**Drug Metabolism and Interactions**

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UCLA School of Nursing

**Why Do Nurses Need to Know?**

- Can we take the guess work out of predicting how a person will respond to a medication?
- Dosing cancer chemotherapies with BSA only—narrow therapeutic windows
- Adverse drug reactions cost annually $5.6 billion
- About 20 drug labels mention reactions that may be influenced by genetic differences

**Summer Reading List**

- **Importance of Drug Metabolism**
  - Therapeutic effect and/or toxicity may be different (adverse?) if metabolic process altered
  - Drug interactions may be predictable dependent on metabolic pathway

**Review of Drug Metabolism**

- Process that changes structures and properties of a chemical compound
- Chemical alteration of a drug in the body (Phase 1, Phase II reactions)
- Products of drug metabolism (metabolites) are different from original drug
  - Chemical structure
  - Therapeutic effect
  - Toxicity

**Drug Metabolism**

- Most metabolism is enzyme dependent
- Majority of Phase I reactions catalyzed by CYP P450 enzymes
  - CYP3A4 is the most abundant and most important in drug metabolism
  - CYP3A is sensitive to inhibition or induction by concomitantly administered medications.
- Minority non-CYP mediated
- Phase II reactions catalyzed by non-CYP
Cytochrome P450

- 6 main cytochromes
- Responsible for the oxidative metabolism of more than 90% of marketed drugs.
  - CYP 3A4: metabolizes more drug molecules than the others.
  - CYP 1A2
  - CYP 2C9
  - CYP 2C19
  - CYP 2D6
  - CYP 2E1

What is Cytochrome P450?

- Superfamily of haem containing enzymes
- Phase 1 metabolism of many drugs, nutrients, endogenous substances and environmental toxins
- Synthesis of cholesterol, steroids, & prostacyclines
- Involved in the metabolism of many anticancer drugs including IFEX, CXT, VP16, vinblastine, vincristine, norelbin, paclitaxel, docetaxel, and tamoxifen.

Where is Cytochrome P450 Found?

- Strictly bound to membranes of the endoplasmic reticulum and mitochondria
- Primarily in the liver and small intestine
- Smaller amounts in the kidney, lung and brain, placenta

Alterations in CYP Activity

- Genetic factors
- Environmental factors

CYP Activity: Genetic Factors

- Polymorphisms (alteration in phenotype)
  - Genotype refers to a person’s specific allelic composition
  - Phenotype refers to the observable or measurable manifestation of person’s genotype, either by itself or with environmental factors
  - Frequencies vary among ethnic groups
  - Associated with variation in rates of drug metabolism
  - May have important clinical implications for some groups

Identifying Genes Influencing Drug Response- Pharmacogenetic

- www.genetests.org
  - Genetic testing for CYP enzymes commercially available
  - Test only for the most common gene alterations associated with poor or ultrarapid metabolism
  - DNA Microarray analysis
  - SNP- dispersed throughout the human genome, LC chromatography/mass spectrometry analysis of plasma or tumor tissue
AmpliChip CYP 450

- Chip will test for variations in two genes: CYP2D6 and CYP2C19.
- The genes affect how people process about 25% of drugs on the market.
- Initially used primarily for patients using antipsychotic and antidepressant drugs, varies greatly depending on the CYP2D6.
- Company will translate depending metabolic function as poor to ultrarapid.

Genotyping Service

- A genotyping service.
- Cytochrome 450 gene as well as the NAT2, affects efficacy of anti-HIV medications.
- $2000 for the initial test and a subscription of $350 for scientific updates.
- Fewer than 1000 clients so far.
- www.signaturegenetics.com

Effect of CYP2D6 Genotype on Antiemetic Efficacy (Kaiser et al)

- Patients and methods (N = 270)
  - Hesketh level 3-5: 79%
  - Steroid use: 56%
  - Ondansetron 8 mg BID
  - Tropisetron 5 mg QD
- Nausea and vomiting measured by interview
- CYP2D6 genotypes identified by PCR
- Drug serum concentration in tropisetron subgroup

Effect of CYP2D6 Genotype on Antiemetic Efficacy: Results of Kaiser et al

- Genetically defined poor metabolizers (PM) had higher tropisetron concentrations
- PM had lower intensity of N/V
- UM had higher frequency of vomiting (with and without steroids)
- UM had more severe nausea
- Conclusion: Antiemetic treatment with tropisetron or ondansetron could be improved by adjustment for CYP2D6 genotype

Genetic Polymorphism Affects CYP2D6 Metabolism and Varies by Ethnic Group

<table>
<thead>
<tr>
<th>Population</th>
<th>Poor Metabolizers (%)</th>
<th>Ultrarapid Metabolism (%)</th>
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<tbody>
<tr>
<td>Caucasian</td>
<td></td>
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<tr>
<td>American1,2</td>
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<td>German4</td>
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<tr>
<td>African</td>
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<td>5.5, 6.1</td>
<td>4.9</td>
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<td>Nigerian8</td>
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<td>Colombian12</td>
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<tr>
<td>Mexican13</td>
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</table>

Role of Cytochrome P450 Phenotyping in Cancer Treatment

- To address the shortcoming of CYP genotyping, an area of research is developing to determine PHENOTYPE for specific CYPs.
- CYP3A4 most abundant and most important
- No blood test but rather a probe
  - ERβT
  - dexamethasone
  - midazolam
  - urinary cortisol

Effect of Cytochrome P450 Phenotyping on Cancer Treatment

- Effect of CYP2D6 Genotype on Antiemetic Efficacy: Results of Kaiser et al
**First Reported Prospective Study Evaluating Phenotyping in Chemotherapy Dosing**

- Yamamoto et al. (2000) established that the clearance of docetaxel correlates with a measurement of CYP3A4.
  - 30 patients with non-small cell lung cancer
  - Probe done with hydrocortisone and CYP3A4 activity is established based on amount of drug excretion in urine over 24 hours.
- Yamamoto et al. (2005)
  - 59 patients
  - AUC dosing vs BSA dosing

**External Factors Affecting Drug Metabolism**

- **Dietary Factors**
  - Protein
  - Fat
  - Carbohydrate
  - Vitamins
  - Trace Elements
  - Tobacco Smoke
  - Alcohol
  - Pyrolysis Products
  - Grapefruit
- **Environmental Factors**
  - Petroleum products
  - Pyrolysis Products
  - Heavy metals
  - Insecticides
  - Industrial pollutants
  - Motor Vehicle exhaust

**CYP Activity: Environmental Factors**

- Exposure to exogenous substances
  - Substrates
  - Inducers
  - Inhibitors

- Other factors
  - Hepatic dysfunction

**Substrates**

- Many drugs use P450 isoenzymes as substrates for their metabolism
- Drugs can compete for metabolism by the available P450 isoenzyme substrates

**Induction**

- Occurs when drug stimulates increased synthesis of isoforms leading to increased enzyme activity
- Increased metabolism & hepatic clearance of all substrates
- Time course more difficult to predict
- Some drugs capable of inducing many isoenzymes

**Inhibition**

- Substances that inhibit
  - Competitive or noncompetitive
  - Cause decreased metabolism & hepatic clearance
  - Mechanism most responsible for life threatening drug interactions
  - Inhibition is isoenzyme specific (i.e., drugs that affect 3A4 may not affect 2D6)
Inhibition

- Clinical results depend on pharmacologic activities of the parent compound
- Begins with first dose
- Maximal when inhibitor reaches steady state
- Resolution depends on drug half life

Potential Drug Interactions
Ondansetron

<table>
<thead>
<tr>
<th>CYP1A2</th>
<th>CYP2D6</th>
<th>CYP3A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorouracil</td>
<td>Oxaliplatin</td>
<td>Cyclophosphamide, taxanes</td>
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<tr>
<td>Warfarin</td>
<td>Temozolomide</td>
<td>Etoside, irinotecan</td>
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<tr>
<td>Verapamil</td>
<td>Tamoxifen, vinblastine</td>
<td>Diltiazem, verapamil</td>
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<tr>
<td>Triazoline</td>
<td>Vinorelbine</td>
<td>Phenytoin, simvastatin</td>
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<tr>
<td>Thiophosphoryl</td>
<td>Quinidine, quinine</td>
<td>Atazanavir, darunavir</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Cimetidine, ranitidine</td>
<td>Fluoxetine, paroxetine</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Triyclic antidepressants</td>
<td>St John’s wort, trazodone</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Codeine, propoxyphene</td>
<td>Cimetidine, triazolam</td>
</tr>
<tr>
<td>Dehydroepiandrosterone</td>
<td>SSRIis</td>
<td>Azole antifungals, steroids</td>
</tr>
</tbody>
</table>

Example: Aprepitant (Emend®)

- Cytochrome P450 3A4 (CYP3A4)
  - Substrate
  - Moderate inhibitor
  - Inducer

- Cytochrome P450 2C9 (CYP2C9)
  - Inducer

Aprepitant Slightly Induces Warfarin Metabolism

<table>
<thead>
<tr>
<th>Day</th>
<th>Ratio of fold change from baseline (APR/placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
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<tr>
<td>2</td>
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<td>3</td>
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<td>7</td>
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<tr>
<td>8</td>
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</tbody>
</table>

N=11-12
Small inductive effect on warfarin warrants closer monitoring of INR

Aprepitant Is a Moderate CYP3A4 Inhibitor

Example: Aprepitant (Emend®)

- Aprepitant (125 mg Day 1, 80 mg/d Days 2 to 5)
- Aprepitant regimen for CINV produces CYP3A4 inhibition comparable to grapefruit juice and widely used drugs (e.g., diltiazem, verapamil).
Humor is Great Medicine!!

Variability in Drug Effect
- Pathogenesis & severity of disease
- Age
- Nutritional status
- Renal & liver function
- Concomitant illness
- Drug interactions
- Inherited differences in metabolism & disposition of drugs

Drug Interactions
- Knowledge of CYP P450 isoenzyme system has rapidly expanded with knowledge of gene mapping and technology
- Understanding this system can help to prevent or minimize complications from drug interaction through that system

Drug Interaction Process
- Physiochemical
- Pharmacodynamic
- Combined Toxicity
- Pharmacokinetics

Definitions
Pharmacokinetics (PK)
- What the body does to the drug
  - Absorption
  - Distribution
  - Metabolism
  - Excretion

Pharmacodynamics (PD)
- What the drug does to the body
  - Drug action at the receptor site

Outcomes of Drug Interactions
- Potentiation (increased therapeutic +/- AEs)
- Inhibition (decreased therapeutic +/- AEs)
- Unique response that does not occur with either agent alone
Adverse Drug Events

- Nontherapeutic deleterious effects of a medication that has been appropriately prescribed
- Drug interactions (drug-drug interactions)
  - Modification of action of one or more concurrently administered agents
  - Specific time course
  - 33% of all ADRs
  - 50% of cost of ADRs

Implications for Clinicians

Complete careful drug history:

- Prescriptions
- OTC
- CAM
- Smoking
- Grapefruit juice
- Polypharmacy

Implications for Clinicians (cont)

- Knowledge of PK/PD
- Awareness of CYP (and other potential) interactions
- Resources: Use product info; drug interaction references
- Systems issues
- Special population considerations

Polypharmacy

- The average cancer patient is on 5 medications
- Elderly patients average 6 prescription medicines
- Non-cancer related medications may interact with chemotherapeutic regimen leading to an increased risk of adverse events
- Concerns of interactions due to overlapping metabolic pathways

Potential for Drug-Drug Interaction

- Number of Drugs: 2, 3, 4, 5, 6, 7, 8
- Actual Probability of Interaction (%): 5.6, 15.8, 34.3, 46.7, 72, 46, 100

Resources

- Flockhart, DA. Cytochrome P450 drug interaction table
  - [http://medicine.iupui.edu/flockhart/](http://medicine.iupui.edu/flockhart/)
- Hayes, EM. The cytochromeP-450 enzyme system
  - [http://www.edhayes.com/startp450.html](http://www.edhayes.com/startp450.html)
  - [http://www.ncpanet.org/CONTED/cytochrome.html](http://www.ncpanet.org/CONTED/cytochrome.html)
- The Worldwide Physiologist: Cytochrome P450

Challenges
- Rapidly evolving knowledge
- Increasingly important in clinical practice
- Safety and quality
- “Raising the Bar”
- Pharmacogenomics

Patient’s Resiliency
- If your time hasn’t come yet, not even a doctor can kill you!!
  
  Leigh Stocker

Martin Luther King
- “You don’t have to see the whole staircase, just take the first step.”

Any Questions?
- Image not available

Unique Toxicities of Novel Therapy
Carol S. Viele RN, MS
Clinical Nurse Specialist
Hematology-Oncology-Bone Marrow Transplant
University of California San Francisco

Objectives
- At the completion of this presentation the participant will be to:
  - Describe at least 3 unique toxicities
  - Define the symptoms of the 3 toxicities
  - Identify treatment interventions for the toxicities
Gefitinib (Iressa)

- Gefitinib is a molecularly targeted therapy that is an inhibitor of the epidermal growth factor receptor-tyrosine kinase (EGFR-TK) enzyme which is frequently is aberrantly activated in tumor cells
- Approved for treatment of Non-Small Cell Lung Cancer

Acneiform Rashes Observed With Gefitinib

Image not available

Gefitinib (Iressa)

- Pulmonary toxicity:
  - Incidence- 1-5% in the Japanese population, less than 1% in other populations
  - Presentation:
    - Pulmonary edema
    - Non-specific interstitial pneumonia
    - Bronchiolitis obliterans organizing pneumonia (BOOP)
    - Eosinophilic pneumonia
    - Pulmonary hemorrhage

Pulmonary toxicity: (Hypothesis)

- EGFR existing through the cell membrane transmits an EGF signal downstream and activates cell growth
- EGF is a potential factor promoting regeneration of alveolar epithelial cells which play a role in repair of acutely injured lungs
- EGFR inhibitor may impair healing of epithelium and therefore exacerbate an existing lung injury


Gefitinib (Iressa)

- Symptoms:
  - Rapidly progressive dypsnea
  - Rales
  - Rhonchi
  - Hypoxemia
  - Progressive changes on chest film

Symptoms:

- Rapidly progressive dypsnea
- Rales
- Rhonchi
- Hypoxemia
- Progressive changes on chest film

Treatment:

- Ventilate
  - Nasal prongs
  - Face mask
  - Intubation
- Antibiotics
- Steroids
  - High dose- Methylprednisolone
**Gefitinib (Iressa)**

- **Outcome:**
  - Death rate from this agent with this presentation is 0.74% and therefore can be categorized as an infrequent but potentially severe complication.

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**Denileukin Deftitox (Ontak)**

- This is a genetically engineered fusion protein that directs lethal action of the diptheria toxin to cells bearing the IL-2 receptor complex on their surfaces.
- Treatment for both B-cell and T-cell Lymphoma.

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**Denileukin Deftitox (Ontak)**

- **Side Effects:**
  - Vascular leak syndrome - most frequent in the first cycle
    - Edema
    - Hypoalbuminemia < 2.8 gms/dl
    - Hypotension
    - Elevated transaminases

- **Side effect management:**
  - Albumin should be at 3 gms/dl or greater
  - Transaminases should have returned to Grade 1 level (< 2.5 high normal value)
  - Monitor laboratory values carefully
  - Weigh patient prior to each therapy session, monitor for weight gain of > 5 lbs
  - Evaluate for respiratory distress
    - Shortness of breath
    - Edema
    - Rales
    - Rhonchi

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**Erlotinib (Tarceva)**

- Erlotinib is a tyrosine kinase inhibitor associated with the epidermal growth factor receptor (EGFR). Specificity of inhibition with regard to other tyrosine kinase inhibitors has not been fully characterized. EGFR is expressed on the cell surface of both normal and malignant cells.
- Approved for use in Non-Small Cell Lung Cancer.
Acneiform Rash Observed With Erlotinib Treatment

Skin rash in a patient with NSCLC receiving erlotinib 200 mg/day

Image not available

Erlo tinib (Tarceva)

- Pulmonary toxicity is similar to other EGFR inhibitors
  -Interstitial lung disease frequency reported at 0.8% same as placebo group
  -Diagnosis include:
    -Pneumonitis
    -Interstitial pneumonia
    -Interstitial lung disease
    -Obliterative bronchiolitis
    -Pulmonary fibrosis
    -Acute respiratory distress syndrome (ARDS)

Erlo tinib (Tarceva)

- Occurrence- 5 days to 9 months, median 47 days after initiating agent
- Symptoms: If any occur hold drug
  -Dyspnea
  -Cough
  -Fever

Erlo tinib (Tarceva)

- Treatment
  -Discontinue/ Hold drug
  -Oxygen
  -Steroids:
    -Standard dose
    -High dose

Erlo tinib (Tarceva)

- Outcome data:
  -Survival 1 year 31.2% vs Placebo 21.5%
  -Survival median 6.7 months vs Placebo 4.7 months
  -Progression free survival-
    -Tarceva-9.9 weeks median
    -Placebo-7.9 weeks median
  -Response duration
    -Tarceva-34.3 weeks median
    -Placebo-15.9 weeks median

Rituximab (Rituxan)

- A genetically engineered chimeric murine/human monoclonal antibody directed against the CD 20 antigen found on the surface of normal and malignant B lymphocytes
- Effective in the treatment of relapsed/ refractory low grade lymphomas of B-cell origin as well as in diffuse large-B-cell lymphoma
Rituximab (Rituxan)
- Hepatitis B reactivation with related fulminant hepatitis has been reported in some patients with hematologic malignancies receiving rituximab
  - The majority were patients receiving combination therapy
  - Median time to diagnosis of hepatitis was 4 months after starting rituximab and 1 month after the last dose

Rituximab screening
- Screen patients for hepatitis B before dosing
- Evaluate for active hepatitis B infection before dosing
- Monitor for signs of hepatitis for up to several months post dosing
- Monitor all liver function tests closely

Rituximab (Rituxan)
- Treatment:
  - Discontinue drug
  - Antiviral therapy initiated
    - Lamivudine

Bevacizumab is Distinct from Other Agents Targeting the VEGF Pathway
- Image not available

Targeting VEGF: Bevacizumab
- 93% human, 7% murine
- Binds to VEGF with high affinity
- Prevents VEGF from binding to its receptors, inhibits VEGF induced angiogenesis

Bevacizumab: Assessment Parameters
- Baseline assessment
- Medical History
- EKG
- Prior to infusions, assess:
  - Blood pressure
    - In patients with history of hypertension, hypertension may worsen over time and require additional anti-hypertensives
    - In patients with no history of hypertension, hypertension may develop over time
  - Infusion-related symptoms from prior infusion
  - Symptoms occurring since last infusion
  - Changes in prescribed or OTC medications
Bevacizumab (Avastin) Bleeding Pattern

- Non-small cell lung cancer
- Randomized trial 4/13 (31%) Avastin treated patients with squamous cell histology and 2/53 (4%) Avastin non squamous cell histology developed life threatening or fatal pulmonary hemorrhage as compared to 0 of the 32 non Avastin treated patients. Many patients had cavitation or necrosis of the tumor either pre-existing or developing during Avastin therapy.

Bevacizumab: Management of Bleeding/Epistaxis

- Safety consideration for bevacizumab therapy include
  - Patients with known coagulation disorders should not be treated with bevacizumab
  - Low dose warfarin administration has not been associated with an increased risk of serious bleeding
  - Patients with CNS metastases or large tumors located near large arteries may be at increased risk for life-threatening bleeding while receiving bevacizumab therapy
  - Educate patients on signs and symptoms of bleeding

Bevacizumab: GI Perforations

- Monitor patients for GI perforations, wound dehiscence, GI abscesses can develop
- Incidence of occurrence is 2%
- Symptoms and Treatment
  - Abdominal pain
  - Constipation
  - Vomiting
  - Discontinue drug
  - Surgery

Bevacizumab is Distinct from Other Agents Targeting the VEGF Pathway

- Image not available