The Future is Here: Understanding & Applying Pharmacogenetics in Pain Management

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Conflict of Interest Disclosure

• Authors Conflicts of Interest
  – C. Carlson, No Conflict of Interest

Outline

• Brief Review of Genetics
• CYP450 Enzymes
• Pharmacokinetics, Pharmacodynamics, Pharmacogenetics, & Pharmacogenomics
• Phase I & Phase II Metabolism
• Metabolism Phenotypes
• Medication Interactions & Pharmacogenetics
• Case studies
Objectives

1. Describe the fundamentals of the CYP450 enzyme system including the nomenclature & variations in drug metabolism
2. Compare & contrast the genetic & environmental influences on the CYP450 enzyme system
3. List indications for CYP450 testing for pain management & treatment strategies to maximize effectiveness of pain management medications

DNA, Genes, & Chromosomes

DNA
- Deoxyribonucleic acid, is the genetic material in a cell that composes genes

Gene
- Specific segment(s) of DNA that contains the genetic code for a specific protein

Chromosome
- A structure that is a large chunk of DNA containing many genes

Genome
- The human genome has a little bit of genetic variation
  - less than 1 percent of our DNA gives each of us a unique personality, appearance & health profile
- Different gene versions called alleles
- Allele – one member of a pair of genes occupying a specific spot on a particular chromosome that determines a trait. 1
  - If pair of alleles are the same – homozygous
  - If different - heterozygous
- Just beginning to use genetics for dx & tx of medical conditions/predictions of response to medications
Polymorphisms in Genes Impact Medication Responses

• Polymorphisms, also referred to as genetic variance
• Single-nucleotide polymorphisms (SNPs) in the gene encoding for the Mu-Opioid Receptor (MOR) may contribute to variability in the analgesic response to morphine
• Polymorphisms in the genes encoding for opioid transport have been linked to variability in opioid response
• Polymorphisms within metabolizing enzymes have an important effect on an individual's response to opioids (Cytochrome p450)

What Is Cytochrome p450?

• A large & diverse family of enzymes that uses endogenous & exogenous compounds as substrates in enzymatic reactions
• Produced by Cytochrome p450 genes
• Involved in the formation (synthesis) & breakdown (metabolism) of various molecules & chemicals within cells
• Act on a variety of endogenous substrates
  – Including fatty acids, cholesterol, vitamin D derivatives, steroids hormones, & bile acids
• Also act on exogenous compounds
  – Including environmental chemicals, medications, pollutants, & natural plant products

Where are the CYP450 Enzymes located?

• Primarily found in liver cells
  – Also located in cells throughout the body
• Within cells, cytochrome P450 enzymes are located
  1. In a structure involved in protein processing and transport (endoplasmic reticulum)
     • Usually metabolize external substances, primarily medications and environmental pollutants
  2. In the energy-producing centers of cells (mitochondria)
     • Generally involved in the synthesis and metabolism of internal substances
Cytochrome P450 enzymes account for 70 percent to 80 percent of enzymes involved in drug metabolism.

How Did Cytochrome p450 Get Its Name?
- They are bound to membranes within a cell (cyto)
- Contain a heme pigment (chrome & P)
- Absorbs light at a wavelength of 450 nm when exposed to carbon monoxide

CYP450 Nomenclature

Nomenclature system for designating enzymes and alleles of cytochrome P450
Humans Have 18 Families of Cytochrome P450 Genes & 43 Subfamilies

- Top 3 for Drug Metabolism:
  - CYP1 drug metabolism (3 subfamilies, 3 genes)
  - CYP2 drug & steroid metabolism (13 subfamilies, 16 genes)
  - CYP3 drug metabolism (1 subfamily, 4 genes)

CYP450 Opioid Metabolism

- codeine: CYP2D6; CYP3A4
- hydrocodone: CYP2D6; CYP3A4
- oxycodone: CYP2D6; CYP3A4
- fentanyl: CYP3A4; CYP3A5
- methadone: CYP3A4; CYP2C19; CYP2D6
- meperidine: CYP3A4; CYP2C19
- buprenorphine: CYP3A4; CYP3A5; CYP2C19; 2D6
- sufentanil: CYP3A4
- tapentadol: CYP2C9; CYP2C19; CYP2D6; UGT
- oxymorphone: liver, none CYP450
- hydromorphone: primarily UGT, liver
- morphine:
CYP450 Enzymes Involved in Opioid Metabolism

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Metabolizes % of Medications</th>
<th>Functions Metabolized</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D6</td>
<td>20%-30%</td>
<td>Antidepressants, SSRI, TCA, Opioids, Steroids, Anesthetics</td>
</tr>
<tr>
<td>2B6</td>
<td>2%-8%</td>
<td>Methadone, Steroids, Anesthetics, HIV medications, HMG-CoA reductase inhibitors (statins)</td>
</tr>
<tr>
<td>3A4</td>
<td>40%-50%</td>
<td>Opioids (e.g., fentanyl), HIV medications, HMG-CoA reductase inhibitors (statins)</td>
</tr>
</tbody>
</table>

Definitions

- **Pharmacokinetics**
  - An individual’s rate & extent of drug absorption, distribution, metabolism, & excretion

- **Pharmacodynamics**
  - Study of the pharmacologic effect resulting from the interaction between the drug & the biologic system (drug target or receptor)

Definitions Cont.....

- **Pharmacogenetics**
  - An individual’s genetic influence on both the pharmacokinetics & pharmacodynamics
    - Usually looking at individual genes

- **Pharmacogenomics**
  - The science that examines the inherited variations in genes that dictate drug response, predicting whether a patient will have a good or bad response to a drug or no response
    - Looking at all genes in the human genome
Factors Affecting Metabolism & Outcomes

<table>
<thead>
<tr>
<th>Intrinsic (Internal)</th>
<th>Extrinsic (external)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger age¹</td>
<td>Sunlight²</td>
</tr>
<tr>
<td>Female sex¹</td>
<td>Excessive alcohol intake³</td>
</tr>
<tr>
<td>Liver impairment⁶</td>
<td>Medication interactions²</td>
</tr>
<tr>
<td>Race⁵</td>
<td>Older⁴</td>
</tr>
<tr>
<td>Genetic variability⁷</td>
<td>Active lifestyle⁴</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extrinsic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age¹</td>
</tr>
<tr>
<td>Male sex¹</td>
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<tr>
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<tr>
<td>Race⁵</td>
</tr>
<tr>
<td>Genetic variability⁷</td>
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Pharmacogenetics

- The study of how genes affect the individual response to medications
- Intended to maximize efficacy & minimize side effects

Medication Metabolism Typically Occur in Phase I & Phase II Metabolism
Pro-opioids that Require Conversion to an Active Metabolite

- codeine → morphine
- hydrocodone → hydromorphone
- oxycodone → oxymorphone
- tramadol → O-desmethytramadol

These opioids primarily rely on the enzyme CYP-2D6 to make the conversion.

Opioids that act directly on opioid receptors without the necessity of metabolic conversion
- fentanyl
- morphine
- oxymorphone
- hydromorphone
- meperidine

Phase I Metabolism

- Can activate or inactivate a drug
- Codeine, oxycodone, hydrocodone, fentanyl, methadone, & tramadol are metabolized by Phase 1 enzymes
- Final product usually contains a chemical reactive functional group
  - OH, NH2, SH, COOH
- Predominantly oxidative or hydrolytic reactions

Phase I Cont...

- This functional group can be acted upon by the phase II or conjugative enzymes
- Main function of Phase I metabolism is to prepare the compound for phase II metabolism, not excretion.
Phase II Metabolism

- There are several important superfamilies of enzymes active in phase II metabolism
- Enzymes of the UDP-glucuronosyltransferase (UGT) superfamily are important for opioid metabolism
- Morphine, oxymorphone, & hydromorphone are metabolized by phase 2 glucuronidation – UGT Conjugating Enzymes

Phase II Cont....

- Phase II is usually the true detoxification of drugs
- Occurs mostly in cytosol of the cell
- Gives products that are generally water soluble & easily excreted

Differences Between Phase I and Phase II Drug Metabolism

- Active: Works in your body, metabolism, ready to be removed from your body
- Prodrug (Inactive Drug): No effect in your body, metabolism, works in your body, metabolism, ready to be removed from your body
Metabolism Phenotypes

• Poor metabolizers (PMs)
  – Metabolizes medications at a significantly lower rate than normal or not at all
  – Are either heterozygous for different inactivating alleles or homozygous for an inactivating allele
  – Results in increased risk of side effects which could be lethal
  – Need lower doses

• Variations are the results of differences in a person’s genetics, particularly as related to their alleles

Metabolism Phenotypes Cont....

• Intermediate metabolizers (IMs)
  – Metabolizes medications at a somewhat lower rate than normal
  – Carry one allele that is functional & one allele that is nonfunctional – heterozygous
  – Or has 2 partially deficient alleles

• May need a lower dose of the medication

Metabolism Phenotypes Cont....

• Extensive metabolizers (EMs - normal)
  – Metabolizes medications at a normal rate & is the basis for most standard dosaging
  – Have 2 functional alleles

• Ultrarapid metabolizer (UMs)
  – Metabolizes medications at a significantly higher rate than normal
  – Have more than 2 functional alleles from gene duplication resulting in rapid metabolism
  – Results in decreased bioavailability of the drug with poor therapeutic response
  – May need higher dose than the standard for that medication
### Clinical Consequence of Metabolizer Phenotypes on Drug Response

<table>
<thead>
<tr>
<th>Drug type</th>
<th>Metabolizer phenotype</th>
<th>Effect on drug metabolism</th>
<th>Potential consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug, needs metabolism to work (e.g., codeine metabolized to morphine)</td>
<td>Poor to intermediate</td>
<td>Slow</td>
<td>Poor drug efficacy, patient at risk of therapeutic failure Accumulation of prodrug, patient at increased risk of drug-induced side effects</td>
</tr>
<tr>
<td></td>
<td>Ultrarapid Fast</td>
<td></td>
<td>Good drug efficacy, rapid effect</td>
</tr>
<tr>
<td>Active drug metabolized to inactive drug (e.g., morphine to</td>
<td>Poor to intermediate</td>
<td>Slow</td>
<td>Good drug efficacy, rapid effect</td>
</tr>
<tr>
<td></td>
<td>Ultrarapid Fast</td>
<td></td>
<td>Poor drug efficacy, patient at risk of therapeutic failure</td>
</tr>
</tbody>
</table>

### Clinical Consequences of Genetic Polymorphism: Prodrug (Inactive Parent Compound)

- Decreased pain relief
- Low active metabolite
- High doses required for effect
- Increased pain relief
- High active metabolite
- Low doses required for effect

### Clinical Consequences of Genetic Polymorphism: Active Parent Compound

- Increased pain relief
- Risk of adverse events due to accumulation
- Low doses required for effect
- Decreased pain relief
- Drug excreted rapidly
- High doses required for effect
**Drug Interaction Terminology**

- **Substrate**
  - Any medication metabolized by that enzyme
- **Inhibitor**
  - A medication that slows the metabolism of another medication which may result in excessively high blood levels, extended effect, and related toxicity
  - **IF** this is a drug that has to be activated (a prodrug), there may be decreased effect

**Inhibitors**

**Drug Interactions Cont....**

- **Inducer**
  - A medication that boosts the metabolism of another medication, which may result in accelerated breakdown, increased clearance, shorted duration, subtherapeutic levels or withdrawal
    - May also cause increased activity with a prodrug
Implications of Race

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Metabolizer phenotype</th>
<th>Population frequency (%)</th>
<th>Asia</th>
<th>Blacks</th>
<th>Whites</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>Poor</td>
<td>0.4</td>
<td>0.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>3.5</td>
<td>13</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ultrarapid</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Poor</td>
<td>18 to 23</td>
<td>1.2 to 5.3</td>
<td>2.0 to 5.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>30</td>
<td>29</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ultrarapid</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Poor</td>
<td>1.0 to 4.8</td>
<td>1.9 to 7.3</td>
<td>7.0 to 10</td>
<td></td>
</tr>
</tbody>
</table>

Implications of Gender

- CYP3A is more active in women than men
- CYP2D6 is more active in women than men
- CYP1A is more active in men than women
- CYP2E1 is more active in men than women
Medication Interactions & Pharmacogenetics

- Polypharmacy is extremely common in the US\(^1\)
- Adverse effects increase exponentially with ≥ 4 prescription medications\(^2\)
- Medication interactions often occur due to changes in metabolism\(^3\)
- Due to other medications metabolized through the same pathways
- Due to inducers/inhibitors of the same pathways
- Metabolic differences may increase risk for medication interactions

Potential Indicators of a Genetic Metabolic Defect

- Patients reporting little or no pain relief with hydrocodone, codeine &/or tramadol (may indicate a CYP2D6 Poor Metabolizer)
- Patients who report a severe adverse event within 30 minutes of taking an opioid such as codeine, oxycodone or hydrocodone (may indicate a CYP2D6 Rapid Metabolizer)
- Patients reporting numerous opioid allergies or a family history of intolerance to numerous opioids

Cont....

- Patients reporting a past experience that required a higher than typical dose of anesthesia
- Patients with a genetic or inheritable disease that is the cause of their pain E.G ankylosing spondylitis, Marfan’s syndrome
- Patients reporting adverse events to alcohol or the need to use higher amounts of alcohol for any effect
1. Have you ever taken hydrocodone (Vicodin®, Lortab®, or Norco®)?  
   - Yes  
   - No  
   - Never Taken

2. Did you get pain relief from it?  
   - Yes  
   - No  
   - Some

3. Have you taken a pain reliever with codeine in it (Empirin®, Fiorinal®, Fioricol®)?  
   - Yes  
   - No  
   - Never Taken

4. Did you get pain relief from it?  
   - Yes  
   - No  
   - Some

5. Have you ever taken tramadol (Ultram®)?  
   - Yes  
   - No  
   - Never Taken

6. Did you get pain relief from it?  
   - Yes  
   - No  
   - Some

7. Have you taken oxycodone (Percocet®, Oxycontin®), methadone, fentanyl (Duragesic®), or hydrocodone (Vicodin®, Lortab®, Norco®) & had any of the following reactions within 30 minutes after taking your first dose?  
   - Vomiting  
   - Headache  
   - Breathlessness  
   - Flushing  
   - Itching  
   - Dizziness  
   - Allergic reaction

Which drugs gave you the reaction?  

8. Were you ever told that you are allergic to a pain relief medication? If so, which one(s)?

9. Did you have a close relative who is either allergic to a pain medication or finds that he or she does not get pain relief with opioids?  
   - Yes
   - No

Which relative?  

Which medication?  

10. When you had surgery, dental work, delivery, or other medical procedure, did your doctor tell you that you needed more anesthesia or pain relief medication?  
    - Yes  
    - No

11. Have you always had to take a high dose of pain medication to get relief?  
    - Yes  
    - No

12. Do you have a genetic or inheritable disease that is the cause of your pain?  
    - Yes  
    - No

If yes, what is the name of your inherited disease?

13. Have you ever had a severe reaction to any of the following:  
    - Antidepressant  
    - Antihistamine  
    - Antibiotic  
    - Anti-hypertensive

Case Study: Ralph

- 85-year-old male  
- Failed back syndrome  
- Recent event resulted in presentation to physician’s office nearly obtunded

Ralph Cont….

- Patient history  
  - No alcohol use  
  - No history of drug abuse/misuse  
  - PMH: PVD, HTN, dyslipidemia  
  - Medications: ASA qd, propranolol 40mg qd, pravastatin 40mg qd

- Stable for years on current opioid  
- Current pain regimen:  
  - oxycodone ER 60mg Q12h  
  - oxycodone IR 15mg QID prn  
  - duloxetine 30mg BID  
  - lidocaine topical patch 5%
Ralph UDT Results

<table>
<thead>
<tr>
<th>Medication</th>
<th>Form</th>
<th>Outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxycodone</td>
<td>Parent</td>
<td>Positive</td>
<td>28854</td>
</tr>
<tr>
<td>oxymorphone</td>
<td>Metabolite</td>
<td>Positive</td>
<td>608</td>
</tr>
<tr>
<td>noroxycodone</td>
<td>Metabolite</td>
<td>Positive</td>
<td>2284</td>
</tr>
<tr>
<td>duloxetine</td>
<td>Parent</td>
<td>Positive</td>
<td>277</td>
</tr>
</tbody>
</table>

Ralph Pharmacogenetic Test (PGT) Results

Pharmacogenetic Test (PGT) results: CYP2D6 poor metabolize

<table>
<thead>
<tr>
<th>Metabolism Profile</th>
<th>Parent Drug Metabolite(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POOR CYP2D6</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Low</td>
</tr>
</tbody>
</table>

Potential Clinical Impact
- Unexpected therapeutic response
- Increased risk for adverse effects
- Increased risk for medication interactions
- Possible need for dose adjustment or medication change

Ralph Additional Considerations

Pharmacogenetic test (PGT) results: CYP2D6 PM
- He had been stable on her opioid for many years
- But had been started on fluconazole by his PCP for a fungal infection
- Fluconazole is a potent CYP3A4 inhibitor
- Administration of CYP3A4 inhibitors can increase opioid concentrations, thereby prolonging and intensifying both analgesic and adverse effects
- His CYP2D6 PM status put him at an increased risk for medication interactions, and the addition of fluconazole meant both metabolic clearance pathways were inhibited (CYP2D6 & CYP3A4)
Benefits of Pharmacogenetic Testing

<table>
<thead>
<tr>
<th>Potential Benefit</th>
<th>Examples/Comments</th>
</tr>
</thead>
</table>
| Explain or predict patient response to medication | • Higher-than-expected adverse effects
• Lower-than-expected efficacy
• Treatment failure |
| Avoid medication interactions | • Some medications inhibit or induce CYP450 enzymes |
| Reduce the need for opioid rotation | • More predictive opioid trials
• Reduce the likelihood of repeat negative outcomes if rotating between products that are metabolized in the same way |
| Document decision to continue current medication regimen | • Explanation for higher doses to achieve optimal analgesia |
| Individualize treatment | • Help prescribers find the most effective and safest medication for a patient |

James Case Presentation

• 42-year-old male
• Chronic low back pain resulting from car accident
• Referred for inadequate pain relief and pain-related difficulty performing daily activities despite multiple opioid dose increases

James Cont...

Pain characteristics
• Moderate to severe chronic pain

Medication history
• ibuprofen: Inadequate relief
• tramadol: Inadequate relief
• hydrocodone/APAP: Minimal pain relief despite multiple dose increases
James UDT

<table>
<thead>
<tr>
<th>Medication</th>
<th>Form</th>
<th>Outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>hydrocodone</td>
<td>Parent</td>
<td>Positive</td>
<td>5764</td>
</tr>
<tr>
<td>norhydrocodone</td>
<td>Metabolite</td>
<td>Positive</td>
<td>4918</td>
</tr>
<tr>
<td>hydromorphone</td>
<td>Metabolite</td>
<td>Negative</td>
<td>--</td>
</tr>
</tbody>
</table>

UDT indicates that James is taking the prescribed medication:
- No other medications detected that could affect response
- Consider pharmacogenetic testing to guide treatment plan

James Cont..

Pharmacogenetic Test (PGT) results: CYP2D6 poor metabolizer

<table>
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<tr>
<th>Metabolism Profile</th>
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Unexpected therapeutic response:
- Increased risk for adverse effects
- Increased risk for medication interactions
- Possible need for dose adjustment or medication change

More Case Studies

- Elderly lady (high dose oxycodone originally) – opioid rotation to morphine:
  - Calculated equivalent dose - 30% → good analgesia for patient but severe somnolence + cognitive dysfunction
  - CD6 poor metabolizer.
  - Morphine through different pathway (UGT)
  - Usual dosing equivalent calculations NOT applicable
  - Consider starting much lower dose as if first opioid prescription/opioid naive
More Case Studies

Another patient
• Intermediate for 2CP + 2D6, ultrarapid metabolizer 2C19
• Patient on 60mg QID oxycodone but only 40% relief for 3-4 hrs with each dose
2D6 poor metabolizer
• (Changed to oxymorphone IR – 60% relief for 5-6 hours)
Best choices for both patients would be hydromorphone ER, oxymorphone ER, buprenorphine transdermal

Pharmacogenetic Testing may help to:
• Explain & predict patient response to medication & abnormal UDT results
• Avoid medication interactions
• Reduce the number of opioid rotations by avoiding the use of medications that may repeat negative outcomes because of a genetic variant
• Support the decision to continue or change medication regimen
• Find a safe & effective medication for the individual patient

Pharmacogenetic testing may help to:
• Prevent likelihood of an adverse drug reaction
• Increase drug efficacy
• Improve patient medication compliance, especially with knowledge of their genetic test results
• Reduce healthcare costs by preventing adverse events or poor efficacy or unhelpful opioid rotations or trials
References