Analgesics and the Effects of Pharmacogenomics

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Disclosures: none
Learning Objectives

2. Identify the most common polymorphisms in drug-metabolizing enzymes that influence analgesics.
3. Describe strategies for modifying analgesic regimens based on pharmacogenomics.
Before there was the need for analgesia, there was...
Multifactorial Influences

- Personality
- Socio-economic status
- Environment
- Prior stress or trauma
- Secondary gain
- Genetics
Genetic influence on pain sensitivity

Genetic influence on analgesic medications
Genetic Influences on Pain
- Cases of Absent Pain

- Some rare cases explained by genetics
- Loss-of-function mutations
  - α-subunit of voltage-gated sodium channel
  - Other components that regulate functioning and homeostasis of nervous system

Genetic Influences on Pain
- Twin Studies

• 2007- Thermal & chemical noxious stimuli
  ▪ 98 pairs of twins
  ▪ 22-55% of variability was genetic

• 2008- Thermal noxious stimuli
  ▪ 96 twins
  ▪ Cold-pressor pain
    • 7% of variability was genetic
  ▪ Heat pain
    • 3% of variability

Smith M et al. *Clinical Genetics* 2012
Norbury T et al. *Brain* 2007
Genetic Influences on Pain
- Twin Studies

• 2012- Thermal noxious stimuli, \( \mu \)-agonists
  ▪ 112 pairs of twins
  ▪ Pain tolerance and opioid analgesia
  ▪ Cold-pressor pain
    • 24-32\% of variability was genetic
  ▪ Heat pain
    • 12-60\% of variability was genetic

Angst M et al. *Pain* 2012
Analgesics and Genetics: Pharmacokinetics and Pharmacodynamics
Genetic variation affects Pharmacokinetics

- Distribution
- Metabolism
- Absorption
- Elimination

Pharmacokinetics
Genetic variation affects pharmacokinetics

- Distribution
- Metabolism
- Absorption
- Elimination
Analgesic Metabolism
Pharmacokinetics
- Phase I Enzymes

• Cytochrome P450 superfamily
• Alter the chemical structure of drugs
  ▪ Six most significant CYPs
    • 3A4/5  37-60% of drugs
    • 2D6   15-25% of drugs *CODEINE*
    • 2C19  10%
    • 1A2   9%
    • 2E1   2%
    • 2B6   4%
<table>
<thead>
<tr>
<th>Drug</th>
<th>P450</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analgesics</strong></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Phase II (+3A4/5, 2E1)</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>3A4/5</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>2C9, 3A4/5</td>
</tr>
<tr>
<td>Codeine</td>
<td>2D6</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>2C9</td>
</tr>
<tr>
<td>Etodolac</td>
<td>2C9</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>3A4/5</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>2D6, 3A4/5</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2C9, 3A4/5</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2C9, 2C8</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>2C9</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>2C9, 3A4/5</td>
</tr>
<tr>
<td>Meperidine</td>
<td>2B6, 3A4/5, 2C19</td>
</tr>
<tr>
<td>Methadone</td>
<td>2B6, 2C19, (3A4/5?)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>2C9, 1A2, 2C8</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>2D6, 3A4/5</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>2C9</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>3A4/5</td>
</tr>
<tr>
<td>Tramadol</td>
<td>2D6, 2B6, 3A4/5</td>
</tr>
</tbody>
</table>

**Pharmacokinetics - Phase I Enzymes**

Zanger et al. *Analytical and Bioanalytical Chem* 2008
CYP 2D6

- 2D6 is highly polymorphic
- Alleles defined as
  - Normal, Reduced, Non-functional

<table>
<thead>
<tr>
<th>Metabolizer (Phenotype)</th>
<th>Active alleles</th>
<th>Reduced function</th>
<th>Non-functional alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid (UM)</td>
<td>&gt; 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive (EM)</td>
<td>1-2</td>
<td>0-1</td>
<td>0-1</td>
</tr>
<tr>
<td>Intermediate (IM)</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Poor metabolizers (PM)</td>
<td></td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>
CYP 2D6

- Ultrarapid Metabolizers (UMs)

Mean Prevalence of UM Phenotype (%)

- African/Ethiopian: 29%
- African American: 7%
- Asian: 2%
- Caucasian: 7%
- Northern European: 2%
CYP 2D6

- selected drug targets

• Oxycodone
• Hydrocodone
• Tramadol ➔ pro-drug, requires activation
• Codeine ➔ pro-drug, requires activation
Pharmacokinetics
- Phase II Enzymes

• UGT enzymes
  ▪ Glucuronidation of drugs
  ▪ UGT2B7 has genetic polymorphism

• Many opioids have –OH (hydroxyl) group
  ▪ Morphine, M3G, M6G
  ▪ Codeine
  ▪ Hydromorphone
  ▪ Oxymorphone
  ▪ Naloxone and Naltrexone
Case report: Codeine & Tonsillectomy

Codeine and morphine pathway

Pharmacokinetics:

Representation of the candidate genes involved in metabolism of codeine and morphine.

Legend

This pathway depicts, in a stylized human liver cell, the principal candidate pharmacogenes involved in the pharmacokinetics of codeine and morphine. Modulation of the pharmacokinetic conversion of codeine to morphine by variation in the CYP2D6 gene is a well-known example of pharmacogenetics.

Codeine and morphine are pain relief drugs in the opiate family. Both drugs are found naturally in the poppy plant, Papaver somniferum, but for commercial use, codeine is usually synthesized from morphine, which is more abundant in nature. In addition to their analgesic effects, both drugs have antitussive effects and antidiarrheal activity. Side effects include respiratory depression, constipation, sedation and addiction.

Codeine is a less potent agonist of the mu opioid receptor (OPRM1) than morphine and is considered a safer alternative in an outpatient setting.

However, recent reports of severe adverse events in breastfed infants whose mothers had altered metabolism of codeine [PMID: 16920476, 18719619] have led to an FDA warning on prescription of codeine to nursing mothers [http://www.fda.gov/bbs/topics/NEWS/2007/NEW01685.html].

The principal pathways for metabolism of codeine occur in the liver, although some metabolism occurs in the intestine and brain [PMIDs: 18187562, 8875123]. Approximately 50-70% of codeine is converted to...
Case report: Codeine & Tonsillectomy

- 4 year-old boy (27.6 kg) with obstructive sleep apnea and recurrent tonsillitis
- Underwent adenotonsillectomy
- Discharged on POD #1
- Prescribed codeine 8 mg/dose q 4-6 hrs
  - Received a total of 4 doses

Case report: Codeine & Tonsillectomy

• POD #2
  ▪ Parents found him pulseless
• Postmortem analysis revealed bronchopneumonia and suggested respiratory arrest
• Codeine and Morphine blood levels were measured…

# Case report: Codeine & Tonsillectomy

<table>
<thead>
<tr>
<th>Drug/Metabolite</th>
<th>Measured Blood Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Within expected range</td>
</tr>
<tr>
<td>Morphine</td>
<td>17.6 ng/mL</td>
</tr>
</tbody>
</table>

Therapeutic morphine concentration is 4.5 +/- 2.1 ng/mL

Genetic variation also affects Pharmacodynamics

- Receptor morphology
- Receptor duplication
- Target site concentration
- Downstream events

Pharmacodynamics
µ-Opioid Receptor

- *OPRM1* encodes µ-Opioid Receptor
- G protein-coupled K+ channel
- 118A>G SNP influences binding of opioids and activation
  - G/G genotype has less benefit from opioids
  - However, less adverse effects as well

Oertel, B. et al. *Pharmacogenet Genomics* 2006
κ-Opioid Receptor

- *MC1R* encodes Melanocortin-1 receptor
- Improved analgesia of κ-opioid agonists in red-haired, fair-skinned women
  - 75% carry 2 or more inactive variants
  - Consider incorporating κ-opioid analgesics in these patients (e.g. pentazocine)
- Non-gender specific μ-opioid agonist pain modulation
  - Potency of morphine increased in inactive variants

Mogil, J et al. *Proc Natl Acad Sci USA* 2003
Genetic variation also affects **Pharmacodynamics**

- Target site concentration
- Receptor morphology
- Receptor duplication
- Downstream events
ABCB1/MDR1 transporter

• Removes drugs from intracellular compartment
• 3435 C>T SNP, T/T genotype has 4-fold less protein expression
  ▪ Require less oral opioids for analgesia
  ▪ Possibly due to increased drug absorption and concentration at site of action
• 2677 G>T/A SNP
  ▪ A allele protective of central side effects

Genetic variation also affects Pharmacodynamics.

- Receptor morphology
- Receptor duplication
- Target site concentration
- Downstream events

Pharmacodynamics
Catechol-O-methyltransferase

- Metabolizes and inactivates catecholamines
- Regulator of Dopamine, Epinephrine, and Norepinephrine in the pain pathway
- 472 G>A SNP
  - Patients require less morphine
  - Perhaps low-function COMT leads to up-regulation of μ-opioid receptor

Rakvag T et al. *Pain* 2005
Berthele A et al. *Neuroimage* 2005
OPRM1 and COMT likely interact with Pain through their respective genotypes.

- **OPRM1 genotype**
- **COMT genotype**
- **ABCB1 genotype**
ABC B1 & OPRM1 interaction

- Morphine analgesia
- ABCB1 transporter
  - T allele = less function
- OPRM1 mu-opioid receptor
  - G allele = less affinity of receptor for morphine

Average pain, nausea, and sedation scores in the early postoperative period with morphine PCA.

(A) Pain scores.
No significant difference in terms of pain relief was found among the combinations of genotypes.

(B and C), Sedation & nausea scores. Significant difference when genotypes OPRM1 and COMT were combined. (*P<0.05; **P< 0.01).

Kolesnikov Y. et al. Anesthesia & Analgesia 2011
Non-Opioid Analgesics and Genetics
NSAIDs

• Example: Ibuprofen
• Major metabolic enzyme is CYP2C9
  - Some 2C9 polymorphisms decrease enzyme function
• UGTs metabolize 10-15%

Mazaleuskaya L et al. *Pharmacogenet Genomics* 2015
CYP2C9 Genotype and NSAID clearance

*3/*3 genotype has only 25% of the clearance as compared to *1/*1 (wild type) genotype
Translational Potential of Genetics

• More important than dose adaptations could be genetic guidance on the choice of analgesic
• Genetics-based dosing regimens?
• Chronic pain population...large potential for benefit
## Adjustment of Morphine Dose?

### TABLE 1. Preliminary Recommendation for Dose Adaptations Based on SNPs: For Carriers With 1 Variant or a Combination of Variants of OPRM1, COMT, and MCR1

<table>
<thead>
<tr>
<th>OPRM1 118G</th>
<th>COMT 472A</th>
<th>2 × MCR1 Nonfunctional SNP</th>
<th>Resulting Factor by Which the Individual Dose May be Adapted</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>—</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>—</td>
<td>0.67</td>
<td>—</td>
<td>0.67</td>
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<tr>
<td>—</td>
<td>—</td>
<td>0.67</td>
<td>0.67</td>
</tr>
<tr>
<td>2</td>
<td>0.67</td>
<td>—</td>
<td>1.33</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>0.67</td>
<td>1.33</td>
</tr>
<tr>
<td>—</td>
<td>0.67</td>
<td>0.67</td>
<td>0.40</td>
</tr>
<tr>
<td>2</td>
<td>0.67</td>
<td>0.67</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Lotsch J & Geisslinger G *Pain* 2006
**CPIC Guidelines for Codeine Therapy in the Context of CYP2D6 Genotype**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for Codeine</th>
<th>Recommendations for codeine therapy</th>
<th>Classification of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>Increased formation of morphine, risk of toxicity</td>
<td>Avoid codeine. Consider morphine or nonopioid. Consider avoiding tramadol</td>
<td>Strong</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Normal morphine formation</td>
<td>15-60 mg q4 hrs</td>
<td>Strong</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Reduced morphine formation</td>
<td>15-60 mg q4 hrs. If no response, consider alternative</td>
<td>Moderate</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Greatly reduced morphine formation, insufficient pain relief</td>
<td>Avoid codeine. Consider morphine or nonopioid. Consider avoiding tramadol</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Crews K et al. *Clin Pharm Ther* 2012
WARNING: DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE

Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.

INDICATIONS AND USAGE

Codeine sulfate is an opioid analgesic indicated for the management of mild to moderately severe pain where the use of an opioid analgesic is appropriate. (1)
References


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