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…

PAIN

Multifactorial Influences

Genetics

Secondary gain

Socio-economic status

Environment

Prior stress or trauma

Personality

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 was genetic

Analgesics and Genetics:
Pharmacokinetics and Pharmacodynamics

Genetic variation affects Pharmakinetiics
- Distribution
- Metabolism
- Absorption
- Elimination

Genetic variation affects Pharmakinetiics
- Distribution
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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%

Zanger et al. Analytical and Bioanalytical Chem 2008

CYP 2D6

• 2D6 is highly polymorphic
• Alleles defined as
  • Normal, Reduced, Non-functional
  - Metabolizer Phenotype
    - Activity Score
    - Active alleles
    - Reduced function
    - Non-functional alleles

Ultrarapid > 2 > 2
Extensive 1-2 1-2 0-1 0-1
Intermediate 0.5 1 1
Poor 0 2

CYP 2D6 - Ultrarapid Metabolizers (UMs)

Frequency of 2D6 metabolizer phenotypes in Caucasians

<table>
<thead>
<tr>
<th>Metabolizer Phenotype</th>
<th>Activity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid (UM)</td>
<td>1-2%</td>
</tr>
<tr>
<td>Extensive (EM)</td>
<td>77-92%</td>
</tr>
<tr>
<td>Intermediate (IM)</td>
<td>2-11%</td>
</tr>
<tr>
<td>Poor (PM)</td>
<td>5-10%</td>
</tr>
</tbody>
</table>
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

- 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 suggested respiratory arrest
  - Codeine and Morphine blood levels were measured…

Drug/Metabolite Measured Blood Concentration

- Codeine: Within expected range
- Morphine: 17.6 ng/mL

Therapeutic morphine concentration is 4.5 +/- 2.1 ng/mL
Case report: Codeine & Tonsillectomy

Genotyping revealed a gene duplication that led to an ultrarapid (UM) genotype


Genetic variation also affects 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 2005
Chou, W. et al. Anesthesiology 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

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

Ross J et al. Cancer 2005
Genetic variation also affects 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

OPRM1 and COMT likely interact

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

Non-Opioid Analgesics and Genetics

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPRM1 Normal</td>
<td>Normal</td>
<td>Decreased receptor response</td>
</tr>
<tr>
<td>ABCB1 Decreased pump activity</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
NSAIDs

- Example: Ibuprofen
- Major metabolic enzyme is CYP2C9
  - Some 2C9 polymorphisms decrease enzyme function

Mazakoukaya 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

Mazakoukaya L et al. Pharmacogenet Genomics 2015

CYP2C9 Genotype and NSAID clearance

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

Translational Potential of Genetics

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 alternative</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>


CPIC Guidelines for Codeine Therapy in the Context of CYP2D6 Genotype

FDA Black Box Warning

CODEINE SULFATE: codeine sulfate solution
TAGI Pharma, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CODEINE SULFATE ORAL SOLUTION safely and effectively. See full prescribing information for CODEINE SULFATE ORAL SOLUTION.

CODEINE SULFATE ORAL SOLUTION

INDICATIONS AND USAGE

This product is a narcotic analgesic indicated for the management of mild to moderately severe pain where the use of an opioid analgesic is appropriate.

WARNING: DEATH RELATED TO ULTRA-RAPID METABOLISM CODEINE TO MORPHINE

Respiratory depression and death have occurred in relatives who received codeine following surgery and/or traumatic injury and had evidence of being ultra-rapid metabolizers (CMY2D6*11) who were taking a "standard" dose of codeine.

What are graduating ENT residents planning to use in their practice?

<table>
<thead>
<tr>
<th>Analgesic Regimen</th>
<th>Percent of ENT Residents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen/Hydrocodone</td>
<td>25.5%</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>19%</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>17%</td>
</tr>
<tr>
<td>Acetaminophen/Oxycodone</td>
<td>14.9%</td>
</tr>
<tr>
<td>Acetaminophen/Codeine</td>
<td>8.5% (highlighted)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>8.5%</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

Cheng et al. Otolaryngol Head Neck Surgery 2013

What are graduating ENT residents planning to use in their practice?
**The Individual Patient..**

- Better therapeutic outcome
- Successful management of “condition” in real world might increase from 60% to 90+% 
- Futile therapeutics would decrease 
- Cost-benefit across drugs and conditions would improve

"Imagine if we could readily evaluate the opioid metabolism or receptor function of patients during their preoperative assessments and develop perioperative pain treatment plans targeted specifically to each one."
- Mark Warner, M.D. Rovenstine Lecture 2006

**Resources**

- Pharmacogenomics Knowledge Base
  - [www.pharmgkb.org](http://www.pharmgkb.org)
- Pharmacogenomics Research Network (PGRN)
  - [www.pgrn.org](http://www.pgrn.org)
- FDA genomics resource
  - [http://www.fda.gov/drugs/scienceareas/pharmacogenetics/](http://www.fda.gov/drugs/scienceareas/pharmacogenetics/)

**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</th>
<th>COMT</th>
<th>2 x MCR1</th>
<th>Nonfunctional SNP</th>
<th>Resulting Factor by Which the Individual Dose May Be Adapted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1.33</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1.33</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Lotsch J & Geisslinger G Pain 2005

**References**


References


References


