PHARMACOGENETICS & DRUG IDIOSYNCRASY

M. Imad Damaj, Ph.D.
Associate Professor
Pharmacology and Toxicology
Smith 656A, 828-1676, mdamaj@hsc.vcu.edu

Inter-individual Differences in Drug Efficacy

<table>
<thead>
<tr>
<th>Group</th>
<th>Incomplete/absent efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT2-antag</td>
<td>10-25%</td>
</tr>
<tr>
<td>SSRI</td>
<td>10-25%</td>
</tr>
<tr>
<td>ACE-I</td>
<td>10-30%</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>15-25%</td>
</tr>
<tr>
<td>Tricycl. AD</td>
<td>20-50%</td>
</tr>
<tr>
<td>HMGCoAR-I</td>
<td>30-70%</td>
</tr>
<tr>
<td>Beta-2-agonists</td>
<td>40-70%</td>
</tr>
</tbody>
</table>

May 1975: Five interns at St. Mary’s Hospital in London participated in a study of the effects of debrisoquine (40 mg), an antihypertensive agent.

Robert Smith only: dizziness and severe orthostatic hypotension

Pharmacogenetics

Same symptoms
Same findings
Same disease (?)

Same Drug....

Different Effects

? Possible Reasons:
Non-Compliance...
Drug-drug interactions...
Chance...

Genetic Differences

PEOPLE ARE DIFFERENT!
The Gene for...

Much individuality in drug response is inherited (polymorphism)

PHARMACOGENETICS
The study of genetically controlled variations in drug response

Human genome contains 30,000 to 40,000 genes
100,000 different proteins: possible drug targets

0.1% = almost 3 million single nucleotide polymorphism in which a nucleotide is exchanged for another at a given position

Ethnic Differences Correlate well with Genetic Background

0.1% = almost 3 million single nucleotide polymorphism in which a nucleotide is exchanged for another at a given position

99.9% Identical
To be important SNPs must affect either function or amount of a protein

GENETIC POLYMORPHISMS

Pharmacokinetic
- Metabolizing Enzymes
- Transporters
- Plasma protein binding

Pharmacodynamic
- Target Proteins
- Receptors
- Ion channels

Idiosyncratic Response
Variation in Target Proteins
Variations in target proteins or their pathways can influence the outcome of pharmacotherapy.

- **Amount**
- **Structure**
- **Function**

Variation in β2-Adrenergic Receptor
β2-Receptor mediates the relaxation of smooth muscle in small airways.

β2-Receptor agonists are used for asthma.

Variation in β2-Adrenergic Receptor
β2-Receptor is a G-protein receptor: highly polymorphic.

Amino Acid 16:
- 60% Hispanic/Caucasian SNP for glycine G16
- The other 40% arginine R16

Variation in β2-Adrenergic Receptor
- Individuals with G16 variant acutely downregulate β2-receptor in response to agonists
- Albuterol is less effective in G16 individuals
- First step toward developing an effective pharmacological strategy for such patients

Variation in Enzymes of Drug Metabolism

- **Poor Metabolizer**
- **Ultra-Metabolizer**
- **Multiple genes**
- **Deleted gene**
- **Toxicity**
- **Normal Response**
- **Diminished Response**

PGt and Drug Metabolism
Same dose but different plasma concentrations.

Patient A
- **GCCCCGCTC**
- Wild type

Patient B
- **GCCCCACCTC**
- Mutation

Wild type

Mutation

Time

Concentration

Time
**PGt: Possible Impact on PK and Dose-Response**

- **Efficacy:** reduction in anxiety and symptoms of depression
  - Example: Nortriptyline
- **Safety:** tachycardia, arrhythmias and drowsiness

---

**Atypical Plasma Cholinesterase**

- Hydrolysis by pseudocholinesterase
- Choline → Succinylmonocholine

- A rapid acting, rapid recovery muscle relaxant - 1951
- Usual paralysis lasted 2 to 6 min in patients
- Occasional pt exhibited paralysis lasting hrs
- Cause identified as an "atypical" plasma cholinesterase

---

**Antianginal Drugs (Nitrates)**

- Isosorbide Dinitrate; ISORDIL, ISORBIDRATE
- Nitroglycerin (Glyceril Trinitrate); NITRO-BID, NITROSTAT
- Isosorbide -5-Mononitrate; IMDUR, ISMO

---

**Atypical Plasma Cholinesterase**

- Atypical plasma cholinesterase has 1/100 the affinity for succinylcholine as normal enzyme
- Occurs in 1:2500 individuals

---

**Antianginal Drugs & Methemoglobin Reductase**

- Methemoglobin is hemoglobin that has been oxidized from the ferrous (Fe++) to the ferric (Fe+++) state, thus unable to bind oxygen.
- The NADH- methemoglobin reductase enzyme reduces methemoglobin to hemoglobin.
- Methemoglobinemia results from either inadequate enzyme activity or too much methemoglobin production.
**Antianginal Drugs & Methemoglobin Reductase**

- Deficiency of methemoglobin reductase is inherited as an autosomal recessive trait and occurs with increased frequency in Inuit and Alaskan Native Americans.
- Heterozygotes have approximately 50% enzyme activity but without cyanosis, although they are predisposed to the development of toxic methemoglobinemia when exposed to nitrates and other stress.

A family illustrating the inheritance of a deficiency in methemoglobin reductase.

**XENOBIOTICS SUBJECT TO POLYMORPHIC ACETYLATION IN MAN**

<table>
<thead>
<tr>
<th>Hydrazines</th>
<th>Arylamines</th>
<th>Carcinogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>isoniazid</td>
<td>dapsone</td>
<td>benzdine</td>
</tr>
<tr>
<td>hydralazine</td>
<td>phenylzine</td>
<td>β-naphthylamine</td>
</tr>
<tr>
<td>phenyldrazine</td>
<td>sulfamethazine</td>
<td></td>
</tr>
<tr>
<td>acetylhydrazine</td>
<td>sulfapyridine</td>
<td></td>
</tr>
<tr>
<td>hydrazine</td>
<td>aminogluthimide</td>
<td></td>
</tr>
</tbody>
</table>

**Drugs metabolized to amines**
- sulfasalazine
- nitrazepam
- clonazepam
- caffeine

**N-ACETYLTRANSFERASE POLYMORPHISM**


**ETHNIC DIFFERENCES IN THE DISTRIBUTION OF ACETYLATOR PHENOTYPE**

<table>
<thead>
<tr>
<th>Population</th>
<th>% Slow</th>
<th>% Hetero Fast</th>
<th>% Homo Fast</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Indians</td>
<td>59</td>
<td>35.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Caucasians</td>
<td>58.6</td>
<td>35.9</td>
<td>5.5</td>
</tr>
<tr>
<td>Blacks</td>
<td>54.6</td>
<td>38.6</td>
<td>6.8</td>
</tr>
<tr>
<td>Eskimos</td>
<td>10.5</td>
<td>43.8</td>
<td>45.7</td>
</tr>
<tr>
<td>Japanese</td>
<td>12</td>
<td>45.3</td>
<td>42.7</td>
</tr>
<tr>
<td>Chinese</td>
<td>22</td>
<td>49.8</td>
<td>28.2</td>
</tr>
</tbody>
</table>


**OXIDATION POLYMORPHISM**

Many CYP450 Enzymes Are Polymorphic: Example CYP 2C19 & CYP 2D6

- Responsible for metabolism of 40% of all Rx drugs

**CYP2C19 Polymorphism**

- First detected from unusual response to anti-epileptic drug mephenytoin (dysphoria/sedation)
- 3-6% of Whites and African Americans, but up to 25% of Chinese/Japanese/Koreans are PMs
- The common true null mutations leading to PM status result from splicing defects (*2) or the loss of start (*4) and stop (*3) codons

<table>
<thead>
<tr>
<th>CYP2C19</th>
<th>Exon</th>
<th>Cysteine (Cys)</th>
<th>Trp</th>
<th>Glu</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19*1</td>
<td>4</td>
<td>GAG</td>
<td>TCG</td>
<td>TCA</td>
</tr>
<tr>
<td>CYP2C19*2</td>
<td>4</td>
<td>TAG</td>
<td>TCG</td>
<td>TCA</td>
</tr>
<tr>
<td>CYP2C19*3</td>
<td>5</td>
<td>CAG</td>
<td>CCG</td>
<td>GGG</td>
</tr>
</tbody>
</table>

(40 bp deletion from mRNA and premature stop 20 aa downstream in new exon-5)
Phenytoin

A non-linear kinetics after moderate doses

Phenytoin Metabolism

- Aromatic hydroxylation
- Deficient para-hydroxylation will lead to increase phenytoin levels
- Increased toxicity: nystagmus, ataxia and motor impairment

Frequency of CYP2C19 Poor Metabolizers

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africans</td>
<td>4.1</td>
</tr>
<tr>
<td>African-Americans</td>
<td>1.4</td>
</tr>
<tr>
<td>Caucasians</td>
<td>2.8</td>
</tr>
<tr>
<td>Chinese</td>
<td>13.6</td>
</tr>
<tr>
<td>Japanese</td>
<td>20.3</td>
</tr>
<tr>
<td>Koreans</td>
<td>13.7</td>
</tr>
<tr>
<td>Amerindians</td>
<td></td>
</tr>
</tbody>
</table>

CYP2C19 Substrates

- S-mephenytoin
- hexobarbital
- R-mephobarbital
- phenytoin
- diazepam
- citalopram
- R-warfarin (8-OH)
- propranolol (in part)
- imipramine
- clomipramine
- amitryptiline
- proguanil
- teniposide
- nilutamide
- indomethacin
- moclobemide

Cure rates for H. pylori infections may depend upon CYP2C19 genotypes

- 62 patients with duodenal or gastric ulcer
- treated with omeprazole 20 mg and amoxicillin
- 20% of Asian and 4% of whites are homo. variant

CYP 2D6 POLYMORPHISM

The polymorphism of CYP 2D6 (debrisoquine 4-hydroxylase) has been studied in great detail, as metabolic differences have first been described for debrisoquine and sparteine (antipsychotics)

- localized on chromosome 22
- Of the 75 alleles, 26 exprime CYP2D6 protein
- see http://www.imm.ki.se/CYPalleles/cyp2d6.htm
CYP 2D6 Polymorphism (II)

<table>
<thead>
<tr>
<th>Designation</th>
<th>Characteristic mutation(s)</th>
<th>Enzyme activity</th>
<th>Allele frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6*1</td>
<td>Wild type</td>
<td>Normal</td>
<td>30</td>
</tr>
<tr>
<td>CYP2D6*2</td>
<td>G349C, C294T, G650C substitutions</td>
<td>Normal</td>
<td>30</td>
</tr>
<tr>
<td>CYP2D6*3</td>
<td>A485G deletion</td>
<td>Deficient</td>
<td>2</td>
</tr>
<tr>
<td>CYP2D6*4</td>
<td>G1301A substitution</td>
<td>Deficient</td>
<td>2</td>
</tr>
<tr>
<td>CYP2D6*5</td>
<td>T240C deletion</td>
<td>Deficient</td>
<td>2</td>
</tr>
<tr>
<td>CYP2D6*6</td>
<td>A369C substitution</td>
<td>Deficient</td>
<td>0-1</td>
</tr>
<tr>
<td>CYP2D6*7</td>
<td>G296A deletion</td>
<td>Deficient</td>
<td>0-1</td>
</tr>
<tr>
<td>CYP2D6*8</td>
<td>G650C substitution</td>
<td>Deficient</td>
<td>0-1</td>
</tr>
<tr>
<td>CYP2D6*9</td>
<td>C294T, G650C, G1301A substitution</td>
<td>Decreased</td>
<td>1-5</td>
</tr>
<tr>
<td>CYP2D6*11</td>
<td>C294T substitution</td>
<td>Deficient</td>
<td>0-1</td>
</tr>
<tr>
<td>CYP2D6*12</td>
<td>G1301A substitution</td>
<td>Deficient</td>
<td>0-1</td>
</tr>
<tr>
<td>CYP2D6*13</td>
<td>Hybrid, 294C-295A, 260C-296C, 296C-297C</td>
<td>Decreased</td>
<td>1-5</td>
</tr>
<tr>
<td>CYP2D6*14</td>
<td>G1301A substitution</td>
<td>Deficient</td>
<td>0-1</td>
</tr>
<tr>
<td>CYP2D6*15</td>
<td>T240C deletion</td>
<td>Deficient</td>
<td>0-1</td>
</tr>
<tr>
<td>CYP2D6*16</td>
<td>Hybrid, 299C-300A, 297C-298C, 298C-299C</td>
<td>Decreased</td>
<td>1-5</td>
</tr>
<tr>
<td>CYP2D6*17</td>
<td>Gene duplication</td>
<td>Increased</td>
<td>1</td>
</tr>
<tr>
<td>CYP2D6*18</td>
<td>Gene duplication</td>
<td>Increased</td>
<td>1-5</td>
</tr>
<tr>
<td>CYP2D6*19</td>
<td>Gene duplication</td>
<td>Deficient</td>
<td>0-5</td>
</tr>
</tbody>
</table>


CYP 2D6 Polymorphism (III)

Variability of debrisoquine-4-hydroxylation

Frequency of CYP 2D6 Poor & Rapid Metabolizers

<table>
<thead>
<tr>
<th>Race</th>
<th>Poor</th>
<th>Rapid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasians</td>
<td>5-10%</td>
<td>rare</td>
</tr>
<tr>
<td>Asians</td>
<td>1-2%</td>
<td></td>
</tr>
<tr>
<td>Ethiopians</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Spaniards</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

CYP2 D6 Substrates

- Antidepressants
  - Haloperidol
  - β-Blockers
- Dextrometorphan
- Codeine
- Amphetamine
- Flecainide
- Phenformin

Types of Idiosyncratic Responses

- Drug toxicity due to deficient metabolism
- Increased sensitivity to drug effect
- Novel drug effect
- Decreased responsiveness to drug
- Abnormal distribution of material

IDLIOYNSYCRATIC EFFECTS

- Not caused by variations in target proteins or metabolizing enzymes
- Chance interaction between the drug and some unusual aspect of the physiology
- Hard to predict
Increased Sensitivity to Drug Effect

- Nitrites and other drugs causing methemoglobinemia (due to oxidizing effects) -- basis is abnormal hemoglobins (M and H)
- Aminoglycoside antibiotic-induced deafness* -- basis unknown; apparent transmission by females
- Chloramphenicol-induced bone marrow depression* -- basis unknown

Drugs and Chemicals Unequivocally Demonstrated to Precipitate Hemolytic Anemia in Subjects with G6PD Deficiency

- Acetanilide
- Methylene Blue
- Nitrofurantoin
- Primaquine
- Acid
- Sulfacetamide
- Nalidixic
- Naphthalene
- Sulfanilamide
- Sulfaypyridine
- Sulfamethoxazole

Glucose-6-Phosphate Dehydrogenase Activity

Effects >100 million worldwide

- Glucose-6-Phosphate Dehydrogenase Activity

- Reduced NADPH - H+ → Glutathione
- Enhanced RBC Membrane Fragility
- Anemia ↔ Hemolysis

INCIDENCE OF G6PD DEFICIENCY IN DIFFERENT ETHNIC POPULATIONS

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazic Jews</td>
<td>0.4</td>
</tr>
<tr>
<td>Sephardic Jews</td>
<td>53</td>
</tr>
<tr>
<td>Kurds</td>
<td>24</td>
</tr>
<tr>
<td>Iraq</td>
<td>15</td>
</tr>
<tr>
<td>Persia</td>
<td>10</td>
</tr>
<tr>
<td>Cochin</td>
<td>5</td>
</tr>
<tr>
<td>Yemen</td>
<td>&lt;4</td>
</tr>
<tr>
<td>North Africa</td>
<td>8</td>
</tr>
<tr>
<td>Iranians</td>
<td>8</td>
</tr>
<tr>
<td>Greeks</td>
<td>0.7-3</td>
</tr>
</tbody>
</table>

INCIDENCE OF G6PD DEFICIENCY IN DIFFERENT ETHNIC POPULATIONS

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese</td>
<td>2</td>
</tr>
<tr>
<td>Filipinos</td>
<td>13</td>
</tr>
<tr>
<td>Indians-Parsees</td>
<td>16</td>
</tr>
<tr>
<td>Javanese</td>
<td>13</td>
</tr>
<tr>
<td>Micronesians</td>
<td>&lt;1</td>
</tr>
<tr>
<td>African-Americans</td>
<td>10</td>
</tr>
</tbody>
</table>

Primaquine

- Haemolysis is pronounced in individuals who are glucose 6-phosphate dehydrogenase deficient (~10% of black American males).
- Primaquine itself is not toxic to erythrocytes.
- It has been proposed that there is extensive metabolism to unstable catechols and quinones.
- Primaquine metabolites can place the erythrocyte under oxidative stress.
- If not rectified, oxidative stress results in oxidation of haemoglobin and critical protein thiols, with Heinz body formation and lysis.
Porphyrias are associated with overproduction of porphyrins: acute abdominal pain, psychosis, “purple pee”.

Acute intermittent porphyria the exacerbation is induced by barbiturates, sulfonamides, and griseofulvin.

Acute intermittent porphyria:

\[
\text{succinyl-CoA} + \text{glycine} \rightarrow \text{ALA synthase} \rightarrow \text{Porphobilinogen Deaminase (PBG)}
\]

- Malignant Hyperthermia & Halothane
  - Malignant Hyperthermia: 1/20,000 with succinylcholine
  - Classic: rapid rise in body temperature, muscle rigidity, tachycardia, rhabdomyolysis, acidosis, hyperkalemia
  - Life threatening: I.v. dantrolene
  - Genetic defect in the muscle
  - Mutations in the Ryanodine receptor (calcium release channel)
  - Halothane induces potentiation of Ca activity in susceptible patients

Distinguishing Toxic, Idiosyncratic and Allergic Responses to Drugs

<table>
<thead>
<tr>
<th></th>
<th>Toxic</th>
<th>Idiosyncratic</th>
<th>Allergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-related</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>What drugs</td>
<td>All</td>
<td>Few</td>
<td>Many</td>
</tr>
<tr>
<td>Prior exposure</td>
<td></td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Mechanism</td>
<td>Receptor</td>
<td>Receptor</td>
<td>Ag-Ab</td>
</tr>
<tr>
<td>Effect antagonized</td>
<td>Antagonists</td>
<td>Antagonists</td>
<td>Anti-H; SAD</td>
</tr>
</tbody>
</table>

Allergic skin reaction

Penicillin rash

Genetically Based Optimization of Drug Dosing

- Responders
- Non-responders
- Toxic responders

PHARMACOGENETICS & CLINICAL PRACTICE

Take two genes and call me in the morning.
Genetically Based Optimization of Drug Dosing

Non-responders

Toxic responders

Current Applications of Pharmacogenetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease</th>
<th>Gene</th>
<th>PGx Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-MP</td>
<td>ALL</td>
<td>TPMT</td>
<td>Safety &amp; Efficacy</td>
</tr>
<tr>
<td>Melacine</td>
<td>Melanoma</td>
<td></td>
<td>Safety</td>
</tr>
<tr>
<td>5-FU</td>
<td>Colorectal Cancer</td>
<td>TS</td>
<td>Safety</td>
</tr>
<tr>
<td>Herceptin</td>
<td>Breast Cancer</td>
<td>HER2</td>
<td>Efficacy</td>
</tr>
</tbody>
</table>

Pharmacogenetics: Use in drug delivery

ALL, 6MP and polymorphic TPMT

Children $\downarrow$ TPMT $\rightarrow$ Toxicity

Children $\uparrow$ TPMT $\rightarrow$ Poor response

Pharmacotherapy of Tomorrow?

Today
empirical prescription
"mass market"

Future
rational prescription
"individualized"

Physician Dx; clinical info

define & treat

Drug a
Drug b
Drug c
Drug d

Individual physician experience
Cost: time, money & well-being

Informed physician diagnosis
Savings: time, money & illness

Pharmacogenetics: to deliver 'right medicine, right dose, to right patient'
Personalized Medication in the Future

In the future (? years), your doctor will be able to select the best drug to treat your disease and the appropriate dose based on knowledge of your specific genetic makeup!