCN9A, HLA-B, LDLR, ESR1/2
Drugs Used for Management of Pain

- Pain:
  - Opioids
  - NSAIDs
  - Cannabinoids
  - Muscle relaxants
  - Anticonvulsants
  - Others

- Mood:
  - Anxiolytics
  - Amphetamines
  - Antidepressants

- Sleep:
  - Benzodiazepines
## Opioids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Times more potent than codeine</th>
<th>Prodrug?</th>
<th>Plasma Half-life (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol</td>
<td>1</td>
<td>Y</td>
<td>4-8</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>6</td>
<td>Y</td>
<td>3-9</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
<td>N</td>
<td>1-7</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td>Y</td>
<td>3-6</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>70</td>
<td>N</td>
<td>8-10</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>400</td>
<td>N</td>
<td>26-42</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1000</td>
<td>N</td>
<td>3-12</td>
</tr>
<tr>
<td>Carfentany</td>
<td>100,000</td>
<td>N</td>
<td>7-8</td>
</tr>
</tbody>
</table>
Simplified Codeine Metabolism

This pathway diagram was downloaded from http://www.pharmgkb.org with permission given by PharmGKB and Stanford University (accessed August 29th, 2013)
CYP2D6 Phenotypes

- Poor (PM)
- Intermediate (IM) to Normal (Extensive, EM)
- Ultra Rapid (UM)

Can be affected by genotype and non-genetic factors
## CPIC guidance: CYP2D6 PM

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for codeine metabolism</th>
<th>Recommendations for codeine therapy</th>
<th>Classification of recommendation for codeine therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor metabolizer</td>
<td>Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief</td>
<td>Avoid codeine use due to lack of efficacy. Consider alternative analgesics such as morphine or a nonopioid. Consider avoiding tramadol.</td>
<td>STRONG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for codeine metabolism</th>
<th>Recommendations for codeine therapy</th>
<th>Classification of recommendation for codeine therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>Increased formation of morphine following codeine administration, leading to higher risk of toxicity</td>
<td>Avoid codeine use due to potential for toxicity. Consider alternative analgesics such as morphine or a nonopioid. Consider avoiding tramadol.</td>
<td>STRONG</td>
</tr>
</tbody>
</table>

# Example CYP2D6-Related Drugs

<table>
<thead>
<tr>
<th>Substrates activated by CYP2D6</th>
<th>Substrates inactivated by CYP2D6</th>
<th>Strong inhibitors</th>
<th>Moderate-Weak inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Fluoxetine</td>
<td>Fluoxetine</td>
<td>Diphenhydramine</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Paroxetine</td>
<td>Paroxetine</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Amphetamine</td>
<td>Quinidine</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Atomoxetine</td>
<td>Bupropion</td>
<td>Methadone</td>
</tr>
</tbody>
</table>
## Examples of CYPs and Analgesics

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>CYP2D6</th>
<th>CYP2C19</th>
<th>CYP2B6</th>
<th>CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td></td>
<td></td>
<td>Inactivated</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Codeine</td>
<td>ACTIVATED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td></td>
<td></td>
<td>Inactivated</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>Inhibitor</td>
<td>Inactivated – minor route</td>
<td>Inactivated</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Morphine</td>
<td>Inactivated – minor route</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>ACTIVATED</td>
<td></td>
<td></td>
<td>Inactivated</td>
</tr>
<tr>
<td>Tramadol</td>
<td>ACTIVATED</td>
<td>Inactivated – minor route</td>
<td>Inactivated</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

➢ Pharmacogenomic testing can add to the information used to guide drug and dose selection, and personalize pharmacotherapy

➢ Pre-therapeutic CYP2D6 genotype testing may identify patients at risk for therapeutic failure or adverse effects when administered codeine, and potentially other CYP2D6 substrates
References

Review articles:

Websites:
- http://www.pharmgkb.org/page/cpic
- http://www.cypalleles.ki.se
- http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm
Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership**: ARUP Laboratories
- **Consultant or Advisory Role**: ARUP Laboratories
- **Stock Ownership**: None declared
- **Honoraria**: None declared
- **Research Funding**: None declared
- **Expert Testimony**: None declared
- **Patents**: None declared
Thank you for participating in this Clinical Chemistry Trainee Council Pearl of Laboratory Medicine.

Find our upcoming Pearls and other Trainee Council information at www.traineecouncil.org

Download the free Clinical Chemistry app on iTunes today for additional content!

Follow us: