Pharmacogenomics: Genetic variations in drug metabolism and utilization

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Disclosure

• No real or potential conflict of interest to disclose.
• No off-label, experimental or investigational use of drugs or devices will be presented.

Objectives

• Upon completion of the learning activity the participant will be able to:
  – Define pharmacogenomics and pharmacogenetics.
  – Describe the clinical implications of genetic variations in drug metabolism.
  – Identify select at-risk populations for genetically influenced adverse drug reactions.

What factors do we take into consideration...

• When prescribing a medication?
  – Beyond indication and evidence?
    – Age, perhaps gender
    – Height/weight
    – Renal/hepatic function
    – Comorbidity
    – Allergy

Beyond that...

• Prescribing tends to be a “one size fits all” proposition.

Our clinical observation...

• You prescribe the identical doses of the same drug to three different patients who are same gender, approximately same weight, height and physical condition.
  – One has a robust clinical response.
  – One has intolerable adverse effects.
  – One has virtually no clinical response.
Could there be a genetic basis for this observation?

African Americans = A Fairly Homogenous Group with Similar Genetics
Assumption: Reasonable or not?

Goldstein in NEJM
• “One of the most striking features of modern medicines is how often they fail to work. Even when they do work, they are often associated with serious adverse reactions. Indeed, adverse reactions to drugs rank as one of the leading causes of death and illness in the developed world. How can we improve the success rate?”

Serious Adverse Drug Reactions
• Annual toll in USA
  – 6 to 7% of all hospitalizations
  – 2-day increase in average length of hospitalization
  – 100,000 deaths annually

Per Ingelman-Sundberg
• “The search for pharmacogenomic biomarkers that could be used to identify patients at increased risk for drug-related toxic effects has often focused on variation within genes encoding drug-metabolizing enzymes. Altered enzymatic activity can lead to elevated levels of the substrate drug, or alternatively, increased amounts of a reactive metabolite, either of which could have toxic effects.”
Precision (Personalized) Medicine Initiative (PMI)

...bold new research effort to revolutionize how we improve health and treat disease, empowering health care providers to tailor treatment and prevention strategies to individuals’ unique characteristics.

– Source: http://www.fda.gov/ScienceResearch/SpecialTopics/PrecisionMedicine/default.htm

Pharmacogenetics vs. Pharmacogenomics

• Pharmacogenetics defined
  – Individual variation in drug metabolism and distribution
  – Most often influences by a single gene

• Pharmacogenomics defined
  – Pharmacogenetics + variation among individuals in drug targets and disease mechanism
  – Likely involves multiple genes

Though both terms are used interchangeably, what we are talking about is...

The molecular study of genetic factors that determine drug efficacy and toxicity

Pharmacodynamics

• Study of biochemical and physiological effects of drugs
  – What the drug does to the body and/or disease
  – Includes drug’s mechanism of action

Pharmacokinetics

• What the body does to the drug
  – ADME mnemonic
    • Absorption
    • Distribution
    • Metabolism (biotransformation)
    • Excretion

Human Genome Project Pharmacogenomics

Pharmacokinetics: ADME

**Absorption**
- (skin, lungs, GI tract, parenteral)

**Distribution**
- (throughout body, especially to needed site of action)

**Metabolism**
- (biotransformation)
- (liver, GI tract, other)

**Elimination**
- (kidney, GI tract, others)

Definitions

- **Genome**
  - All the DNA in an organism

- **Genomics**
  - The study of genes and their function

Definitions (continued)

- **Allele**
  - One of a number of different forms of a gene
  - Each person inherits two alleles for each gene, one allele from each parent.
  - Alleles may be the same or may be different from one another.

Factors Influencing Medication Effect

- **Nongenetic factors**
  - Typically variable across the lifespan
  - Age
  - Organ function
  - Concomitant therapy
  - Drug interactions
  - Disease state

- **Genetic factors**
  - Typically stable across the lifespan
  - Drug-metabolizing enzymes
  - Drug transporters
  - Drug targets

Pharmacogenetics: PK vs. PD

- **PK genetic influences**
  - Drug absorption, distribution, metabolism, excretion
  - Influence dose requirements and/or adverse effects

Pharmacogenetics: PK vs. PD (continued)

- **PD genetic influences**
  - Drug targets
  - Receptors, transporters, intracellular signaling pathways, enzymes and metabolic pathways
  - Influence drug efficacy
**Possible PK vs. PD Genetic Examples**

- **40 yo woman on paroxetine 10 mg daily**
  - “I could hardly keep my eyes open during the day then could not sleep at night.”

- **50 yo woman hx SSRI use**
  - “I tried citalopram and it really did not do anything. Sertraline works great.”

On the same day in practice, two patients seen with the same problem and given the same medication...

One is of Northern European ancestry.

One is of east African ancestry.

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**Both are given Atomoxetine (Strattera®) for ADHD.**

- **Northern European**
  - Reports excessive nervousness, poor sleep, “never even closed my eyes;” stops the medication after a few days of use.

- **East African**
  - Reports excessive nervousness for a few hours after taking medication, no problem with sleep; “It works at first then seems to wear off quickly.”

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**Select References**

- Genomics and Drug Response
  - Liewei Wang, M.D., Ph.D., Howard L. McLeod, Pharm.D., and Richard M. Weinshilboum, M.D.

- National Center for Biotechnology Information,
  - One Size Does Not Fit All: The Promise of Pharmacogenomics
  - Available at http://www.ncbi.nlm.nih.gov/books/NBK115549/

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**FDA Rule 21 CFR 201.57**

- “...if evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, the labeling shall describe the evidence and identify specific tests needed for selection or monitoring of patients who need the drug...”

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**Cytochrome P450 Isoenzymes**

- **Defined**
  - Isozymes responsible for the biotransformation of many drugs and other substances
  - Facilitates change from fat- to water-soluble to allow for distribution and/or elimination or inactive compounds to active metabolites
Medications
Parent Drug to Metabolite

- Amitriptyline ---> nortriptyline
- Codeine ---> morphine
- Primidone ---> phenobarbital
- Valacyclovir ---> acyclovir

Proportion of Medications Metabolized/Biotransformed by Select CYP450 Isoenzymes

CYP 2C9/19
- 13%
CYP 1A2
- 15%
CYP 2D6
- 25%
CYP 3A4
- 47%

Fitzgerald Health Education Associates

Pharmacogenomics: Genetic variations in drug metabolism and utilization

CYP450 Isoenzymes: Describing the Terms

Substrate
Utilizes a specific enzymatic pathway

A medication or substance that is metabolized by the isoenzyme, utilizing this enzyme in order to be modified so it can reach drug site of action and/or be eliminated

Inhibitor
Blocks a specific enzymatic pathway, keeps substrate from exiting.

Blocks the activity of the isoenzyme, limiting substrate excretion, allowing increase in substrate levels, and possible risk of substrate-induced toxicity

Inducer
Pushes the substrate out the exit pathway

Accelerates the activity of the isoenzyme so that the substrate is pushed out the exit pathway, leading to a reduction in substrate level
Biology as destiny?

- Is there a family history of idiosyncratic reactions?
- Might explain the unexplainable
  - "Codeine does nothing but make me and everyone in my family nervous. I can take Vicodin® or Percocet®."

The Highway Model of Drug Metabolism via CYP450

- Everyone has potentially a two-lane drug metabolizing highway.

CYP450
Extensive Metabolizer (EM)

- 2-lane drug metabolizing highway
  - Both lanes are open.
  - Traffic is moving.
  - "Normal" drug doses are biotransformed (metabolized) within parameters mentioned in the prescribing information.

CYP450
Intermediate Metabolizer (IM)

- 2-lane drug metabolizing highway
  - One lane is open and moving.
  - Other lane is closed or moves slowly.
  - Standard drug doses might not be tolerated.
  - Both lanes are closed.
CYP450
Ultra Metabolizer (UM)
• All lanes open
• Extra lanes
• Fast traffic
• Rapid metabolism of medications with potential toxicity or loss of therapeutic effect

CYP2D6
2–6% of Total Hepatic CYP450
• Inducers
  – Pregnancy
• Inhibitors
  – Quinidine, paroxetine, fluoxetine

CYP2D6
2–6% of Total Hepatic CYP450 (continued)
• Substrates (about 25% of all Rx drugs)
  – Metoprolol, amitriptyline, paroxetine, haloperidol, risperidone, codeine, dextromethorphan, methadone

CYP2D6
Population-based Variations
• Intermediate metabolizer
  – 7–12% of population
• Poor metabolizer
  – Up to 35% of population

CYP2D6
Population-based Variations (continued)
• Ultra metabolizers
  – Relatively infrequent among northern Europeans
  – Select east African populations, as much as 29%
CYP 2D6: Absent or Slow-acting Form?

- “Codeine makes me nervous but morphine is OK.”
- “Robitussin DM® keeps me up all night.”


- Life-threatening opioid intoxication in a patient with bilateral pneumonia who was given codeine for cough
  - Metabolized/bioactivated by CYP2D6, patient with ≥3 gene copies, thus an ultra metabolizer
  - Norcodeine metabolized by CYP3A4, patient on antibiotic that is a CYP3A4 inhibitor
  - Coupled by transient renal impairment

Metabolic Pathways of Codeine Biotransformation

Pharmacogenomic Alert


Pharmacogenomic Alert (continued)

- In the reported case, the mother, who had given birth to a healthy full-term infant who was exclusively breastfeeding, had 30 mg codeine tablets and was initially taking 2 tablets every 12 hours, and subsequently took 1 tablet every 12 hours from day 2–14 post partum. Unfortunately, the baby was found dead on day 13.

Pharmacogenomic Alert (continued)

- Postmortem analysis of the baby showed blood concentrations of morphine were 70 ng/mL; infants exposed to codeine-containing products have morphine serum concentrations of 0.5–2.2 ng/mL.
Pharmacogenomic Alert (continued)

- A stored sample of the mother’s breast milk showed a morphine concentration of 87 ng/mL, well above the usual concentration of 1.9 to 20.5 ng/mL usually noted with the use of codeine 60 mg every 6 hours.

What might we hear from patients with genetic variations in drug metabolism (CYP 2D6) who are placed on nortriptyline?

Mean Plasma Nortriptyline Concentrations after Single 25 mg Oral Dose in Subjects with 0, 1, 2, 3, or 13 Functional CYP2D6 Genes

Back to our patients on Atomoxetine (Strattera®)

- Northern European
  - Reports excessive nervousness, poor sleep, “never even closed my eyes”; stops the medication after a few days of use.

- East African
  - Reports excessive nervousness for a few hours after taking medication, no problem with sleep; “It works at first then seems to wear off quickly.”

Atomoxetine (Strattera®) Per PI: CYP450 2D6 Substrate

- No differences between “normal” metabolizers (extensive metabolizers or EMs) and slow metabolizers (poor metabolizers or PMs) in serious adverse events experienced.

Atomoxetine (Strattera®) Per PI: CYP450 2D6 Substrate (continued)

- Non-serious adverse events such as decreased appetite, insomnia, and depression occurred in at least 2% of PM patients and either twice as frequently or statistically significantly more frequently in PM patients compared with EM patients.
CYP 2D6
 Ultra Metabolizer

- “Codeine really snows me at first then does not help with the pain unless I take it every 2 hours.”
- “Robitussin DM® does nothing to help my cough.”

Other problems we already know about...

- CYP2D6 altered genotype
  - Associated with risperidone adverse reactions and discontinuation due to adverse events
- CYP2C9, CYP2C19 altered genotypes
  - Phenytoin dose need adjustment

Clopidogrel (Plavix®) and Genetic Variations in Drug Metabolism

- Clopidogrel (Plavix®)
  - Prodrug metabolized to active form that allows platelet aggregation inhibition
  - CYP2C19 substrate
    - Source: Detail-Document; Prescriber’s Letter 2010; 17(5):260505.

Genetic Variations in CYP450 2C19

- Intermediate metabolizers
  - 30% European ancestry
  - 40% African Americans
  - 55% Asian ancestry

Genetic Variations in CYP450 2C19 (continued)

- Poor metabolizers
  - 3% of overall population
    - 2% European ancestry
    - 4% African Americans
    - As high as 20% in some Asian groups
Clopidogrel (Plavix®) and Genetic Variations in Drug Metabolism

- Yield
  - At least 1/3 reduction in levels of clopidogrel's active metabolite
  - Higher risk of death in PM, IM from cardiovascular causes, MI, or stroke compared vs. EM (2.1% vs. 8%, p=0.01), increased risk of stent thrombosis (2.6% vs. 0.8%, p=0.02)

FDA Action on Clopidogrel

- Addition of "Boxed Warning" about reduced effectiveness with genetic differences in CYP450 2C19

Tamoxifen

- Selective estrogen receptor agonist/antagonist
  - Antiestrogen therapy in breast cancer
- Prodrug metabolized CYP450 2D6
  - Metabolites as much as 100-fold more potent as antiestrogen form than tamoxifen

Drug Interaction Consideration

- Tamoxifen and CYP 2D6 inhibitors
  - Paroxetine, fluoxetine, sertraline
  - Yield higher rate of breast cancer recurrence

Tamoxifen: Pharmacogenomic Implications

- FDA mandated warning
  - With use in 2D6 PM
  - No guidance on testing, dosing, clinical decision-making

CYP2C9 Substrates: About 25% of All Medications

- Example of substrates
  - S-warfarin, glipizide, many NSAIDs, amitriptyline, phenytoin, tamoxifen, THC (tetrahydrocannabinol)
- Inhibitors
  - Fluconazole, fluvastatin, zafirlukast
- Inducer
  - Rifampin
CYP2C9

- Phenotype prevalence in general population
  - 10% PM, 7% UM, 35% IM
- Example of PM results
  - Warfarin 2.5 mg
  - A whiff of marijuana
  - Low dose phenytoin

Time to Stable Warfarin Dose

- Extensive (normal) metabolizer
  - 4–5 days
- Intermediate metabolizer
  - 8–10 days
- Poor metabolizer
  - 12–15 days
  - Source: http://genelex.com/pharmacogenetic-tests/cyp2d6/, website with extensive information about genetics in healthcare, sponsored by Genelex

For Additional Information About Genetically-based Warfarin Dosing

- http://genelex.com/patients/drugs/warfarin/
  - Information at Genelex’s website about testing
- www.fda.gov/bbs/topics/NEWS/2007/NEW01684.html
  - Advisory from FDA about warfarin dosing and warning

SLCO1B1 (Solute Carrier Organic Anion Transporter 1B1)

- What is it?
  - Gene codes for organic anion transporter 1B1 responsible for hepatic uptake and metabolism of statins
  - Variant to SLCO1B1 results
    - Decreased statin hepatic update to take
    - Less statin effectiveness in LDL reduction
    - Higher blood levels after dosing
    - Increased risk of myopathy

SLCO1B1 (Solute Carrier Organic Anion Transporter 1B1) (continued)

- Inherited SLCO1B1 variants
  - 1 copy=4.5-fold increase in risk for statin-induced myopathy
  - 2 copies=17-fold increase in risk for statin-induced myopathy
  - Source: http://www.bostonheartdiagnostics.com/science_portfolio_statin.php
For additional information:
The Clinical Pharmacogenomics Implementation Consortium: CPIC Guideline for \textit{SLCO1B1} and Simvastatin-induced Myopathy, Available at \url{http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3384438}

Should we be routinely checking for genetic variants in drug biotransformation?

The Pro and Con
\begin{itemize}
\item \textbf{Pro}
  \begin{itemize}
  \item With NTI medication, can minimize under/over treatment, streamline drug dosing particularly in initial dosing
  \end{itemize}
\item \textbf{Con}
  \begin{itemize}
  \item Inconsistent clinical trials, emerging FDA mandates, current evidence fails to demonstrate improved outcomes with most medications.
  \end{itemize}
\end{itemize}

Drug Reaction/DNA Drug Sensitivity Testing
\begin{itemize}
\item \textbf{Genetic analysis}
  \begin{itemize}
  \item CYP1A2
  \item CYP2D6
  \item CYP2C9
  \item CYP2C19
  \item CYP3A4
  \item CYP3A5
  \item NAT2
  \end{itemize}
\end{itemize}

FDA Table of Pharmacogenomic Biomarkers in Drug Labels
\begin{itemize}
\item \textbf{Includes list of medication with pharmacogenomic warnings in prescribing information}
  \begin{itemize}
  \item Currently approximately 100 medications on list
  \item Antiretrovirals, cancer chemotherapy, cardiovascular, psychiatric/neurological medications most often listed.
  \end{itemize}
\end{itemize}

FDA Table of Pharmacogenomic Biomarkers in Drug Labels
Available at \url{www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm}
Conclusion

- Be at the cutting edge of practice by learning about pharmacogenomics.
- Keep your eyes and ears open for new recommendations.

End of Presentation

Thank you for your time and attention.
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