Pharmacogenomics: The Promise of Personalized Drug Therapies

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Objectives
- Differentiate between pharmacogenetics and pharmacogenomics
- Define benefits of personalized therapies
- Identify various drug-drug interactions and their adverse effects and provide clinically-relevant examples of drug metabolism pharmacogenomics

Factors Contributing to Interindividual Variability in Drug Disposition and Action
- Age
- Race/ethnicity
- Sex
- Weight
- Gender
- Concomitant Diseases
- Concomitant Drugs
- Social Factors
- GENETICS

Personalized Medicine

The principle of personalized medicine assumes that drug response is intricately linked to changes in pharmacokinetics or pharmacodynamics of the drug as a result of the patient’s genotype.

Therefore, personalized medicine represents the application of pharmacogenetics to individualize drug therapy to the benefit of the patient.

DHHA: Personalized Health Care Initiative
- 2006 Secretary Michael O. Leavitt defined PHC (Personalized Health Care) PHC as
  - “the combination of basic scientific breakthroughs of the human genome with computer-age ability to exchange and manage data”
- The knowledge created through the completion of the human genome is enabling researchers to characterize variations in the biology of individual patients
- Gene-based medicine will help create more effective treatments for large patient subpopulations

Dr. Scordo has no financial relationships with commercial interests to disclose
Any unlabeled/unapproved uses of drugs or products referenced will be disclosed

Personalized Medicine

The principle of personalized medicine assumes that drug response is intricately linked to changes in pharmacokinetics or pharmacodynamics of the drug as a result of the patient’s genotype.

Therefore, personalized medicine represents the application of pharmacogenetics to individualize drug therapy to the benefit of the patient.
* Convened working group
* creating tools for electronic transmission of health records and information;
* conduct innovative research to delve more deeply into the effect of genes on disease progression;
* establish a regulatory environment that supports effective development of drugs, diagnostics, and other means to reach specific patient subpopulations;
* translate genetic information to clinical practice

If a woman with breast cancer tests positive for human epidermal growth factor receptor 2 (HER-2), she can be given Herceptin (trastuzumab), which suppresses excess HER-2 and cuts the risk of disease recurrence by 50%.

?!will patients carry cards with microchips encrypted with personal genetic information that will enable delivery of highly individualized prescriptions???

**Interindividual Variability in Drug Response**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Drug Class</th>
<th>Rate of Poor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Beta-agonists</td>
<td>40-75%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Various</td>
<td>30%</td>
</tr>
<tr>
<td>Solid Cancers</td>
<td>Various</td>
<td>70%</td>
</tr>
<tr>
<td>Depression</td>
<td>SSRI, tricyclics</td>
<td>20-40%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Sulfonylureas, others</td>
<td>50%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>NSAIDs, COX-2 inhibitors</td>
<td>30-60%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Various</td>
<td>25-75%</td>
</tr>
</tbody>
</table>

**Effectiveness of drugs:**

- Hypertension Drugs 10-30%
- Heart Failure Drugs 15-25%
- Anti Depressants 20-50%
- Cholesterol Drugs 30-70%
- Asthma Drugs 40-70%

**No Medicine Is Perfect!**

People do not respond to medicines in the same way:
- Adverse events may occur in some people, not in others
- Dosages can be different
- Efficacy can vary

Variable responses to medicines are known to occur in some populations
Variable responses (particularly rare adverse events) are often difficult to predict
Personalized medicine is not so new...

Homer’s Odyssey

“drugs can be either therapeutic or poisonous”

Does one size fits all?

People react differently to drugs

“One size does not fit all...”

Some factoids...

- Adverse drug reactions (ADRs):
  - Caused 5% of hospitalization
  - Experienced by 10% of the hospitalized patients
  - 700,000 injuries/deaths per year
  - Estimated to be the 4th or 6th leading cause of death in the US for the hospitalized patients back at 1998
  - 59% of drugs causing ADRs are metabolized by polymorphic enzymes
  - 7-22% of other randomly selected drugs are substrates for polymorphic enzymes
  - Polymorphisms occur in transporters, receptors, and other therapeutic targets are also associated with interindividual variability in drug response
Quality Use of Medicines or Personalized Medicine

That is.....

For any given disease which is the right drug for a given person?

What is the right dose?

And I know this how?

What’s in a name? (con’t)

- Pharmacogenomics
  - Broader term
  - Reserved for the analysis of genomes and genomic expression as they relate to drug responses
  - Aims to develop personalized medicine, adapted to each person’s genetic makeup and environment

What’s in a name?

- Pharmacogenetics
  - Originally defined in 1959 by Frederick Vogel as “clinically important hereditary variation in response to drugs”
  - Allows for patient stratification based on responses to drugs by studying the association between diseases & their corresponding alleles and SNPs
  - Discipline established in 1962 by Werner Kalow’s monograph Pharmacogenetics

Current Concept of Pharmacogenomics

Pharmacogenetics

Smaller Effect: Multiple Variants

Large Single Variant Effect

Single Gene

Small Number of Genes

Complex Biological Pathway

Whole Genome

TABLE 1

Dugs withdrawn from the US market between 1997 and 2001 (through 2004a)

<table>
<thead>
<tr>
<th>Year</th>
<th>Withdrawn Approval</th>
<th>Drug name#</th>
<th>Use</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>1973</td>
<td>Tibolone</td>
<td>Obese Heart valve abnormality</td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>1991</td>
<td>Revalor-H</td>
<td>Obese Heart valve abnormality</td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>1987</td>
<td>Lomustine</td>
<td>Rhabdomyosarcoma</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>1997</td>
<td>Budesonide</td>
<td>Oral diabetes</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>1998</td>
<td>Allergen*</td>
<td>(Leukotra) Acute liver failure</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>1995</td>
<td>Nimodipine</td>
<td>(Sildenafil) Torsades de Pointes drugdrug interactions</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>1994</td>
<td>Grepodrug</td>
<td>(Rasagiline) Torsades de Pointes</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>1999</td>
<td>Aprepitant</td>
<td>(Protac) Acute liver failure</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>1998</td>
<td>Itraconazole</td>
<td>(Ketoconazole) Torsades de Pointes</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>1997</td>
<td>Tegopen</td>
<td>(Itraconazole) Torsades de Pointes</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>1997</td>
<td>Sertolactone</td>
<td>(Sertaconazole) Torsades de Pointes</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>1996</td>
<td>Rosiglitazone</td>
<td>(Rosiglitazone) Torsades de Pointes</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>1999</td>
<td>Rosiphen**</td>
<td>(Venlafaxine) Sudden death</td>
<td></td>
</tr>
</tbody>
</table>

# Drug names are in parentheses.
*Reintroduced to the market in 2012 with new restrictions to patients severely affected with heart valve problems.
**Updated information reflects discussions at an FDA Advisory Committee meeting held in Bethesda, MD, February 14 to 16, 2012.
Clinical Application Pharmacogenetics
Kristine A. Scordo, PhD, RN, ACNP-BC, FAANP

Pharmacogenetics
- study of correlation between genetic traits and response to therapeutics (efficacy and adverse effects)

Pharmacokinetics
- study of availability of therapeutic in body

Pharmacodynamics
- study of drug and target interaction

Absorption/Excretion

Distribution

Receptors

Transporters/Channels

Enzymes

CYP450: 76% of ADRs are dose dependent
CYP450 is one of the best characterized metabolic protein complexes

Pharmacogenetic Tree

Pharmacogenomics
- Describes what the drug does to the body
- Describes what the body does to the drug

Pharmacogenomic science

Potential of Pharmacogenomics
- Improving drug safety
  - If a specific genotypic variant is found to be associated with an adverse reaction, avoid Rx in patients with this genotype
- Adjusting dosage
  - Knowledge of genotypes with specific pharmacokinetic characteristics could be used to adjust the dosage of affected drugs-reduces trial-and-error approach of Rx to determine most effective dosage
- Enhancing efficacy
  - Many widely used treatments reported to work in only 40% of patients. Pharmacogenetics may identify responsive and nonresponsive patients or offer new medicines designed on the basis of the genetics of the disease
- Drug pricing
  - Improving the pricing or sale worth of drugs could be according to their worthiness for specific genomic strata of the population
Genetic Polymorphisms
A Key to Human Individuality
- Polymorphisms are subtle differences in our genome
- Polymorphisms are common
  - We are 99.9% identical at the DNA level
  - But this still leaves ~3,000,000 specific DNA differences between you and others
- Such differences affect our appearance, behavior, susceptibility to disease and response to medications

Single Nucleotide Polymorphisms (SNPs) A key to human variability
DNA sequence variation at a single nucleotide that may alter the function of the encoded protein

Functional protein
Functional but altered protein

SNP = single nucleotide polymorphisms

CYP450 Gene Nomenclature

<table>
<thead>
<tr>
<th>Family Subfamily</th>
<th>Gene</th>
<th>Allele Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 2 C 19 *1</td>
<td>(normal allele)</td>
<td></td>
</tr>
<tr>
<td>Variant alleles (named in order of discovery):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP 2 C 19 *2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP 2 C 19 *3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP 2 C 19 *4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Major CYP450 enzymes involved in drug metabolism

- CYP1A2
- CYP2C9
- CYP2C19
- CYP2D6
- CYP2E1
- CYP3A4
- CYP3A5

Enzyme Activity

- Normal
- Reduced (50-70%)
- Reduced (5-15%)
Drug Metabolizing Enzymes

Examples of Drug Metabolism
Pharmacogenomics

Table 1. Pharmacogenomics of Phase I Drug Metabolism.

<table>
<thead>
<tr>
<th>Drug Metabolizing Enzyme</th>
<th>Frequency of Phase I Metabolism in Patients</th>
<th>Representative Drugs Metabolized</th>
<th>Effect of Polymorphism</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Approximately 10% of the population</td>
<td>Tobacco</td>
<td>Enhanced drug effect</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Approximately 30% of the population</td>
<td>Phenytoin</td>
<td>Increased drug action</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Approximately 20% of the population</td>
<td>Warfarin</td>
<td>Enhanced drug effect</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Approximately 20% of the population</td>
<td>Oxycodone</td>
<td>Increased drug action</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Approximately 10% of the population</td>
<td>Verapamil</td>
<td>Enhanced drug effect</td>
</tr>
</tbody>
</table>

*Examples of genetically polymorphic phase I enzymes are listed that can alter drug metabolism, including selected examples of drugs that have clinically relevant variation in their effects.

Figure 4. Pharmacogenetics of Norbuphenin.
Mean plasma concentrations of norbuphenin after a single 25-mg oral dose are shown in subjects with 0, 1, 2, 3, or 13 functional CYP2D6 genes. Modified from Dunin et al. with the permission of the publisher.

Genetic polymorphisms in drug metabolism

To test or not to test?
Traffic Light for Drugs

Case Example

66 year old male recently started on warfarin due to hx of chronic atrial fibrillation and DVT. INRs subtherapeutic at a dose of 25mg/day. No other medication or diet changes. Which genetic change(s) affect(s) the pharmacokinetics of warfarin dosing in this patient?

a) P450 2C9 (CYP2C9) polymorphism
b) VKORC1 polymorphism/mutation
c) JAK 2 V617F mutation
d) VKORC1 polymorphism/mutation and P450 2C9 (CYP2C9) polymorphism
e) Haven’t a clue!
Historically, warfarin dosing was based on an empiric starting dose—usually what you believe the patient will be maintained on.

Multitude of drug interactions of P450 enzyme contribute to the variability of warfarin metabolism and influence INR results.

Some patients are outliers—either marked sensitivity or resistance to typical doses.

**CYP2C9**
- CYP2C9*2, CYP2C9*3 – most common variants
- Seen in 20-40% of Caucasians, <10% Asians and African Americans
- Associated with reduced CYP2C9 enzyme activity
- Variant alleles associated with:
  - lower mean doses of Warfarin
  - longer times to stabilization of INR
  - higher risk for bleeding events

**Warfarin Pharmacogenomics**
- CYP2C9 SNPs account for a small amount of variability in warfarin doses (~10%)
- VKORC1 SNPs explain a larger portion of variability in warfarin doses (~20-25%)
- Almost 50% of variability in warfarin doses can be explained by a combination of factors:
  - VKORC1 SNPs
  - CYP2C9 SNPs
  - Non-genetic factors (age, weight, concomitant drugs, concomitant disease states)
Influences warfarin effectiveness

- Age
- Race/ethnicity
- Weight
- Alcohol consumption
- Compliance
- Genetics
- Diet
- Smoking
- Disease states
- Organ dysfunctions
- Drug-drug interactions

Medicare: January 2010

**Influences warfarin effectiveness**

- Age
- Race/ethnicity
- Weight
- Alcohol consumption
- Compliance
- Genetics
- Diet
- Smoking
- Disease states
- Organ dysfunctions
- Drug-drug interactions

**Patient with Multiple CYP2 Drug Metabolism Deficiencies**

A 54-year Caucasian woman with a seven year history of: persistent malaise, headache, muscle tension, jaw clenching, hypervigilance & severe anxiety. She became increasingly preoccupied with her somatic condition, stopped working, withdrew from her usual activities. She spent a huge amount of time and effort on medical care seeing a variety of providers. However, she had multiple ADEs.
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DNA Guided Drug Selection

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DNA Guided Drug Selection
CYP2D6 and Codeine

Codeine requires activation by CYP2D6 in order to exert its analgesic effect.

Due to genetic polymorphisms, 2-10% of the population cannot metabolize codeine and are resistant to the analgesic effects.

Interindividual variability exists in the adequacy of pain relief when uniform doses of codeine are given.

Factoids.....

- At the American Academy of Pain Medicine 23rd Annual Meeting (2007), a presentation on the clinical effect of genotyping chronic pain patients revealed:
  - 80% of patients reporting ADRs were shown to have poor CYP2D6 metabolism.
  - Some methadone patients seeking higher doses were Ultra Metabolizers; proof that they were not exhibiting drug-seeking behavior.

CYP2D6 Phenotypes

NEJM 2003; 348:529

CYP2D6 Polymorphisms

- CYP2D6 is responsible for the metabolism of a number of different drugs
  - Antidepressants, antipsychotics, analgesics, cardiovascular drugs
- Over 100 polymorphisms in CYP2D6 have been identified
- Based on these polymorphisms, patients are phenotypically classified as:
  - Ultrarapid metabolizers (UMs)
  - Extensive metabolizers (EMs)
  - Poor metabolizers (PMs)

CYP2D6 Phenotypes

<table>
<thead>
<tr>
<th>Population Frequency of Cytochrome P450 (CYP) Metabolizer Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor (no or low enzyme levels)</td>
</tr>
<tr>
<td>CYP2D6</td>
</tr>
</tbody>
</table>

Extensive Metabolizers (EM)
- two normal alleles
- often majority of population
- normal metabolizers

Poor Metabolizers (PM)
- lack functional enzyme
- Accumulation of active drug can produce adverse reactions
- May need lower dose to achieve same effect
CYP2D6 Phenotypes
- Intermediate Metabolizers (IM)
  - have one functional and one deficient allele
  - have two partially defective alleles that cause reduced metabolism
- Ultra-Rapid Metabolizers (URM)
  - duplicated functional CYP2D6 genes with extremely high metabolic capacity
  - May need greater dose or slow release formulation

Inhibitors
Drug interactions can also cause a patient to be a PM (poor metabolizer)
Example:
- Paroxetine (Paxil)
  - Potent 2D6 inhibitor
  - Co-administration will make 2D6 EMs (extensive metabolizer) into PMs

Genetic cause of hyperglycemia in treatment of type 2 diabetes mellitus
- Subtypes of diabetes - MODY (Maturity Onset Diabetes of the Young)
- Heterozygous mutations HNF-1alpha (Hepatocyte Nuclear Factor)
  - Most common cause of maturity onset diabetes of the young-account for 1-2% of all diabetes
  - Case reports suggest patients more sensitive to hypoglycemic effects of sulfonylureas than those with type 2 diabetes

Strattera® (Atomoxetine)
- Treatment of attention deficit hyperactivity (ADH) disorder
  - CYP2D6 poor metabolizers have 10-fold higher plasma concentrations to a given dose of STRATTERA compared with extensive metabolizers
  - Approximately 7% of Caucasians are poor metabolizers
  - Higher blood levels in poor metabolizers may lead to a higher rate of some adverse effects of STRATTERA
CYP2C19 and Proton Pump Inhibitors

- Proton pump inhibitors are used to treat acid reflux and stomach ulcers
- Ulcer cure rates using omeprazole and amoxicillin by CYP2C19 phenotype:
  - Rapid metabolizers: 28.6%
  - Intermediate metabolizers: 60%
  - Poor metabolizers: 100%


Clopidogrel: Factoids

- Clopidogrel is a pro-drug—requires metabolism mainly by CYP2C19 enzyme to form the active thiol metabolite
- Both genetic (e.g. polymorphism) and acquired (e.g. drug–drug interactions) alteration of CYP2C19 may affect the efficacy of clopidogrel metabolism
- Clinical clopidogrel exerts little or no anti-platelet effect in 4-35% of patients who are risk for CV disease

Clopidogrel-PPI Interactions: Conclusions/Recommendations

- Randomized, prospective databases indicate that there is no clinically important adverse interaction between clopidogrel and PPIs. Other studies note adverse outcomes.*
- There had been a recommendation that PPIs be given as blanket gastric protection to all patients at risk of gastric problems taking dual anti-platelet therapy.
- PPIs should be prescribed to patients taking clopidogrel only if they have increased risk of GI bleeding or dyspeptic symptoms that are not controlled with H2 antagonists.
- Pantoprazole (Protonix) would appear to be default PPI

PPIs and Clopidogrel

Clopidogrel and PPIs – The OCLA study

Blind randomized study of 124 patients comparing clopidogrel and clopidogrel + PPI in double antplatelet therapy

PRI: Platelet Reactivity Index as measured by vasodilator stimulated phosphoprotein (VASP)

PPIs (Omeprazole/Prilosec) are strong inhibitors of CYP2C19 activity

\[
\begin{array}{c|c|c}
\text{PRI Variation (‰)} & \text{Omeprazole (n=64)} & \text{Placebo (n=60)} \\
\hline
0 & 32.6 & 43.3 \\
5 & 43.2 & 50.4 \\
10 & 32.6 & 47.7 \\
15 & 32.6 & 50.4 \\
20 & 42.4 & 53.9 \\
25 & 32.6 & 47.7 \\
30 & 32.6 & 47.7 \\
35 & 32.6 & 47.7 \\
40 & 32.6 & 47.7 \\
45 & 32.6 & 47.7 \\
50 & 32.6 & 47.7 \\
\end{array}
\]

p<0.001

Gilard et al. J Am Coll Cardiol 2008;51:256-60.

FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug

- Inhibition of CYP2C19 by PPIs
- Use of alternative anticoagulants or drugs with alternative dosing strategies is necessary
- Patients should be questioned about use of other medications, in particular non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin

*Please refer to the referenced studies for details.
**Recommendations for testing**

- Latest FDA recommendation neither mandated nor explicitly recommended CYP2C19 genetic testing in patients prescribed clopidogrel and only suggested that health professionals should be aware that tests are available to determine patients’ CYP2C19 status.

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**Disease Risk Polymorphisms**

Polymorphisms can predispose individuals to a disease or increase the risk for disease.

If a drug with a known adverse effect is given to a person with a genetic susceptibility to that adverse effect, there is an increased likelihood for that adverse effect.

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**Clotting Factor Polymorphisms, Blood Clots, and Oral Contraceptive Pills**

- Polymorphisms exist in clotting factor genes.
- Oral contraceptive pills alone are associated with an increased risk of blood clots.
- Women who have clotting factor polymorphisms are at an even greater risk for blood clots if they receive oral contraceptive pills.

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**Oral Contraceptive Pills and Blood Clots**

**Table 1: Interaction between factor V Leiden or prothrombin mutation and oral contraceptives (OC) in determining venous thromboembolism (VTE)**

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>OC use</th>
<th>Estimated relative risk of VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>-</td>
<td>1 (reference value)</td>
</tr>
<tr>
<td>Absent</td>
<td>+</td>
<td>Four-fold</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>-</td>
<td>Five- to eight-fold</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>+</td>
<td>20- to 30-fold</td>
</tr>
<tr>
<td>G20210A prothrombin</td>
<td>-</td>
<td>Two- to four-fold</td>
</tr>
<tr>
<td>G20210A prothrombin</td>
<td>+</td>
<td>16-fold</td>
</tr>
</tbody>
</table>

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**Additional Examples**
Hepatitis C

- Interferon-α-2b and ribavirin are used to treat patients with hepatitis C virus
- Different mutations exist in the hepatitis C virus

**TABLE 1: Rates of Response to Treatment Study 2**

<table>
<thead>
<tr>
<th></th>
<th>Peg-IFN-α 2a + RBV</th>
<th>RBV alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>52% (284/531)</td>
<td>49% (231/469)</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>41% (140/341)</td>
<td>33% (112/343)</td>
</tr>
<tr>
<td>Genotype 2-6</td>
<td>73% (123/168)</td>
<td>73% (119/162)</td>
</tr>
</tbody>
</table>

- Knowledge of a person's hepatitis C genotype may help play a role in the therapeutic decision-making process

Abacavir Hypersensitivity Reaction

A 25-year-old HIV-infected man with a CD4 count of 150 cells/mm³ and an HIV-1 RNA level of 20,000 copies/ml is begun on trimethoprim-sulfamethoxazole (Bactrim, Septra) and the antiretroviral regimen abacavir (Ziagen) plus emtricitabine (Emtriva) plus atazanavir (Reyataz). Five days later he calls complaining of a rash on his face, trunk, and arms, but with no associated systemic symptoms.

After discussing the situation with the patient, it is decided to discontinue the trimethoprim-sulfamethoxazole and to continue the antiretroviral regimen with close supervision. During the next few days, the patient’s rash resolves.

Ten days later, however, the patient presents to office complaining of fever, malaise, nausea, and vomiting. He states that the symptoms are most prominent several hours after each dose of abacavir and the symptoms seem to be getting progressively worse with each dose. On examination you note a fine maculopapular rash.

A 25-year-old HIV-infected man with a CD4 count of 150 cells/mm³ and an HIV-1 RNA level of 20,000 copies/ml is begun on trimethoprim-sulfamethoxazole (Bactrim, Septra) and the antiretroviral regimen abacavir (Ziagen) plus emtricitabine (Emtriva) plus atazanavir (Reyataz). Five days later he calls complaining of a rash on his face, trunk, and arms, but with no associated systemic symptoms.

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After discussing the situation with the patient, it is decided to discontinue the trimethoprim-sulfamethoxazole and to continue the antiretroviral regimen with close supervision. During the next few days, the patient’s rash resolves.

Ten days later, however, the patient presents to office complaining of fever, malaise, nausea, and vomiting. He states that the symptoms are most prominent several hours after each dose of abacavir and the symptoms seem to be getting progressively worse with each dose. On examination you note a fine maculopapular rash.

**Which one of the following statement is CORRECT?**

a) Dx is abacavir hypersensitivity reaction and should have his medication discontinued. Once his symptoms have resolved, it is safe to rechallenge the patient with a lower does of abacavir.

b) The onset of symptoms three weeks after initiating antiretroviral therapy makes abacavir hypersensitivity unlikely because the hypersensitivity reaction is usually characterized by an immediate-type reaction.

c) The presence of multiple organ system involvement increases the likelihood that abacavir hypersensitivity is occurring in this individual.

d) This patient is experiencing an abacavir hypersensitivity reaction and should receive therapy with corticosteroids.

e) Sounds like the flu to me!
Abacavir Hypersensitivity

- Antiretroviral (NRTI) used for treatment of HIV (Ziagen)
- 5-8% of patients experience hypersensitivity reactions to the drug
- Hypersensitivity is fatal in rare cases
- Multi-organ systemic illness
- Delayed hypersensitivity reaction ~8-11 days
- Hypersensitivity reaction starts with severe GI symptoms, followed by fever and rash
- Discontinuation of drug reverses symptoms
- Re-challenge of abacavir in hypersensitive individuals can result in life-threatening low blood pressure or death


Abacavir Hypersensitivity

- Hypersensitivity typically believed to be an immunologic reaction
- Hypersensitivity might be genetically linked, and thus predictable
- Human leukocyte antigen (HLA) / Major histocompatibility proteins (MHC) investigated because of known links in other immune responses and allergic reactions
- DHHS recommends screening for HLA-B*5701 before starting any pt on any abacavir-containing regimen

Genetics of Abacavir Hypersensitivity

<table>
<thead>
<tr>
<th></th>
<th>Abacavir hypersensitive (n=16)</th>
<th>Abacavir tolerant (n=167)</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B*5701</td>
<td>14 (78%)</td>
<td>4 (2%)</td>
<td>117 (29-481)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HLA-DR7, HLA-DQ3</td>
<td>13 (72%)</td>
<td>6 (3%)</td>
<td>73 (20-268)</td>
<td>&lt;0.0001</td>
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<tr>
<td>HLA-B*5701,</td>
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</tbody>
</table>

What should have been done differently?

- Test for hypersensitivity – HLA-B*5701
- Start ONE drug at a time and wait a few weeks

Maraviroc (Selzentry)

- CCR5-tropic HIV treatment (CD4 immune cells)
- Ineffective for CXCR4-tropic strains of HIV
- Trofile™ assay to determine patients strain of HIV
- Detect virus that does not act through CCR5 at levels as low as 0.3% of a viral population
- Clinical trial patients selected with Trofile™ assay
A 34-year-old HIV-infected man with a CD4 count of 189 cell/mm3 and long-standing, well-controlled hyperlipidemia presents to the clinic complaining of a four day history of diarrhea, fatigue, leg weakness, total body aches, and muscle pain. He has noticed his urine has been darker than normal. Three weeks prior, he started a new antiretroviral regimen after having virologic breakthrough on a regimen consisting of tenofovir-emtricitabine-efavirenz (Atripla).

PE: T = 38.4°C, HR = 110, and diffuse muscle tenderness

Lab: serum creatinine of 5.2 mg/dl (baseline = 1.0 mg/dl), serum urea nitrogen = 67 mg/dl (baseline = 10 mg/dl), aspartate aminotransferase (AST) level of 632 U/L (baseline = 56 U/L), alanine aminotransferase (ALT) level of 400 U/L (baseline = 25 U/L), creatine kinase = 9700 U/L and slightly elevated amylase level.

Current Medications:
Abacavir-lamivudine (Epzicom): 1 PO daily
Ritonavir (Norvir): 100 mg PO twice daily
Darunavir (Prezista): 600 mg PO twice daily
Trimethoprim-Sulfamethoxazole (Bactrim, Septra): 160 mg/800 mg PO daily
Simvastatin (Zocor): 40mg PO daily

Which of the following statements is the MOST accurate related to this patient’s clinical presentation?

a) The patient’s clinical presentation most likely resulted from simvastatin induced increases in levels of trimethoprim-sulfamethoxazole, which caused hepatic and renal toxicity.

b) Abacavir likely caused a marked increase in the intracellular levels of simvastatin, triggering statin-induced acute rhabdomyolysis and renal failure.

c) The patient’s clinical presentation most likely resulted from simvastatin-induced increases in levels of darunavir, thereby causing hepatic and renal toxicity.

d) The patient’s clinical presentation is best explained by drug-induced rhabdomyolysis and acute renal failure caused by elevated plasma levels of simvastatin. The increased simvastatin levels resulted from co-administration of simvastatin with ritonavir-boosted darunavir.

Recommendations for the Use of Non-Nucleoside Reverse Transcriptase Inhibitors and Statin Drug

Recommendations for the Use of Protease Inhibitors and Statin Drug
Additional issues with Antiretroviral Drugs to treat HIV/AIDS

HIV and Antiretroviral Drugs

Resistance to antiretroviral agents hinders the management of HIV disease.

In the virus, mutations occur which confer drug resistance.

Knowledge of viral genotype (or phenotype) can help guide the selection of antiretroviral therapy.

CYP2C19 polymorphism in Helicobacter pylori–related disorders

- The treatment of H pylori infection requires a multidrug regimen that contains multiple antibiotics plus proton pump inhibitors (PPIs) or histamine-2 receptor blockers for eradication.
- Pharmacogenetic studies revealed potentially important host genetic variability to PPI response; CYP2C19 SNPs define patients as rapid (RM), intermediate (IM), or poor metabolizers (PM).

Asian populations demonstrate a higher frequency of PMs, higher PPI efficacy, and may have better H pylori eradication at standard doses.

With omeprazole the most sensitive to CYP2C19 variation, H pylori eradication rates may vary with specific PPIs and are generally lower; higher PPI doses may be needed in RMs.

Pretreatment PPI genotyping improves H pylori eradication rates but cost effectiveness has not yet been studied.
Competence Standard Statements

Genetics in Emergency Care

All nurses, midwives and health visitors, at the point of registration, should be able to:

- Identify clients who might benefit from genetic services and information through an understanding of the importance of family history in assessing predisposition to disease, seeking assistance from and referring to appropriate genetics experts and peer support resources, and based on an understanding of the components of the current genetic counselling process
- Appreciate the importance of sensitivity in tailoring genetic information and services to clients’ culture, knowledge and language level, recognizing that ethnicity, culture, religion and ethical perspectives may influence the clients’ ability to use these
- Uphold the rights of all clients to informed decision making and voluntary action based on an awareness of the history of misuse of human genetic information, and understanding of the importance of delivering genetic education and counselling fairly, accurately and without coercion or personal bias

Role for APRNs- MTM (medication therapy management)

- Assess and evaluate a patient’s complete medication therapy regimen via a comprehensive or targeted medication therapy review, rather than focusing on a specific therapy product
- By gathering key pieces of information (e.g., all medications a patient is taking, including supplements), can assess potential interactions, recommend alternative therapies to reduce medication-related adverse effects, and effectively collaborate with the individual patient’s other health care providers to improve overall care and treatment outcomes

Role of Pharmacogenomics in the Drug Development Process

Teaching moments-careful histories

- Long QT syndrome
- Cardiomyopathies
- Hematological disorders
- Asthma
- Variations in pain response
Clinical Application Pharmacogenetics
Kristine A. Scordo, PhD, RN, ACNP-BC, FAANP

New product development: A risky and expensive proposition

- Compound Success Rates by Stage:
  - 5,000–10,000 Screened
  - 200 Enter Preclinical Testing
  - 5 Enter Clinical Testing
  - Approved by the FDA

Role of Pharmacogenomics in the Drug Development Process

- ~ 80% of products that enter the development pipeline fail to make it to market
- Pharmacogenomics may contribute to a "smarter" drug development process
  - Allow for the prediction of efficacy/toxicity during clinical development
  - Make the process more efficient by decreasing the number of patients required to show efficacy in clinical trials
  - Decrease costs and time to bring drug to market

Old Paradigm

New Paradigm:

Personalized Medicine: The Right Drug, for the Right Patient, at the Right Time

Ethical, Legal and Social Issues
Genetic Information is:

- Personal
- Permanent
- Predictive
- Prejudicial
- Pedigree-sensitive

Genetics is a Family Affair

Obligations to relatives

Obligations of relatives

Key distinctions between PGx testing and traditional genetic testing

Disease predisposition testing often does not have an obvious treatment

- For PGx testing, an FDA approved drug is the treatment - goal is an adjustment in what managed care is already covering

- Less likely to create new consumer demand for services

- PGx more likely to be cost-effective in short-term as the treatments and alternatives are known

- If PGx testing has adequate +/- predictive value, may be unethical to prescribe without testing

Payer perspective: What will be the impact of pharmacogenomics on total healthcare costs?

Increased healthcare costs

- Higher drug prices
- Expanded patient populations for drugs
- Enforcement of privacy safeguards
- Extended patient protection

- Diagnostic tests required

Decreased healthcare costs

- Avoid use of expensive drugs in non-responders
- Save patients avoidable adverse effects
- Improve compliance
- Improved health outcomes
- System cost offsets

Food for thought*

Promotion of personalized medicine

- All drugs have toxic and beneficial effects which are their intrinsic properties

- Pharmacogenetic testing can only improve the likelihood, but without the guarantee, of a beneficial outcome in terms of safety and/or efficacy

- Determining a patient's genotype may reduce the time required to identify the correct drug and in some cases minimize exposure to potentially ineffective medicines

- Application of pharmacogenetics to clinical medicine may improve population based risk benefit ratio of a drug (society benefit) but improvement in risk benefit at the individual patient level cannot be guaranteed

- The notion of right drug at the right dose is a 21st century fantasy

*Br J Clin Pharmacol/74:4,713
Factoids…

- Integrating pharmacogenomic data into clinical practice will likely increase patient safety and reduce costs. It’s estimated that 1.5 million preventable serious medication errors occur annually in the United States.
- Those numbers translate into $177 billion spent on services associated with the corresponding illness and death.
- In addition, nearly 40% of the compounds in the drug pipeline are targeted therapies. A majority of these drugs will be prescribed for oncology applications and will take into account a patient’s genetic or biomarker information.

Resources

http://www.phrap.org/

References


